DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

NATIONAL INSTITUTES OF HEALTH

NATIONAL CANCER INSTITUTE

NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
February 4-5, 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]
February 4-5, 1991

The National Cancer Advisory Board (NCAB) convened for its 77th regular meeting at 8:00 a.m. February 4-5, 1991, in Building 31, 6th Floor, Conference Room 10, National Institutes of Health (NIH).

NCAB Members

Dr. Paul Calabresi (Chairman)
Dr. David Korn (Chairman)[2]
Dr. Frederick F. Becker
Dr. Erwin P. Bettinghaus
Dr. Roswell K. Boutwell[2]
Dr. David G. Bragg
Mrs. Nancy G. Brinker
Mrs. Helene G. Brown[2]
Dr. Kenneth Chan
Dr. John R. Durant
Dr. Gertrude B. Elion (Absent)
Dr. Bernard Fisher
Dr. Philip Frost
Dr. Walter Lawrence, Jr.
Mrs. Marlene A. Malek
Dr. Enrico Mihich[2]
Dr. Kenneth Olden
Mrs. Irene S. Pollin (Absent)
Dr. Sydney Salmon
Dr. Louise C. Strong[2]
Dr. Howard M. Temin
Dr. Samuel A. Wells, Jr.

President's Cancer Panel

Dr. William P. Longmire
Dr. John A. Montgomery

Alternate Ex Officio NCAB Members

Dr. Miriam R. Davis, NIEHS
Dr. David J. Galas, DOE
Captain Bimal Ghosh, DOD
Dr. John R. Johnson, FDA
Dr. Theodore Lorei, DVA
Dr. Lakshimi C. Mishra, CPSC
Mr. John J. Whalen, NIOSH
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.

[2] Retiring member of National Cancer Advisory Board

Liaison Representatives

Dr. Eve Ida Barak, Associate Program Director for Cell Biology, Division of Cellular Biosciences, National Science Foundation.

Ms. Barbara E. Britt, R.N., M.S.N., President of the Oncology Nursing Society, South Pasadena, California, representing the Oncology Nursing Association.

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. William Garrett, Executive Vice President, National Medical Association, representing the National Medical Association for Mr. Charles Johnson.

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.

Dr. Thomas King, Treasurer, Vincent Lombardi Cancer Research Center, Washington, D.C., representing the American Association for Cancer Research.

Dr. Bernard Levin, Chief of the Section of Digestive Diseases, M.D. Anderson Cancer Center in Texas, representing the American Gastroenterology Association.

Ms. Elaine Locke, Associate Director of Practice Administrations, American College of Obstetricians and Gynecologists, representing the American College of Obstetricians and Gynecologists for Dr. Warren H. Pierce.

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

Dr. Robert Park, Past President, American College of Obstetricians and Gynecologists, Washington, D. C., representing the Society of Gynecologic Oncologists for Dr. Clarence Ehrlich, President.

Dr. John F. Potter, Professor of Surgery, Vincent Lombardi Cancer Research Center, Washington, D. C., representing the Society of Surgical Oncology.

Dr. Jerome Richie, Chairman of the Department at the Brigham and Women's Hospital, Boston, Massachusetts, representing the Society of Urological Oncology.

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

Mr. William Tipping, Executive Vice President and Chief Executive Officer, American Cancer Society, representing the American Cancer Society.

In addition to NCI staff members, meeting participants, and guests, a total of 30 registered members of the public attended the meeting.

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I. CALL TO ORDER AND OPENING REMARKS—DR. DAVID KORN

Dr. Korn called the 77th meeting of the National Cancer Advisory Board (NCAB) to order and introduced the new Chair of the Board, Dr. Paul Calabresi, Professor and Chairman of the Department of Medicine at Brown University, and Physician-in-Chief and Vice President for Academic Affairs at Roger Williams General Hospital in Providence, Rhode Island.

Before turning the meeting over to Dr. Calabresi, Dr. Korn announced that he had just received the minutes of the December Board meeting and had not had a chance to review them; because of this, those minutes may not be distributed during the current meeting.

Dr. Calabresi thanked Dr. Korn and welcomed Board members, staff of the National Cancer Institute (NCI), and members of the public. Dr. Calabresi then asked everyone present to stand for a moment of silence in memory of the late Dr. Armand Hammer, who served as Chairman of the President's Cancer Panel.

Dr. Broder presented Dr. Korn with a plaque as a symbol of appreciation for his years of service as Chairman of the NCAB. Mrs. Helene Brown, a departing member of the Board, presented Dr. Korn with a desk clock with the engraved message "David Korn, M.D., with Deep Appreciation from the NCAB, Class of 1990."

Dr. Calabresi introduced a number of guests representing professional and service organizations. He invited members of the public who wished to express their views on any part of the meeting to do so by writing to Mrs. Barbara Bynum, Director, Division of Extramural Activities (DEA) within 10 days of the meeting. He noted that, for the purpose of assuring continuity and appropriately informed consideration of matters that would be coming before the Board, the departing members of the Board had consented to accept ad hoc appointments to the NCAB for the course of this meeting.

II. FUTURE MEETING DATES—DR. PAUL CALABRESI

Dr. Calabresi called the Board members' attention to the following confirmed meeting dates: May 6-8, 1991; September 23-25, 1991; and November 25-27, 1991. He asked if any members objected to the following dates for 1992 meetings: January 27-29, 1992; May 4-6, 1992; September 21-23, 1992; and December 14-16, 1992. No objections were heard, and Dr. Calabresi announced that they stood confirmed.

III. REPORT OF THE PRESIDENT'S CANCER PANEL— DR. WILLIAM P. LONGMIRE

Dr. Longmire, on behalf of himself and Dr. John A. Montgomery, paid tribute to the late Chairman of the President's Cancer Panel, Dr. Armand Hammer. Appointed by President Reagan in 1981, Dr. Hammer took his responsibility very seriously and set about revitalizing the dormant panel, bringing it into more direct contact with the entire cancer community. He instituted the practice of taking the Panel "on the road" through regional meetings, giving the Panel the opportunity to visit many of the country's Cancer Centers.

The first task of the Panel under Dr. Hammer was a consideration of peer review as part of the National Institutes of Health (NIH) grant process, which resulted in a Panel report to the NIH recommending significant changes in that process. Perhaps the most significant change adopted, Dr. Longmire observed, was the concept of the Outstanding Investigator Grant, designed to provide long range stability to productive investigators for the pursuit of innovative projects. Another task the Panel addressed was a consideration of the role of the Cancer Centers. One benefit of this study was an increased emphasis on outreach efforts through programs initiated at the community level.

Dr. Longmire stated that, in response to the lack of funding for construction of new research facilities and renovation of laboratories, Dr. Hammer offered to personally fund a study of the construction needs of the cancer community. This study, cofunded by the American Cancer Society, was completed in 1985. Dr. Hammer also announced, shortly after becoming the Panel's Chairman, that the Armand Hammer Foundation would present an annual $100,000 prize to the scientist considered to have made the greatest contribution to advance research for the cure of cancer. Dr. Longmire reported that seven such awards have been made to date, including awards to the former NCI Director, Dr. Vincent DeVita, to Dr. Robert Gallo, and to Dr. Steve Rosenberg of the NCI.

In 1988 Vice President George Bush asked Dr. Hammer to undertake a Panel study of drug regulation and its effect on the development of therapies for cancer and AIDS. Dr. Hammer convened a national committee, chaired by Dr. Louis Lasagna; the committee prepared a report, which Dr. Hammer personally presented to the President in the Oval Office.

Toward the end of his tribute to Dr. Hammer, Dr. Longmire described the "Stop Cancer" campaign established by Dr. Hammer to raise additional funds for the NCI; this ambitious undertaking managed to raise a substantial sum of money for the Institute.

Dr. Longmire concluded by stating that he and Dr. Montgomery felt that it had been a privilege to have worked with a person of Dr. Hammer's energy, dedication, and enthusiasm. He noted that Dr. Hammer's philosophy regarding cancer was that a cure would be found, and that he was determined to do everything in his power to realize his dream of a cancer-free society for our children and grandchildren.

Dr. Longmire, again on behalf of himself and Dr. Montgomery as departing members of the President's Cancer Panel, expressed appreciation to Dr. Hammer's Editorial Assistant, Eleanor Connors; to the Panel's staff member, Dr. Elliott Stonehill; to Dr. Broder and his staff; and to the members of the NCAB.

IV. REPORT OF THE DIRECTOR, NATIONAL CANCER INSTITUTE— DR. SAMUEL BRODER

Dr. Broder began by acknowledging the contributions of Dr. Hammer during his three 3-year terms as Chairman of the President's Cancer Panel, and by noting the Institute's appreciation of the service of Drs. Longmire and Montgomery as Panel members. He reported that a President's Cancer Panel meeting was held on December 7th at the University of California at San Francisco, hosted by Drs. Harold Varmus and J. Michael Bishop. Focusing

on the need for increased transfer of technology from the laboratory to the bedside, that meeting resulted in a proposal from members of the audience and participating staff that a greater emphasis should be placed on interdisciplinary support for both basic and clinical science.

Dr. Broder stated that this is a time of change at the NCI. He reported that Dr. Daniel Ihde had been appointed as Deputy Director of the Institute. Dr. Ihde is the Editor-in-Chief of the Journal of the National Cancer Institute and has served as the Deputy Chief and head of the Clinical Investigation Section at the NCI Naval Medical Oncology Branch at the Bethesda Naval Hospital.

Introduction of New Board Members

Dr. Broder introduced the following new Board members and departing Board members: Dr. Frederick Becker from the University of Texas M. D. Anderson Cancer Center in Houston, Texas, succeeding Dr. Roswell Boutwell; Dr. Kenneth Chan from the University of Southern California Comprehensive Cancer Center in Los Angeles, California, succeeding Dr. Louise Strong; Ms. Marlene A. Malek from the Lombardi Campaign Executive Committee for Georgetown University's Lombardi Cancer Center, succeeding Mrs. Helene G. Brown; Dr. Kenneth Olden from the Howard University Cancer Center in Washington, D. C., succeeding Dr. Louis Sullivan; and Dr. Sydney Salmon from the University of Arizona College of Medicine and Arizona Cancer Center in Tucson, Arizona, succeeding Dr. Enrico Mihich. Dr. Broder noted that President Bush had announced his intention to appoint new members for the two remaining seats on the NCAB held by Dr. Gertrude Elion and Mr. Louis Gerstner.

New Scientific Developments Within the NCI

Dr. Broder announced that recently another step had been taken in the development of gene therapy for cancer in the NCI intramural program. Two patients received transfusions of tumor-infiltrating lymphocytes, or TIL cells, taken from their own tumors. These cells had been transduced with genes that produce tumor necrosis factor (TNF), which is a potent soluble toxin for certain tumor cells. Dr. Broder explained that, in theory, these TIL cells will circulate, locate relevant target tumor sites, and then nullify the tumor. He stated that, while this activity is in a preliminary phase, we have passed an extremely important milestone in that gene therapy is now a reality in the armamentarium of the National Cancer Program. This research is being led by Dr. Rosenberg, an NCI surgeon and immunotherapist, and has involved cooperation with Dr. Michael Blaese within the NCI and Dr. French Anderson at the National Heart, Lung, and Blood Institute.

Dr. Broder mentioned another new study using gene therapy to treat children with adenosine deaminase deficiency. The lack of this enzyme, he explained, leads to a catastrophe of the immune system.

Dr. Broder added that it is unclear at this time whether these studies will lead to clinical applications, but he stressed that major historical steps were being taken. He stated his opinion that this area of research is paving the way for gene therapy for such illnesses as thalassemia, sickle cell anemia, cystic fibrosis, and cancers of various types.

Dr. Broder reported that another area of development of new therapies is in the study of agents with unique mechanisms of action. One of these, he noted, is taxol, which has an effect on the mitotic spindle and may also mimic in certain ways the special oncogene called $C\text{-}_{mos}$. Taxol, a natural product isolated from the bark of the western yew tree, appears to be highly active in recurrent ovarian cancer and is potentially active in other cancers. Dr. Broder announced that Dr. Bruce Chabner would present an update on a number of issues related to the use of taxol later in the meeting (see below). He stated that the NCI is making the development of this drug an emergency priority, and has established a collaborative agreement with Bristol-Myers-Squibb, a private pharmaceutical company, to address some of the problems caused by supply shortages. The agreement encourages the production of taxol from bark but also encourages research on alternative resources. The Institute is also encouraging investigator-initiated efforts to synthesize and produce taxol and to identify analogs of taxol through its research grant program.

Dr. Broder observed that taxol is only the first of a number of chemically complicated natural products that will present problems of limited supply and difficulty of synthesis. A major problem to be addressed is providing sufficient quantities of active drugs for patients while maintaining respect for ecological considerations. He announced that, in the near future, the NCI will be hosting a symposium and workshop on a number of issues regarding the development of natural products from around the world. He identified Dr. Michael Grever, Acting Head of the Developmental Therapeutics Program of the Division of Cancer Treatment, as a contact person concerning this meeting.

Turning to another subject, Dr. Broder noted that the NCI has taken part in a number of events this year to help raise awareness of cancer control. On January 23rd, the NCI and the Susan G. Komen Foundation sponsored a second Women's Leadership Summit entitled "Women in the Workplace: The Challenge of Breast Cancer." He observed that Ms. Nancy Brinker of the NCAB is the founding Chairman of the Komen Foundation.

At the meeting, attended by more than 200 corporate leaders, Dr. Broder added, Ms. Marilyn Quayle gave the keynote address and Ms. Barbara Bush hosted a White House reception. Scientists reported on breast cancer research and a number of corporations and organizations described their worksite breast cancer programs.

Honors, Awards, and Staff Changes Within the NCI

Dr. Broder then announced the following honors, awards, and staff changes:

- Dr. Lance Liotta, Chief of the Laboratory of Pathology, received the Lila Gruber Memorial Cancer Research Award presented by the American Academy of Dermatology, in recognition of his work on the molecular biology of metastasis
- Dr. Harold L. Moses, a member of the Division of Cancer Prevention and Control (DCPC) Board of Scientific Counselors, received the Bruce Whipple Award, presented by the American Association of Pathologists, for a distinguished career in research
- Dr. Michael Gottesman, who heads the Laboratory of Cell Biology, Dr. Ira Pastan, who heads the Laboratory of Molecular Biology, and Dr. Gerald

Mikish, a guest worker in Dr. Pastan's laboratory, received the Elkin Prize, awarded by the German Urologic Society for important manuscripts

- Dr. Barry Kramer has been appointed as the Associate Director of the Early Detection and Community Oncology Program of the DCPC
- Dr. George Alexander has been appointed as Chief of the Special Populations Studies Branch in the Cancer Control Science Program
- Dr. Ritva Butrum has retired as Chief of the Diet and Cancer Branch of the DCPC
- Dr. George Litvak came on duty on January 13, 1991, in the Office of International Affairs
- Mr. Stephen Hazen replaced Ms. Mary Cushing as Chief of the Extramural Financial Data Branch
- Ms. Mary Cushing is now the Budget Officer, for Financial Management Branch, NCI
- Ms. Jeannette J. Johnson has been named Chief of the Prevention and Control Contract Section

Dr. Peter Greenwald is initiating the following organizational changes in the DCPC:

- The abolition of the Cancer Control Applications Branch in the Health Promotion Sciences Branch and the Smoking, Tobacco, and Cancer Branch in the Cancer Control Sciences Program
- The establishment of the National Outreach Initiatives Branch in the Cancer Control Sciences Program
- The establishment of the Data Analysis and Coordinating Section in the Special Population Studies Branch
- The establishment of the Public Health Applications Research Branch in the Public Health Agency Section
- The establishment of the Prevention and Control Extramural Research Branch.

These changes are designed to help target specific underserved or difficult-to-reach populations, and do not represent fundamental changes in the mission or focus of the NCI.

Update on the NCI Construction Program

Dr. Broder then presented an update on the NCI construction program. In December, the Acting Director of the NIH transferred approximately $4.8 million to the NCI with directions to award construction grants to two NCI Centers, the University of Colorado and the University of Kansas. This resulted from an RFA competition conducted last summer by the NIH. Last August, the NIH provided the NCI with funds to make five construction grant awards to Cancer Centers at the Jackson Laboratory, Purdue University, the University of Michigan, the University of Southern California, and the University of Wisconsin. Dr. Broder stated that the NCI expects that the NIH will make additional construction grant awards in 1991; he promised to keep the Board updated on future actions.

In January, Dr. Broder added, the NCI issued a plan for the use of approximately $5.4 million in extramural enhancement construction funds from the 1991 appropriation. Four construction grants will be awarded to the Massachusetts Institute of Technology, the University of Michigan, the University of Pittsburgh, and the Fred Hutchinson Cancer Research Center, all resulting from applications submitted directly to the NCI Construction Program. Dr. Broder explained that, while the NCI is still accepting construction grant applications, the availability of funds is uncertain. He added that the expectation is that in the near future the NIH will make some construction funds available to categorical Institutes, in effect as part of an interagency process. On February 1st the NCI received about 20 applications for construction funding, and these will be reviewed through the standard peer review process.

Discussion of the Fiscal Year (FY) 1991 NCI Budget

Turning to budget issues, Dr. Broder noted that the President's budget for Fiscal Year 1992 would be announced today, February 4. He explained that he was not able to discuss the FY '92 budget until it has been formally announced, and thus intended to present tomorrow, February 5, an update and general overview of the budget and planning subcommittee. Dr. Broder presented a slide with information on the FY '91 budget, explaining that the NCI received an initial appropriation of just under $1.8 billion, while the NIH as a whole received slightly more than $8.5 billion. Following legislative revisions, the NCI total for FY '91 was approximately $1.7 billion, and that for the NIH approximately $8.3 billion. The final figures do not reflect, he added, a transfer authority that is made available to the NIH Director, through which 1 percent of any Institute's budget can be reallocated. Dr. Broder further explained that other across-the-board reductions that may apply due to statute or policy will affect final figures during the budget process.

Dr. Broder displayed a second slide comparing FY '90 and FY '91 obligations, noting that the NCI expects the total research project grant pool to go from just under $740 million to approximately $789 million, an increase of about 6.7 percent. The line item for competing grants has gone from just over $171 million to over $200 million, an increase of 17 percent. Cancer Centers have gone from $105 million to $110 million, an increase of about 4.6 percent.

Next, Dr. Broder called attention to the Clinical Cooperative Group Program, the institute's important mechanism for conducting clinical investigation and clinical trials. This item increased from $60 million to just over $62 million, a comparatively small increase of about 3.6 percent.

Dr. Broder displayed a third slide with further comparisons: training (NRSA) awards increased from $36 million to $37 million, an increase of 4.1 percent; the intramural program from $316 million to just under $330 million, increasing about 4 percent; construction from about $5 million to $6.8 million, increasing 36 percent.

The total NCI budget, Dr. Broder concluded, went from $1.634 billion to just over $1.7 billion. This represents an increase of approximately $81 million, or about 5 percent.

While displaying a fourth slide, Dr. Broder stated that he wanted to focus on issues related to the NCI's growth pattern, explaining that this was an area in which the Institute

especially needed the Board's advice and attention. He noted that, looking at constant dollars since 1980, defined as "what you could purchase in 1980 with modifications based on inflation," the NCI's purchasing power has actually fallen by about 6 percent as of February 1991. Two mechanisms within the Institute have grown by more than the rate of inflation—the research project grant program and the intramural program. The research project grant line has had the most significant true growth in terms of spending power. Dr. Broder added, however, that there are still many meritorious projects in the research grant pool that cannot be funded due to budget realities. The growth in the intramural program, he noted, has included the significant undertaking of AIDS-related responsibilities since 1985; most of the funds for AIDS activities in the NCI have been programmed for intramural use. Thus, he concluded, the activities committed to cancer research have not followed the same pattern of increase.

Dr. Broder described several areas within the NCI that have experienced a decrease in spending power. The first area he mentioned was the Cancer Centers Program, which is down by about 14 percent. Two areas described as having very significant decreases were the Clinical Cooperative Group mechanism and the Cancer Prevention and Control line item. Dr. Broder expressed concern about the need to develop innovative approaches to meeting the needs of these areas. He added that Research Contracts have fallen about 50 percent during this same period of time.

In response to a question on how the adjustment for constant dollars was done, Dr. Broder consulted Mr. Hartinger, Chief of the Financial Management Branch, who stated that the biomedical research deflator was used. Dr. Broder expanded on this point by explaining that, if the NCI had used a medical or hospital deflator for the Cooperative Groups, an even greater reduction in purchasing power in constant dollars would have been demonstrated, since increases in many of the clinical costs related to biomedical research have outstripped the rate of inflation.

Dr. Broder expressed his personal view that a balance between all programs is necessary. While basic research is important, he said, the NCI also has a commitment to clinical trials in both prevention and treatment.

Dr. Mihich asked two questions concerning whether the gene therapy program included activities directed toward understanding the specificity of the TIL cells. One question concerned the specificity of tropism for the tumor. Dr. Mihich noted that the fact that the cells are found in the tumor doesn't mean necessarily that they will concentrate only on the tumor once reinoculated. He asked whether this was being monitored in the NCI program. His second question concerned shutting off the production of TNF once the tumor has been destroyed. He asked whether TNF was being measured by ELISA methods, since TNF is liable to imbalance the immune system after the tumor has been eliminated.

Dr. Broder responded by stating that these areas of concern were included in the design of the gene therapy project. He continued by suggesting that Dr. Rosenberg be invited to the May Board meeting to provide an update on this project, including the issues of tumor homing and specificity raised by Dr. Mihich. Dr. Broder noted that within the research project grant pool the NCI encourages investigator-initiated proposals to address these issues in addition to encouraging new research and development in vaccines in the broadest sense of that term.

Mrs. Brown asked whether any delay in the appointment of a new President's Cancer Panel would affect the transmittal of a new bypass budget. Dr. Broder said that, as the NCI interprets its authority, the bypass budget can be prepared and submitted directly to the President and/or the OMB, but that if new Panel members are appointed the usual process will be followed.

To questions concerning the number of Cancer Centers and percentage of approval of proposals for Centers, Dr. Broder answered that in 1980 the number was approximately 60 and that the NCI would try to have approximately 59 Centers with core grant approval by the close of business 1991. He stated that, previously, about 20 percent of those proposals recommended for funding were funded; however, he noted, in the current fiscal year and in the future, no blanket downward negotiation will be used, so that Centers will receive funding based on intensive scientific review with due attention to cost containment requirements.

In response to a question on alignment of the Year 2000 goals with the NCI accomplishments based on 1990 statistics, Dr. Greenwald stated that 1990 statistics would not be available until late 1992 or early 1993.

V. LEGISLATIVE UPDATE—MS. DOROTHY TISEVICH

Ms. Tisevich presented to the Board a brief overview of legislative highlights from the 101st Congress, which just ended, and legislation introduced so far in the 102nd Congress. During the 101st Congress, 11,787 bills were introduced, of which 667, or 6 percent, were passed. The NCI legislative office tracked about 100 bills concerning cancer research, as well as some other bills on issues such as ethics reform, procurement integrity, human fetal tissue transplantation, patenting and licensing, and science education.

Ms. Tisevich referred Board members to information in their notebooks on significant legislative activity during the past few months and reviewed several of these items:

- A stripped-down NIH reauthorization bill was passed by House and Senate; this bill established the National Center for Medical Rehabilitation Research at NIH as well the National Foundation for Biomedical Research. Many provisions in the original reauthorization bills were omitted, such as appropriations for NCI research and prevention and control programs, women's health issues, and fetal tissue transplantation, but are expected to be reintroduced in the near future.
- The Omnibus Budget Reconciliation Act of 1990 (OBRA) was signed into law November 5th; this brought closure to the budget debate between Congress and the Administration. This bill changes the budget process by establishing spending caps for programs through 1993 and gives OMB increased authority in the early review of draft legislation and in scoring of spending associated with appropriations bills to determine when sequestration is triggered. It replaces the automatic October 15th sequester with three sequesters, all occurring 15 days after adjournment of Congress. Another provision was coverage of mammography screening as a Medicare benefit as of January 1, 1991.
- Also on November 5th, legislation creating the Senior Biomedical Research Service (SBRS) was signed. The SBRS, a recruitment tool that allows

portability of retirement benefits from other systems, is open to individuals who have made outstanding contributions in biomedical research or clinical research evaluation, have doctoral degrees in biomedicine or related fields, and are qualified for GS-15 appointments. Membership is limited to 350.

Ms. Tisevich then described some activities of the 102nd Congress:

- A briefing on surrogate markers was attended by representatives of the NCI, NIAID, and FDA. Major issues discussed were the process for using surrogates in evaluating new drug applications for anti-HIV drugs, and validation of surrogates.
- New legislation introduced in the 102nd Congress includes bills to:
  - Advertise the health effects of tobacco through electronic and print media
  - Provide a tax credit for employers who provide mammography screening for their employees
  - Require States to enact laws requiring physicians and surgeons to inform breast cancer patients of alternative treatments
  - Add colon cancer screening as a Medicare benefit
  - Authorize additional funds for NCI research in ovarian and breast cancer (including a bill directing $30 million to be used to support basic research in early detection and causation in Fiscal years '92 through '96)
  - Authorize an additional $35 million for breast cancer research in areas other than treatment or clinical trials
  - Overturn honoraria restrictions for Federal employees enacted through the Ethics Reform Act of 1989, reinstating the ability of low- and midlevel employees to receive compensation for work not related to their official duties
- Other bills include legislation addressing radon awareness, veterans' compensation, low level radiation waste policies, procurement reform, technology transfer, Federal employee compensation, and Government travel; these are covered in greater detail in the Legislative Update Package in the Board members' notebooks.

Ms. Tisevich concluded by discussing some bills introduced during the 101st session of Congress that were not enacted but are expected to be reintroduced in the 102nd Congress. In addition to the NIH reauthorization and other issues mentioned above, another bill that will probably be reintroduced is a refundable tax credit for qualified cancer screening tests, introduced earlier by Senator Connie Mack of Florida.

Senator Brock Adams of Washington is expected to reintroduce the Breast Cancer Screening Safety Act of 1990, which would authorize regulation of mammography services and radiological equipment, and would establish a National Mammography Registry. Comments from NCI and other Public Health Components, Ms. Tisevich added, are being consolidated by the department.

Ms. Tisevich concluded by noting that, for the remainder of the 102nd Congress, prevention, women's health, aging, and special populations will be the dominant themes.

In response to a question on how proposed additional funds for ovarian and breast cancer research would be distributed, Ms. Tisevich stated that if the bills she had described were passed, they would simply authorize additional funds, and that it would be up to the appropriation committees to provide the money in appropriation bills. She added that, even if additional funds were not made available, the NCI could receive language directing the Institute to provide additional support in these areas.

VI. REMARKS BY THE EXECUTIVE VICE PRESIDENT, AMERICAN CANCER SOCIETY—MR. WILLIAM TIPPING

Mr. Tipping began by stating that his topic would be the relationship between the American Cancer Society (ACS) and the Comprehensive Cancer Centers, as well as the overall theme of making better use of scarce resources. He observed that cancer control work usually involves citing impersonal statistics such as incidence, mortality, and other types of data, whereas one is brought closer to cancer itself through personal stories, such as one man's losing fight against lung cancer or a child's successful battle against leukemia.

Mr. Tipping referred to a six-part series on cancer, broadcast by the McNeil-Lehrer television program, which featured such stories. He reminded the Board members that this series also featured an interview with Dr. Broder of the NCI, who stated the case for using the technology we already have in controlling cancer. Mr. Tipping read a quotation from the interview with Dr. Broder:

> Simple things we know about right now can make a profound difference in controlling cancer. Prevention is not only possible, it is ultimately cost effective. As has been mentioned more and more often today, it is for public health the most compelling priority. In cancer, prevention forms one corner of the triangle in controlling health costs, with risk reduction and early detection the other two. . . .
>
> Cancer fighters have to be realists, we can't wait on a promissory note. If we add up all the knowledge we have, and if we could add in as well more access to health care and acceptance of cultural habits and biases, we would be in great shape for the rest of the decade.

Mr. Tipping noted that Dr. Broder's emphasis on expanding human knowledge in addition to medical know-how, as well as his concern for better communication and understanding of motivation, match the concerns of the ACS. The Society, he stated, seeks to extend and improve its range of activities within all communities, including those of the poor and socioeconomically disadvantaged. He observed that, while the Society's work in support of research is highly regarded, its most visible role is providing information and education on prevention, risk reduction, and early detection through 3,422 community-based units throughout the country. This approach is anchored by the Society's emphasis on the physician-patient relationship. Mr. Tipping called the attention of the Board to a fact sheet on the American Cancer Society with organizational, income, and program information for 1991.

The Society's mission, Mr. Tipping said, is behavior modification, and that is why education is such an important component of its work. The ACS shares with the Cancer Centers a focus on prevention as being not only principal but practical in terms of today's health programming. He acknowledged minorities and women as two populations that are likely to benefit most rapidly from prevention efforts. He further noted that public expectations in terms of prevention are growing, and that a majority of Americans are now willing to make lifestyle changes. The public and the media are asking for more ideas on what choices are available.

Mr. Tipping suggested that the NCI and the ACS share the same charge to provide concrete guidance, but differ organizationally. This, he said, leads to different spheres of influence and different strengths. While the Cancer Centers work internally, reaching communities through hospital staff or subsidized clinics, the Society works externally through special events and volunteer efforts. The Society has also tapped into the educational structure with a school health program that emphasizes good health habits, using cancer as a subtext.

Mr. Tipping continued that it would be unconscionable to disregard opportunities to work together in communities, and that it would be unfortunate to set up competing activities in a time of financial constraints and competition for research funds. He acknowledged that working in tandem requires concerted effort and can be time-consuming in the beginning, but he argued that the NCI and the ACS must build on what has already been started to make the most of what Americans expect if we are to continue to hold their trust. He referred to a recent meeting in Houston of ACS volunteers and staff with leaders of the Comprehensive Cancer Centers to discuss these issues, and expressed the hope that this step can replenish enthusiasm for achieving a balance between collaboration and independence. He noted that relationships are already being built between ACS and Cancer Centers, giving as examples efforts in New York State, Philadelphia, Florida, Ohio, Virginia, and Wyoming.

Mr. Tipping concluded by observing that a decision to acknowledge mutual ownership of the franchise of cancer control is difficult but necessary. There is a need, he argued, for the NCI and the ACS to get together on the day-to-day interaction necessary to protect the lives of our citizens, keeping in mind the lone individual battling his or her own cancer.

Following Mr. Tipping's remarks, Dr. Bettinghaus said that he was in complete agreement with Mr. Tipping and spoke in support of cooperation with the NCI and the ACS, the major voluntary cancer prevention organization. He observed that in his own State of Michigan, and probably in other States, there is little recognition in the mind of the general public of the difference between the NCI and the ACS; he further noted that most people, if asked who does cancer research, would answer, the American Cancer Society. There are also a number of less reputable organizations competing for funding, he noted, that are confused in the public mind with both the NCI and the ACS.

Dr. Lawrence also spoke in support of cooperation between the NCI and the ACS, and expressed appreciation to Dr. Broder for inviting Mr. Tipping to address the Board.

Dr. Calabresi thanked Mr. Tipping for his important presentation an indicated his strongest endorsement for full cooperation between the NCI and the ACS. He stated that he is currently President of the Rhode Island Chapter of the ACS and that in his State, cancer prevention, early detection, and several research projects of their Cancer Center and the ACS are closely integrated.

VII. ETHICS REVIEW—DR. ELLIOTT STONEHILL

Dr. Stonehill explained that members of the NCAB are Special Federal Employees during the Board meetings and during their travel time to and from the meetings. As such they are subject to various aspects of the standards of conduct applied to Federal Government employees. He stated that Section J of the Department of Health and Human Services Standards of Conduct specifically pertains to experts, consultants, and advisory committee members. This section, he noted, is included in the Board members' notebooks.

Reading from Section J, Dr. Stonehill noted that the potential for a conflict of interest exists when there are financial arrangements between a member of an advisory board and any organization whose income might be affected, or appear to be affected, by decisions of that board. He said that when matters arise for discussion or decision that relate to a member's financial holdings, financial holdings of anyone in a member's immediate family, or outside organizations with which members are associated, those members are to abstain from participation. If such discussions take place during an open session, members with a potential conflict of interest may remain in the room, but must refrain from participation in the discussion. However, if the same issues come up in a closed session, such as a session during which grant awards will be discussed, members with a potential conflict of interest must leave the room during the part of the session relevant to the potential conflict of interest.

Dr. Stonehill then called attention to other pages in the members' notebooks that list areas of potential conflict of interest with reference to specific Federal statutes, including 18 U.S.C. 203 and 205 (sections 203 and 205 of Title 18 of the United States Code).

Most frequently, Dr. Stonehill explained, conflict arises because of awards to institutions with which Board members are affiliated. Waivers are granted in the case of 22 States that maintain multicampus institutions; the waiver applies if an award is being considered for a branch of a large system and a Board member is affiliated with a different branch of that system.

As special employees, Dr. Stonehill continued, Board members have access to confidential materials, such as grant applications and review summary statements, and are expected to respect their confidentiality by refraining from disclosing them or from discussing these matters with colleagues.

In closing, Dr. Stonehill mentioned that Board members will be asked to fill out documents concerning their financial holdings and outside interests, and should notify him of any changes in these holdings and interests. He explained that these documents are not made available to anyone through the Freedom of Information Act, and no copies are made.

A question was raised about a case in the Federal Circuit Court in Western Wisconsin in which a Federal judge appears to have expressed extreme displeasure with some policies and regulations of the Office of Scientific Integrity (OSI), an office within the NIH. Dr. Broder offered to invite a representative of the OSI to speak on the question at the next Board meeting. Dr. Stonehill elaborated that the OSI is not concerned with internal NIH organizations, and thus does not have jurisdiction over the NCAB.

VIII. IMPLEMENTATION OF POLICY ON INCLUSION OF WOMEN AND MINORITIES IN STUDY POPULATIONS—MRS. BARBARA BYNUM

Mrs. Bynum began by relating that, at the December meeting, she had distributed a draft policy and procedures statement to the then-current Board members concerning the announced NIH policy regarding the inclusion of women and members of minority groups in all clinical research studies supported by the NIH. She explained that she was returning to this subject for two reasons: firstly, to apprise new members of the Board's obligations in this regard; and, secondly, to make the final NIH operating guidelines for implementing this policy available to all Board members. She pointed out that this document, referred to as an "instruction and information memorandum," could be found in the members' notebooks.

Mrs. Bynum further noted the establishment, within the Office of the NIH Director, of an Office of Women's Health, temporarily headed by Dr. Ruth Kirchstein, and an Office of Minority Affairs, directed by Dr. John Ruffin. She referred members to Ms. Schneider of the NCI for more information on the activities of the Office of Women's Health.

Mrs. Bynum called the Board's attention to a statement on page three of the NIH guidelines, which states that if women or minorities are excluded or are inadequately represented in clinical research, particularly in the population-based studies, a clear and compelling rationale for exclusion or inadequate representation should be provided.

The staffs of the NCI and other NIH funding components, she said, are dealing on a case-by-case basis with applications for support that were received before February 1st of this year, when this policy was to be implemented, and with ongoing studies receiving support prior to this date, to determine where study groups can be modified without compromising the outcomes of the studies. Applications now being received are required to be fully consistent with this policy, and all RFAs and RFPs must contain language admonishing applicants to address these issues.

Mrs. Bynum observed that a question often asked is whether investigators will be required to focus on inappropriate endpoints as a result of this policy, or if costs will escalate because of changing the population to comply. The answer, she said, is that the study design of a proposed project must demonstrate adequate consideration of gender and race or ethnicity in the context of their appropriateness to the scientific endpoints involved. No one, she added, is asked to produce a design that is overly inclusive if these considerations are not pertinent to the objectives of the study. In addition, the design of a proposed study can be considered in the context of the overall portfolio of the Institute or program that is issuing the award; sometimes a study will be seen as just a single part of an overall approach to addressing a problem.

Mrs. Bynum explained that while the term "clinical studies" is used, the policy applies to prevention and intervention studies as well as to therapeutic trials.

Starting this month, she continued, the Division of Research Grants will assign a code to applications based on the adequacy of the study design in terms of inclusivity. Awards will not be made until appropriate adjustments have been made in the studies to make them acceptable under this policy.

In conclusion, Mrs. Bynum pointed out in the members' notebooks specific instructions concerning the review process. Their options in reviewing applications that do not appear to comply with this policy include; recommending that an application be deferred; recommending that it be approved conditionally pending adjustment; or recommending approval based on its place in the overall portfolio.

Asked whether there is any reason to think that the NCI is not in compliance with this policy at present, Mrs. Bynum replied that after a review of extant projects at the time this policy was announced, some adjustments were made in those that were not in compliance.

IX. UPDATE ON ETHICAL CONSIDERATIONS FOR THE HUMAN GENOME PROJECT—DR. ERIC JUENGST

Dr. Juengst began by stating that the ethics program of the Human Genome Center, located in the Lister Hill Center, is the largest and most elaborate attempt within the NIH to provide an organized form of support for educational projects, policy making projects, and research projects in order to get a grip on the ethical, legal, and social implications of research. The goal is to anticipate the sorts of issues that might arise from the applications of genome research. Dr. Juengst distributed copies of an announcement that describes the menu of issues identified by the program. He noted that almost any issue related to the practice of applied human genetics turns out to be fair game for study under the ethics program.

Dr. Juengst observed that launching such a program involves the coordination of a wide range of perspectives, including a number of extramural communities that are new to NIH and the kinds of programs it sponsors. He stated that the initiative was "one of Jim Watson's brain children," who committed the Center to spend three percent of its extramural funds on these sorts of studies. Nancy Wexler, of Columbia University, who is on the program's advisory committee, was appointed to set up a working group to design and coordinate the program. Dr. Juengst added that the Department of Energy (DOE), a partner in the genome project, has also committed to spending three percent if its extramural funds in this area.

The Program, he continued, is part of the Center's Research Grants Branch, primarily as an extramural program; the three percent share of the budget for FY '91 comes to about $2.5 million. The first announcement was made in January 1990, and the first crop of applications are beginning to come out of the review process. However, he added, word of mouth led to enough proposals coming in "over the transom" to get some initiatives off the ground in 1990. A number of these have been in the form of conferences, he noted, but there have been a number of substantive research projects as well.

Dr. Juengst called attention to one study that the Institute of Medicine (IOM) of the National Academy of Sciences will be initiating in the next few months with NIH and DOE support. This study will look at the professional policy issues associated with the integration of new genetic diagnostic tests into mainstream medical practice.

The working group mentioned previously is focusing on several topical issues: the first is that being addressed by the IOM study, relating to standards of care that ought to guide the delivery of DNA-based diagnostic and prognostic tests. The group, Dr. Juengst stated, sees this

as the probable topic of the first wave of applications, and is concerned that the infrastructure to deliver these tests responsibly be in place. This means, he said, that issues of health professional training and laboratory control are at stake, as well as educational materials that may be required to help patients understand the nuances of these tests.

A second topical area concerns privacy and confidentiality. Genetic information, Dr. Juengst noted, is associated with identity in very strong ways in our culture, and people will put a great deal of stock in predictions derived from genetic information. Genetic information can also be stigmatizing, particularly information about future health risks. On the other hand, he noted, genetics is a family affair, and the discovery that a patient's family members may be at risk raises further confidentiality issues. He added that the program is working with the Office of Protection from Research Risk to help scientists work out adequate protections in this area.

A third topic discussed by Dr. Juengst was the question of fairness in the use of genetic information by third parties, such as employers, insurers, educational institutions, and other social institutions. He said that one institution of concern to the Congress in this respect is the health insurance industry; he added that a couple of studies are underway on the use of hereditary risk information, and that the working group has set up a multidisciplinary task force to look at insurance issues, including questions about the insurability of genetic services.

Another high priority for the program, according to Dr. Juengst, is public education. While public education programs don't always fit neatly within the NIH review and funding process, he observed, the program is nevertheless trying to organize efforts to promote both school-based and out-of-school education about genetics, genome research, and their social implications. These efforts include the cofunding, with the NCI and other Institutes, of a public television series on the future of medicine.

In concluding, Dr. Juengst observed that the concerns of the Center's ethics program overlap with the concerns of the NCI in a number of areas, including the development of risk markers for various forms of cancer. He speculated that the two organizations would be collaborating more and more.

A participant asked whether the NCI had any program looking at the implications of studies of the genetic component of cancer. Dr. Adamson answered that a workshop is planned on the family syndrome related to the P53, including ethical considerations. Dr. Strong added that the issues related to cancer do not differ substantially from those related to other diseases with genetic components, and that the NCI should build on the groundwork laid by the genome project.

In response to questions about the insurance issue, Dr. Juengst said that the insurance industry was being involved in the work of the task force on insurance issues previously mentioned. He added that some representatives of that industry have stated that at this point they do not have enough information on genetic technology to know what their policies will be.

Dr. Juengst was asked by a participant to bring the Board up to date on pending legislation in this area. He reported that the Privacy of Genetic Information Act was introduced but not passed last year; this bill closely paralleled the Privacy of Medical Information Act that governs medical records. He said that it was not clear whether the bill on privacy of genetic

information went much further than the existing law. He added that he had been told the bill would probably come back before the Congress this year.

To an observation that, if genetic testing can be supported by a third party carrier, the carrier automatically has a right to that information, Dr. Juengst replied that this is not necessarily the case. He cited the precedents associated with HIV testing, but agreed that third party payment does make protection of information more complicated.

X. NIH PLAN FOR MANAGING THE COSTS OF BIOMEDICAL RESEARCH—MRS. BARBARA BYNUM

Dr. Calabresi noted that the NIH Deputy Director for Extramural Research had asked the advisory boards or councils for each of the NIH institutes to discuss the draft NIH financial management plan.

Mrs. Bynum introduced the topic by explaining that Congress had indicated its desire that NIH implement fiscal management procedures to improve cost containment in the management of its extramural grants portfolio. A hearing was held at NIH on December 17, 1990, for public testimony on an NIH proposal, called the 10-Point Plan, for responding to the Congressional directives. Dr. Korn was among those who testified at the hearing. A summary of the public testimony appears in the current NIH Peer Review Notes, a copy of which is included in the Board's notebooks.. On December 18, 1990, the Director's Advisory Committee (DAC) modified the 10-Point Plan and developed the draft NIH Plan for Managing the Costs of Biomedical Research that was sent to each Board member before the meeting.

Dr. Korn began the discussion by clarifying that when he testified at the December 17th hearing he indicated for the record that he was not there to represent the NCAB. He stated that the numbers of new and competing grants that could be funded have declined in the past couple of years, in spite of significant increases in NIH budgets. The primary factors that led to this were the increasing costs of research and the decisions during the 1980s to extend the average length of grants and to sharply increase the number of new and competing awards.

These decisions led to more and more of the total appropriation being committed to the out years of these awards. In response to concerns in the scientific community about the declining numbers of awards, the House Appropriations Committee directed the NIH to develop a cost management plan for increasing the numbers of grants, reducing the average duration of funding, and holding year-to-year cost increases to four or five percent.

Dr. Korn stated that the most serious issues are philosophical and have to do with how one manages a finite research budget. While the NCAB has been sensitive to the importance of investigator-initiated grants and expressed strong support for them, there are other mechanisms for the funding of science that cannot be ignored, including clinical trials and prevention and control work, that are associated with targeted efforts such as minority health, drug development, and the AIDS epidemic. He expressed concern that if specific numbers of investigator-initiated grants must be met, there will be little room within the budget for other opportunities.

Sentiments expressed at the December 17th hearing and the DAC meeting warning against the NIH locking itself into restraints that would make it impossible to manage the budget, Dr. Korn concluded, are not reflected in the final NIH plan, and the result is likely to be frustration at not meeting target numbers or a continuation of arbitrary down negotiations that the plan was intended to eliminate.

Dr. Temin stated that the NIH plan did not resolve the problem of the overload on the Study Section mechanism when seventy-five percent of the deserving grant applications reviewed cannot be funded.

Dr. Durant observed that the NIH plan also targets growth in research training, which down the road will make the problem of choosing among applications bigger.

Dr. Mihich asked whether the NIH plan was a reversible document. Mrs. Bynum replied that the plan is a draft and that the Board was asked to discuss the plan and make recommendations. Dr. Mihich identified the most serious concern with the plan as item B, Costs and Numbers of Grant Awards, in the section on Research Project Grants. He expressed concern that the requirement of this part of the plan for the Board and NCI staff to develop rigorous cost control principles would place additional burdens on staff and could result in longer delays in awarding grants. He further observed that there would be severe subversion of the peer review system if the Board were asked, as this draft of the plan states, to adjust the amounts of grants and grant programs based on a consideration of scientific relevance. The Board, Dr. Mihich noted, is not equipped to served as a Study Section for the assessment of scientific aspects of grants. He questioned whether this provision of the plan might mean that it would fall upon NCI staff to perform this function, and suggested that the involvement of the Board in the process would be problematic.

Dr. Broder noted that this process will require ongoing interaction among the NCI, the NCAB, the peer review community, and the investigators. Congress has clearly expressed its intention that the costs of grants be addressed. Dr. Broder argued that direct costs are already a function of the peer review process and that the comments of study sections on the reasonableness of requested direct costs are taken seriously. With respect to indirect costs, he noted that the Institute is not equipped and does not have the authority to set indirect cost structures; the Institute, while concerned about indirect costs, must address them from the point of view of the total cost of a grant. The Institute is not allowed to use an across-the-board formula in order to fit a certain target number of grants into a given amount of money. Specific funding amounts must be linked to scientific issues based on discussions on each grant.

Dr. Broder expressed his opinion that it is possible to do what the Congress has asked without violating the spirit of the way the Institute has been conducting the grant-making process. While greater sensitivity to cost effectiveness is required, fundamental changes are not likely in the way grants are reviewed, prioritized, and funded.

Dr. Wells asked whether the implementation of this plan would begin in Fiscal Year 1991. Dr. Broder responded that if the Board has concerns, Dr. Calabresi could ask for motions or appoint a group of Board members to study the plan quickly so that the Board could pass its

concerns along, but that there is some sense of urgency in bringing the plan to closure in order for the NIH to respond to congressional concerns as directed.

Dr. Wells asked a question about what form the approval and disapproval of grants would take as a result of the plan. Mrs. Bynum answered that the plan removes the concept of disapproval, and that in making its recommendations of scientific merit, Study Sections will not give a disapproval to a grant application unless it is not in compliance with standards for research. The denominator will include all applications accepted for peer review, and the numerator will be all those which ultimately received funding; the resulting percentage will be the success rate. Applications will receive a priority score and, in some grant categories, a percentile ranking. All but the bottom tier (the percentage to be determined) will be reviewed by the Board, but the bottom tier will not be removed from the total population or denominator. In order to clarify the language used in the plan, Mrs. Bynum explained that the expression "would not be reviewed" means that the applications in the bottom tier would not be reviewed by the advisory council. They would still undergo peer review, would be included in the denominator, and would be available if the Board chose to identify one or more individual grants to be considered in terms of its (their) scientific relevance.

Dr. Broder urged all Board members to read the specific language in the relevant congressional reports. He explained that in effect the Congress has questioned the sincerity of a system in which applications that have been given extremely poor priority scores, which they feel the Study Section has had no desire to fund, are kept in the denominator and thus described as being approved.

Dr. Mihich observed that even if an application receives a poor priority score, the investigator has a right to a rebuttal, and this would bring this application into consideration for special action. He then called attention to the part of the plan that requires the Board to review applications within close range of the payline in terms of anticipated benefits and total costs. He stated that if the close range envisioned in the plan is 1 percentile up or down, this might limit the number of grants involved, and they could be reviewed under special action. But, he argued, if the range is two or three percentile points then the Board becomes in effect a second study section. Dr. Mihich suggested that the Board is not qualified to play this role. If the intent is simply to be more conscientious about costs, he concluded, then this paragraph should be amended.

In response to a question from Dr. Olden, Mrs. Bynum reported that the scientific community had been provided with an opportunity to comment on the plan before its final implementation. She stated that the draft of the NIH plan had been sent to all of the institutions on the NIH mailing list as well as over 40 professional societies and that an opportunity was provided for public testimony at the December 17th hearing. In reply to Dr. Olden's question on the anticipated change in the number of funded new and competing grants that would result from the plan, Mrs. Bynum stated that to her knowledge no estimate of an increase in numbers of grant awards was available.

Dr. Salmon expressed concern that the Board is not qualified to make judgements concerning the indirect cost rates of institutions applying for grants.

Dr. Korn observed that the increased duration of funding was urged for good reasons by scientists to produce stability so that researchers with a proven track record could be relieved of the necessity of going through the application process every two or three years. He also noted that the success rate has been used as a political slogan by some scientific groups to say that there is not enough money in the system because only a certain percentage of approved applications are funded. It remains to be seen whether removing the bottom 25 percent of all applications from the Board's review will make applicants feel any better.

In response to questions from Dr. Temin about how limits on increases in costs are to be implemented, Dr. Broder explained that the limits on the length of awards as well as on increases in costs will be based on averages. In cases where longer awards are made, some other awards will have to be shorter in order to balance the longer ones. Special justification for scientific reasons will be necessary to go beyond four years; some extensions may be for five years, and the Institute will be obligated to find within its portfolio a 3-year award to match the 5-year extension to maintain the average of four years.

Dr. Temin asked whether a new category of grant could be established in which a successful applicant would be funded for three years and then administratively submit a one-page request for renewal with a budget and be assured of a 95 percent chance of going on for another three years on merit. Mrs. Bynum answered that such a concept probably could not be implemented unilaterally by the NCI, but that the NIH might consider it to be an interesting notion.

Dr. Calabresi suggested that at this point a working group be appointed to discuss the Board's comments and develop recommendations tonight to be discussed further at tomorrow's open session. He asked Dr. Enrico Mihich, Dr. Sydney Salmon, and Dr. Samuel Wells to serve on the working group and volunteered to chair it himself. He asked for any further comment before proceeding.

Dr. Durant echoed Dr. Salmon's concerns about asking the Board to make decisions on the indirect costs of institutions or making such considerations a principal focus of review decisions. Dr. Broder agreed that analysis of an institution's indirect costs is not a legitimate or legally authorized function of the NCI. He explained that the Institute simply has to be able to tell the Congress in good faith that total costs have been evaluated and that the taxpayer is getting the best value for the money being spent on research. He argued hypothetically that if the NCI staff and the NCAB decided, between two applications with the same priority score, that one with a total cost of $500,000 should have a better chance of being funded than one with a total cost of a million dollars, this would be a legitimate function of the review process and would not be substantially different from the way in which the Institute's business has been done in the past.

Dr. Becker suggested that the document should not contain careless wording, and that if averages are to be used the document should reflect this. He added that when the plan cites instances "where the perceived quality of the applications is statistically indistinguishable," it is mixing apples and oranges; quality, in his opinion, cannot be statistically analyzed. Finally, he observed that the plan refers to cofunding of non-overlapping areas. He argued that you cannot

cofund a non-overlapping area. He expressed confidence that the subcommittee would look at some of the terms that had been used carelessly.

XI. CLOSED SESSION

A portion of the first day of the meeting was closed to the public because it was devoted to a meeting of the Special Actions Subcommittee.

XII. INTRODUCTORY REMARKS AND REPORT ON THE PRESIDENT'S FISCAL YEAR 1992 BUDGET—DR. SAMUEL BRODER

Introductory Remarks

Dr. Calabresi announced that the second day of the meeting would begin with reports from the Executive Secretaries of the Board's subcommittees, following introductory remarks by Dr. Broder.

Dr. Broder began by explaining that, for the benefit of new Board members, the format of this meeting would depart from usual NCAB practice by essentially conducting all the subcommittees in the full agenda of the total NCAB. This was planned to give new members an opportunity to see what each subcommittee does and to make decisions about which subcommittees they would like to attend in addition to those to which they are assigned.

Dr. Broder noted that subcommittees can be an extremely efficient way for Board members to start giving the NCI policy advice, by studying important problems and reporting back to the full NCAB, which can serve as the focal point for action. He gave as an example the contributions of the Subcommittee on Cancer Centers, which has helped with a number of issues related to the overall planning of the Cancer Centers Program, particularly with the issue of comprehensive status.

Dr. Broder explained that subcommittees can meet separately from the full NCAB and, theoretically, in any location. He added that subcommittees are required to notify Mrs. Bynum and conform to the Federal Advisory Committee Practice Act, and that closed subcommittee meetings could not be held without meeting specific requirements. He urged that all subcommittees, after finishing their indepth analysis and intensive review of policy issues, return to the full NCAB for further discussion and action.

Bypass Budget

Dr. Broder then moved on to the topic of the bypass budget, explaining that the NCI is the only categorical institute within the NIH that has the authority to publish a professional needs budget. He expressed hope that, since the NCI would soon be working on the Fiscal Year 1993 bypass budget, which is due September 1st, the Board would look at the FY '92 bypass budget and begin thinking about suggestions for the FY '93 bypass budget, which will be taken up in more detail at the May meeting. He asked any members who have any ideas to write to Judy Whalen, Executive Secretary of the Subcommittee on Planning and Budget.

He explained that the bypass budget is intended to express valid scientific needs that, if funded, could materially affect death and suffering caused by cancer. It is not, he said, a political document intended to focus on "what do we think we can get." Dr. Broder stressed that the bypass budget is taken extremely seriously and often serves as a template for draft legislation; it also serves, he added, as an important planning document. He also urged the Board members to remember, as they represent the National Cancer Program around the country, that the bypass budget is written as an organic, balanced whole and that parts of the budget should not be removed and discussed out of context.

Fiscal Year 1992 Budget

Dr. Broder then asked Dr. Calabresi for permission to go ahead with his discussion of the FY '92 budget. He displayed a slide with a review of the FY '91 budget. A second slide showed that the FY '92 budget provides the NCI with a total of just over $1.8 billion, an increase of approximately 5.6 percent, while the NIH as a whole has increased by about 6 percent, to $8.775 billion.

Dr. Broder showed a third slide comparing the FY '91 and FY '92 budgets at the operating level. He pointed out that the research project grants have historically been the dominant part of the budget. The noncompeting line in the FY '92 budget has been raised to $613 million, an increase of about 5.4 percent. The competing line has been raised to approximately 226 million, an increase of just under 13 percent. The grants covered by these items include primarily what are called R01s and P01s—investigator-initiated proposals that are reviewed first by the NIH Division of Research Grants, with the exception of some that are reviewed by special committees in the NCI Division of Extramural Activities.

Dr. Broder moved to the Cancer Centers Program, which has increased to $113 million, an increase of 2.4 percent. He noted that in the 1980s the only growth in the Centers Program has been associated with allocations for AIDS activities. Since 1989, he added, there has been comparatively more growth in this program. Nevertheless, in spite of the significance of the Centers Program in technology transfer and addressing the needs of underserved populations, the program has fallen 14 percent in constant dollars since 1980. Dr. Broder emphasized the need to find innovative ways of addressing this problem. However, he noted, this is not the program that has endured the most significant cuts.

Dr. Broder then moved to the line for Clinical Cooperative Groups, which has a FY '92 budget of approximately $66 million, an increase of 6 percent. In constant dollars, he said, this program is down about a third; this is an underestimate of actual loss of purchasing power, Dr. Broder added, because the standard biomedical research deflator being used does not account for the medical costs that are associated with clinical trials. He urged the Board to work with the Institute on innovative ways of offering new opportunities for investigator-initiated clinical research.

Dr. Broder suggested that some of the NCI's recent initiatives for making the system more responsive to investigator-initiated clinical research, including recent studies by Dr. Jay Freireich on the status of clinical research, be placed on the agenda for the May meeting of the NCAB. Dr. Brian Kimes noted that a newsletter describing the work of Dr. Freireich was being

prepared for the Cancer Center directors, and that copies of this newsletter would be distributed to all NCAB members.

Dr. Broder concluded that the research grant pool is now just over the one billion mark, an increase of about 6.2 percent.

A participant expressed concern about the lack of increase in cancer education funds. Dr. Broder replied that the cancer education line is considered extremely important and that, as in other fiscal years, flexibility will be used in putting new resources into this line. While it is too early in the budget process to discuss details, he said, the R25 mechanism and other mechanisms will be used in this area to create flexibility. The Institute is trying to use the R25 mechanism to focus on issues such as prevention training and public health orientation for medical oncologists.

Dr. Broder's next slide showed that the NRSA's (training grants) were increased to $418 thousand, an increase of 1.1 percent. Research and development contracts increased to $191 million, an increase of about 2.2 percent. The intramural program grew to about $349 million, an increase of 6 percent. He reminded the Board that these figures represent both cancer and AIDS activities, which are no longer separated. AIDS is roughly 10 percent of the budget, he noted. This year the NCI is issuing requests for applications for investigator-initiated research in certain AIDS-related areas.

Research management, he continued, has increased from $81 million to $91 million; this item includes a $7.2 million contribution to the National Health Interview Survey. Dr. Broder asked Dr. Greenwald to elaborate; Dr. Greenwald explained that the National Center for Health Statistics has never been budgeted for the full cost of the National Health Interview Survey, and has asked various institutes for contributions to support specific sections of the survey. This year, Dr. Greenwald continued, the department decided to supplement the survey with allocations from the budgets of NIH institutes. Dr. Broder observed that, while the research management line shows a 14 percent increase, this increase includes the allocation for the survey.

Dr. Broder noted that research management is often seen as an administrative support area that can be trimmed for efficiency purposes because it does not contain core functions; however, it does contain some core functions, he argued, including the Cancer Information Services (CIS). When asked by a participant whether the name of this line item could be changed to reflect the importance of the CIS, Dr. Broder answered that the budget format is standardized across the NIH; he promised to investigate ways to clarify the scope of activities included under this item in budget presentations.

Cancer prevention and control increased to just under $90 million, an increase of 4.8 percent. Dr. Broder reminded the Board that, in terms of losses in constant dollars, this line is in a tie with the cooperative group line, having lost about a third in purchasing power since 1980. He asked the Board to advise the NCI on seeking innovative ways to generate prevention knowledge, particularly through investigator-initiated research.

The line for construction shows a net decrease of about 71 percent; Dr. Broder noted, however, that the $2 million in this line is primarily a buildings and facilities line for repairs and maintenance, not for extramural construction.

Dr. Broder mentioned that research and development contracts are at the bottom of the pack in terms of constant dollars, having lost about 50 percent since 1980. He asked for input from the Board on the Institute's policies with respect to the role contracts should play in research.

In response to a question about the allocation for the National Health Interview Survey, Dr. Greenwald replied that the NCI has planned to budget $2 million next year for contributions to the survey for cancer control data, and is now hoping that this $7.2 million allocation will make it possible to obtain the needed information without the additional $2 million expenditure.

Asked why the training grants are virtually flat, Dr. Broder explained that the OMB had decided that these were areas that were not going to grow, and that this decision was not a reflection of the bypass budget's expression of professional needs.

A participant asked for more information on the one percent transfer authority given to the NIH Director. Dr. Broder explained that the NCI has made a case that there are very high priority needs within the Institute; he hopes to be able to retain the one percent to support those programs that have shown less growth than others. He noted that the growth in Cancer Centers had not originally been reflected in the President's budget, but had been created because of a recognition of need. If resources are available, he added, the NCI will try to do comparable things with other high priority areas, including training grants. Dr. Broder added that it doesn't help to train investigators if there are not enough opportunities for them to work. The funding of investigator-initiated research projects, he said, carries with it a collateral training function.

Dr. Mihich offered his observation that, while the bypass budget "evaporates" within the NCI when the President's budget is presented, it remains alive in other ways, and can serve as an inspiration to the Congress in its manipulations of the budget. While the NCI can no longer support the bypass budget, he said, others in the room can organize private initiatives.

Dr. Broder moved on to another slide that presented information on research project grants. The total number of grants, for FY '91 was 3,076, including 840 competing grants, with a 27 percent funding rate. The total number for FY '92 is 3,164, including 897 competing, with a 29 percent funding rate; this represents an increase of 2.9 percent for all grants and almost 7 percent for competing grants. The total for FY '92 is the largest number of grants in the history of the NCI.

The average length of award in FY '92 will be 4.0 years. The average cost in dollars for noncompeting grants will increase to $274 thousand, an increase of 4.2 percent. For competing grants, the average will be $252 thousand, an increase of 5.9 percent. These averages include both R01s and program project grants. An average of R01s alone, Dr. Broder added, comes to about $170 thousand.

Dr. Broder asked that the Board examine a number of factors that drive the costs of proposals, such as: length of award and its effect on out-year costs; salaries; and transfer of projects from one institution to another.

Dr. Broder called attention to further information on the slide concerning program grant dollars that are committed to two specific mechanisms: MERIT grants and outstanding investigator grants. He explained that certain high priority proposals are designated such that, in their renewal phase, they are given extensions with a minimum of administrative burden. The total costs of such MERIT-designated proposals is increasing from 5.6 percent to 6.5 percent of the total research grant line; the MERIT renewals are increasing from 0.7 percent to 1.3 percent.

Outstanding investigator grants (OIGs), he continued, are 7-year awards to investigators in support of their career contributions rather than for specific projects. Based on recommendations of the NCAB, Dr. Broder noted, the NCI is making efforts to limit these awards to about 8.1 percent of the project grant pool, the same level as in FY '91. This means that, as new OIGs come into the system, some that are coming up for recompetition will not be funded. Dr. Broder asked the Board for advice in deciding what percentage of the total dollar pool should be committed to MERITs and OIGs.

In response to a question from a participant, Mary Cushing reported that, when the MERITs reach a state of equilibrium, starting in FY '92, the MERIT awards and OIGs together will go to 15 percent of the research project grants budget. Dr. Broder observed that, since it has a 7-year component, the OIG mechanism adds very seriously to out-year costs and places a burden on the effort of maintaining an average length of award of 4.0 years.

Asked what percentage of total awards were comprised of MERITs and OIGs, Dr. Broder replied that these categories constitute 7 percent of the total number of awards. He added that, when a project is given the designation of MERIT award following peer review, nothing happens until it is ready for extension. While limits have been placed on these awards, he explained, there are commitments based on the fact that some grants that have been designated as MERITs have not yet reached the extension phase. The NCI is also more conservative now, he added, in permitting fold-over of grants from sister categorical institutes into the NCI's out-year costs.

Dr. Broder concluded his slide presentation by observing that over the past few years the average length of awards has increased from 3.3 to 4.3 years, and that this obviously puts a strain on out-year costs and means that the total research project grant pool must expand just to absorb the commitment base. If the Congress allocates less than that amount, he continued, it works a hardship on new and competing grants.

Dr. Temin asked whether, in terms of this discussion, members could be provided with information on the fates of the OIGs the Board voted on last time, because of the political questions that have arisen about which ones were funded and which ones weren't. Dr. Broder answered that such information could be provided to the Board, but that it must remain confidential and could not be distributed or discussed in an open session. Dr. Temin suggested that if, within the 15 percent set aside for MERITs and OIGs, a shift were made toward more MERIT awards of five years with 3-year extensions and fewer 7-year OIGs, it would be easier to achieve an average of 4.0 years for the grants in the rest of the pool.

Dr. Broder suggested that the Chairman consider asking the appropriate subcommittee to look at the relevant facts and figures, to be supplied by the NCI, and report back to the NCAB.

Dr. Adamson added that significant factors have come to play in the budget that were not foreseen, such as a number of taps and two sequesters under the Gramm-Rudman-Hollings Act, that affect long-term budget planning.

Asked whether there is a track record on how well MERIT grant recipients have done when they come back to compete again, Dr. Broder replied that while there is not a very large database, he believed they are highly competitive; he stated that 18 out of 21 will probably succeed. He added for clarification that, when a 5-year award is designated as a MERIT grant and then extended for three years, it goes into the computer as a 5-year grant and a 3-year grant, not as an 8-year grant.

Mrs. Bynum mentioned that, as a result of the discussions of the internal working group and the executive committee, the NCI is in the process of revising the OIG guidelines. She said that she had told Dr. Calabresi this matter should be brought before the Board rather quickly because of the competing continuations that the NCI expects to be submitted this year. The format may have to be a separate Planning and Budget Subcommittee meeting because, in order to get the applications to the next January council round, they would have to be submitted by June or July. She said that she would discuss the timing further with Dr. Calabresi and then develop a plan.

Dr. Broder stated that the Board would be given budget updates as the year goes along, as well as reports on hearings in the Senate planned for mid-March and House appropriation hearings scheduled for mid-April.

Dr. Calabresi thanked Dr. Broder for his presentation, and added for the record that he supported very strongly what had been said about the need for more clinical investigation. He noted the danger that there may not be enough opportunity to translate into clinical reality the basic science that is being supported.

XIII. NCAB SUBCOMMITTEES: SCOPE AND PURPOSE

Planning and Budget Subcommittee—Ms. Judith Whalen

Ms. Whalen, the NCI's Planning Officer, reported as Executive Secretary of the Planning and Budget Subcommittee. The subcommittee, she said, meets three to four times a year, usually at the end of a full NCAB meeting.

The subcommittee is charged with advising the NCI Director on planning and budget, which are closely connected. The Subcommittee provides advice on the budget process, by commenting on the President's Budget and advising on assumptions that go into the bypass budget. Ms. Whalen invited Board members to send her their comments as part of the process of constructing the assumptions for the FY '93 bypass budget.

The subcommittee also writes the NCAB's biennial report, covering Board actions for the previous two years, as well as recommendations for future actions; this becomes part of the council volume of the NIH Director's Biennial Report, a legislatively mandated report to the

Congress. This September, Ms. Whalen concluded, the subcommittee will begin work on the 1991-1992 NCAB report.

Dr. Mihich called attention to the materials provided by Ms. Whalen which list the women's dietary intervention project, and noted that the Board had voted to identify this as a feasibility study. Ms. Whalen noted that the material Dr. Mihich mentioned was based on the FY '92 bypass assumptions submitted in September 1990, and that this would be updated in the FY '93 assumptions.

Activities and Agenda Working Group—Dr. Paulette Gray

Dr. Paulette Gray, Chief of the Review Logistics Branch in the Division of Extramural Activities, reported as Executive Secretary of the Activities and Agenda Working Group. The aim of the Subcommittee on Activities and Agenda is to assist the NCI Director in establishing priorities of subjects to be presented at Board meetings in order to maximize for Board members the informational value of the meetings. The subcommittee meets as a committee of the whole on the last day of scheduled Board meetings and may at that time recommend agenda items for future Board meetings. The Working Group was formed in 1989 to promote efficient use of meeting time to discharge the NCAB's mandated review responsibilities. The Working Group has proposed measures to address the most effective way for Board members to review summary statements and the overall status of research support, as well as making recommendations affecting other operational aspects of the Board's functions.

AIDS Subcommittee—Dr. Judy Karp

Dr. Judy Karp, Special Assistant to the NCI Director, reported as Executive Secretary of the AIDS Subcommittee. The NCI, she stated, has been involved in AIDS research since the early stages of the epidemic, with a commitment to basic and clinical research in disease pathogenesis, the natural history of HIV infection, drug discovery and development, and other areas, working in concert with the NIAID, other NIH institutes, and other Federal agencies. A special purview of the NCI is AIDS-related malignancies.

The subcommittee meets primarily to update Board members and others regarding the progress and challenges of AIDS-related areas in which the NCI is involved and to provide scientific and administrative insight to the NCI. Meetings are open and are organized around a central theme, such as the recent meeting on current trials with anti-retroviral drugs. Key investigators from NCI, NIAID, or other agencies are invited to present data.

Cancer Centers Subcommittee—Dr. Brian Kimes

Dr. Brian Kimes, Associate Director of the Centers, Training and Resources Program, DCBDC, reported as Executive Secretary of the Cancer Centers Subcommittee. Before moving on to the specific charge of the subcommittee, Dr. Kimes observed that, under Dr. Broder, the NCI has made an effort to restore the vigor and spirit of the Cancer Centers Program and promote an increased dialog between the Institute and the 57 active Centers. There has also been a successful effort to involve Cancer Center directors in the advisory groups that assist the NCI.

Dr. Kimes noted that a Cancer Center is more than the Cancer Center Support Grant, known as a P30— it consists of that small grant plus research and training grants, private support, care and service activities, and community outreach activities. A Cancer Center director, he stated, has similar responsibilities to the community that the NCI has on the national level.

The Cancer Centers Subcommittee serves a critical advisory capacity to the NCI; its major charge is advising on the Cancer Center Program, with a minor charge of advising in the area of construction. He reported that the NCI has funded or is preparing to fund nine construction grants over the last two years, and eight of these have gone to Cancer Centers.

The subcommittee played a critical role in the formulation of the guidelines for obtaining NCI-designated comprehensive status. The guidelines are now operating on a peer review basis, and 24 Comprehensive Cancer Centers have been designated so far. A report on the status of these guidelines and how they are being used was planned for this meeting, but has been postponed until the next meeting.

The subcommittee also provided critical input that led to the formulation of the FY '91 strategic plan for the Cancer Centers. This document was included in the FY '91 bypass budget.

Issues to be discussed in the future include the question of caps on Cancer Centers and a proposed expansion of the program that would create "regional enhancement cancer centers" in order to meet the legislative mandate for geographic diversity.

Environmental Carcinogenesis Subcommittee—Dr. Richard Adamson

Dr. Adamson, Director of the Division of Cancer Etiology, reported as Executive Secretary of the Environmental Carcinogenesis Subcommittee. The subcommittee was established to examine national needs and problems in environmental carcinogenesis and to monitor progress in this area.

During the last two years the subcommittee reviewed the history of the NCI Carcinogenesis Bioassay Program and its transfer to the National Toxicology Program; it also reviewed the transfer of the Radiation Effects Branch from the Division of Cancer Treatment to the Division of Cancer Etiology. The subcommittee had an extensive presentation of the four intramural branches and one extramural branch of the Epidemiology and Biostatistics Program to review its mission, its organization, and its ongoing studies within the Division of Cancer Etiology. Particular attention was paid to the Occupational Epidemiology Section within this program. The subcommittee also focused on alar at one meeting, with presentations from the FDA and the EPA on their actions. Issues to be considered in the future include carcinogens in food that result from cooking and current studies, both intramural and extramural, concerning pesticides.

Information and Cancer Control for the Year 2000 Subcommittee—Mr. J. Paul Van Nevel

Mr. J. Paul Van Nevel, head of the NCI Office of Cancer Communications, reported as Executive Secretary of the Information and Cancer Control for the Year 2000 Subcommittee. This subcommittee provides advice on all information and education programs operated by the NCI and on the Cancer Control Programs operated by the Division of Cancer Prevention and Control. Programs advised by the subcommittee include the International Cancer Information Center, PDQ, the Cancer Information Service, and a wide range of public education and information programs.

The subcommittee was given, last year, the responsibility for providing concept review of all contracts arising in the Office of the Director. Most of these are in support of the institute's information dissemination programs.

One of the most noteworthy accomplishments of the subcommittee in the last several years has been the sponsorship of a series of public hearings around the country designed to encourage public awareness of the NCI's Year 2000 goal of reducing cancer mortality by 50 percent. Hearings were held in Los Angeles, Dallas, Atlanta, Miami, and Philadelphia. A report was widely distributed to schools, businesses, and health departments.

A task for the subcommittee in the future is the review of Cancer Information Service contracts. The Institute is in the process of completing a management study of the Cancer Information Service, which will be used to guide the concept for renewal of those contracts in late 1992.

Subcommittee on Minority Health Professional Development—Dr. Vincent Cairoli

Dr. Vincent Cairoli, Chief of the Cancer Training Branch, reported as Executive Secretary of the newly-named Subcommittee on Minority Health Professional Development. In opening with a brief history of the subcommittee, Dr. Cairoli related that, in the Fall of 1988, the NIH examined the status of minorities in the NCI biomedical community and found that the results were dismal. A focus on minority representation on NIH training grants also revealed poor minority participation, with a total minority involvement of 4 to 6 percent, and a Black representation of about 1 percent.

The NIH then republished a directive to training grant directors to make greater efforts to recruit minorities. In February 1989 the NCAB formed an ad hoc Subcommittee on Minority Manpower Development to assist the NCI director in developing procedures for meeting the requirements for a minority recruitment plan. The subcommittee's mandate was to discuss any issues related to minority involvement in cancer-related biomedical research training.

In explaining why concepts related to improving minority professional development were being brought before the NCAB for consideration instead of to the Boards of Scientific Counselors, Dr. Cairoli explained that some early programs involving minority training were imbedded in a program that, after NCI reorganization, became the Division of Extramural

Activities, which does not have its own Board of Scientific Counselors. Another problem is the urgency associated with the commitment to use FY '91 dollars for this purpose.

It was decided to bring these concepts to this NCAB meeting and to have representatives of two Boards of Scientific Counselors (BSC) present. Dr. Carolyn Woodfield represented the Division of Cancer Biology, Diagnosis, and Centers BSC. The representative of the Division of Cancer Treatment BSC was unable to attend due to a serious family illness.

Dr. Cairoli explained that the mechanisms that these concepts will use are the so-called K grants, which are career grants that help bring investigators from postdoctoral (or post-medical) training to the point at which they can compete for R grants. These career grants are for three to five years, depending on individual needs and objectives. Their objectives are to strengthen clinical oncology at minority medical schools and to get young minority clinical faculty to involve special underserved populations in their research.

Dr. Cairoli introduced Dr. Lemuel Evans, Director of the Comprehensive Minority Biomedical Program of the Division of Extramural Activities, to present the concepts.

Dr. Evans began by stating that the proposed mechanisms for developing a program concept entitled Minority Health Professional Training Initiative fall roughly into two categories: Phase I—those addressed to young clinicians, who are seen as the real targets of this initiative; and Phase II—those addressed to institutions, primarily minority health professional schools.

Dr. Evans displayed a slide that presented basic information on six awards, three to be initiated in FY '91 and three in FY '92. It was deemed important to announce the Phase I mechanisms—the K07s, K08s, and K14s, in sufficient time to make several FY '91 awards for each mechanism.

A second slide was used to describe the K07 Academic Teacher Awards, designed to assist leading teacher-investigators at minority professional schools in creating a stimulating environment for cancer research, attracting high quality students, fostering academic career development, and developing multidisciplinary curricula. The next slide described the K08 Clinical Investigator Awards, designed to foster research on special populations and increase the pool of cancer physician-investigators, particularly in medical oncology, nutrition, behavioral medicine, surgical oncology, preventive oncology, and diagnostic and therapeutic radiology. This is a targeted version of the regular clinical investigator award, with a first round set-aside of three awards aimed at young minority investigators at majority institutions.

A third slide described the K14 Minority School Faculty Development Awards. These are open to M.D. or Ph.D. faculty at any level in minority health professional institutions. One purpose of this award is to allow time to do off-site work with established researchers. Dr. Evans stated that the program expects to have a set-aside of three awards.

All RFAs are to compete for FY '91 funds set aside for minority initiatives with a September 30, 1991 start date. A peer review will be conducted by a special review committee impaneled by the Division of Extramural Activities. An R25 grant initiative, the Professional Oncology Education Program, is currently under development. Subject to the availability of funds, the projected costs of the first phase would be somewhat over $1 million. Dr. Evans

showed two additional slides that listed some of the minority schools that are expected to respond to this initiative. Many are members of the Association of Minority Health Professions Schools.

In response to a question about salaries of the K08s compared with nonminority K08 awards, Dr. Evans responded that they are the same. Asked why the K14s are targeted to minority institutions, Dr. Evans responded that the major reason is to target a heretofore overlooked population of individuals.

A participant asked whether recipients of the K07s and K08s are required to link themselves with established investigators. Dr. Cairoli answered that all the career grants, except the K04 Career Development Award, involve a mentor or mentors, often requiring sponsors in both the clinical and basic science areas.

Dr. Salmon moved that the proposed program be approved. Dr. Durant seconded the motion, which was passed unanimously.

Dr. Mihich congratulated Mrs. Bynum and her staff for the development of this minority professional development program within the Division of Extramural Activities, and asked whether it should, as it achieves independence and greater influence, be transferred to the Resource and Training Program. Mrs. Bynum replied that the point was well taken, and that this transfer was planned. She noted that this was the reason for the joint presentation by Dr. Evans and Cairoli.

Innovations in Surgical Oncology Subcommittee—
Dr. Michael Friedman

Dr. Michael Friedman reported as Executive Secretary of the Innovations in Surgical Oncology Subcommittee. He stated that he has served in this capacity in the absence of a surgical oncologist who is responsible for the Extramural Research Program in the Division of Cancer Treatment. The subcommittee is designed to address the concerns raised by surgical oncologists on the NCAB and to serve as a conduit for concerns, ideas, and initiatives from the extramural community. He noted that there has been little activity in this area, and welcomed the opportunity to invite new Board members to bring their concerns to this subcommittee.

Asked whether any progress had been made in obtaining a surgical representative on the NCI staff, Dr. Friedman reported that a promising recruitment effort is underway.

Dr. Calabresi announced his intention of broadening the Innovations in Surgical Oncology Subcommittee to include all areas of clinical investigation. He will appoint a new Subcommittee on Clinical Investigation in order to address these broader objectives, and asked Dr. Friedman to serve as Executive Secretary of this subcommittee. Dr. Friedman agreed.

Dr. Calabresi called the Board's attention to a sheet provided in their notebooks for the purpose of selecting subcommittee assignments. He asked members to indicate those subcommittees in which they are interested to assist him in making assignments.

XIV. TAXOL: AN UPDATE—DR. BRUCE CHABNER

Background

Dr. Chabner began his presentation by describing changes in the drug development program that brought about the discovery of taxol's anti-tumor activity. Approximately six years ago a major change was made in the drug development program with a decision to concentrate on setting up screening systems that more carefully investigate natural products. Dr. Chabner stated that the reason for changing the screening system was because in the drug development program they were of the belief that natural products constituted a major source of promising agents with novel molecular structures. The percent of positive results in screened agents, he added, is much higher from natural sources than from random screening. This fact, combined with the reality that the plants and animals from which these agents are derived are rapidly disappearing due to urbanization and destruction of the forests, served to expedite the investigation of these agents.

Currently, Dr. Chabner said, a number of human tumor cell lines are in the screening process and the program has expanded into more mechanism-based screening through drug development groups supported by grants. He added that the Division of Cancer Treatment is going to have a meeting in three or four months on mechanism-based screening, a screening process in which the molecular mechanisms are studied in conjunction with molecular targets, as opposed to whole animal or even cell line studies. Dr. Chabner noted that molecular mechanism-based screening is the new direction in drug development.

The taxol story, Dr. Chabner said, really began 30 years ago when a number of plants were collected and tested for anti-tumor activity. One of the plants collected was a small ubiquitous tree called *Taxus brevifolia* found in the western United States and in Canada. The tree has very little commercial value aside from making fence posts, although the wood is used by people who like to do sculpture. In the past it has been cut and burned in the timber access and extraction process. The active compound was first isolated in 1962 in *Taxus brevifolia* and was shown to have activity in culture in 1964. The pure compound was isolated and the structure solved in the succeeding seven years and the scale-up, toxicology, and formal testing took place in the 1970s.

The interest in taxol was modest because of the difficulties in obtaining the drug and the fact that it really didn't have striking anti-tumor activity in animal tumor systems. The real interest arose when it was discovered that it belonged to a class of mitotic inhibitors that includes the vinca alkaloids, colchicine, and a number of other natural products. In the case of taxol, it had a unique action with regard to the microtubular system in cells—it blocks the depolymerization of the microtubules and it promotes microtubular formation and the formation of dense bundles of microtubules within cells. Its biologic action of most significance is probably a block in mitosis.

Laboratory Studies

One of the interesting aspects of this drug, Dr. Chabner said, is that it is subject to a unique mechanism of resistance. One mechanism of resistance that taxol displays that is not

unique is the multi-drug resistance mechanism (MDR), which is also found in colchicine. Work performed in Dr. Susan Horowitz's laboratory has shown that resistance to taxol can be mediated by the MDR gene. This concerned Dr. Chabner in clinical testing because he felt that it could display cross resistance with the vinca alkaloids.

A unique aspect to taxol's action is that once the drug gets in the cell, it binds to the microtubular apparatus. As a result of this activity, cells that are resistant to taxol are a different set of cells than those resistant to the vinca alkaloids. There are some cells that are cross resistant and those are the ones that share the MDR type of resistance. But, there are also cells that are resistant to vinca alkaloids that show enhanced sensitivity to taxol and the opposite is also true—cells resistant to taxol can show increased sensitivity to the vinca alkaloids. Further, when tubulin mutants develop their resistance to taxol in culture they become dependent on taxol for growth and, when taxol is removed, the cells can't go through normal mitosis. Dr. Chabner noted that this finding raised two interesting possibilities: one is that many tumors could be cross resistant to taxol if they were the MDR type and, the alternative possibility, that they could show enhanced sensitivity to taxol if they were selected by clinical exposure to vinca alkaloids.

Clinical Studies

The clinical expectations for this drug were not very high given the fact that it had weak activity against what was considered the most predictive system for human cancers—P388. However, it did have some strong activity against solid tumors, the B16 melanoma and certain breast cancer and lung cancer xenografts, for example. The clinical trials for taxol began in 1983. Initially, there were problems with the drug because it is very insoluble and it was put into a formulation that caused hypotension and allergic reactions. It took a period of time to learn how to administer the drug safely and effectively. Eventually, Dr. Chabner explained, they began a schedule in which taxol was given by 24-hour infusion with premedication with steroids and antihistamines.

Four years ago, Dr. Chabner continued, once the Phase 1 trials were over and the Phase 2 trials began and the dose schedule was changed, they began to get hints of clinical activity. The drug first showed activity in refractory leukemias and melanoma. But the real breakthrough came in studies in refractory ovarian cancer. Initially, there was not a lot of interest in this drug for ovarian cancer because the vincas were not terribly useful in this disease. However, because Phase 2 trials are broad based it was tried in refractory ovarian cancer. Currently, Dr. Chabner said, four studies have shown reproducible activity in patients resistant to or who have failed cisplatin regimens. The first study, published in the *Annals of Internal Medicine* about two years ago, showed that 12 of 40 patients responded for periods between 3 and 15 months. Taking only the subgroup of patients whose cancers actively progressed during cisplatin treatment (the very best drug treatment regimen available for ovarian cancer), the response rate was an impressive 20%. Taxol activity was subsequently confirmed in two other trials.

Dr. Chabner stated that some preliminary evidence of activity in breast cancer is being seen. Twenty five patients, all of whom had failed primary treatment for metastatic breast cancer, have been entered in a Phase 2 study at M.D. Anderson, and the response rate is staying in the neighborhood of 40 to 50%. A number of patients are still being studied so the final rate has yet to be determined. In melanoma, the activity rate of taxol is approximately 20%, Dr. Chabner added.

Referring to the toxicity profile of taxol, Dr. Chabner noted that taxol causes primary leukopenia. The initial doses, he said, can be given at quite high levels, however, in the absence of any type of marrow protection, colony-stimulating factor, for example, the subsequent treatments must be reduced. The average dose that is currently being given is between 130 and 170 milligrams per meter squared. This dose causes mucositis and a peripheral neuropathy, which is cumulative, in the 24-hour infusion regimen. Doses as high as 250 milligrams have been given along with G-CSF without the need for dose reduction. At higher doses peripheral neuropathy is the dose-limiting factor, Dr. Chabner explained.

The administration regimen, Dr. Chabner said, leads to some bradycardia and occasionally A-V block, so initial doses have been given in the intensive care unit. Longer infusion regimens may ameliorate this problem. Hypotension during infusion has been a problem, as well, but it is undoubtedly related to the vehicle of administration rather than the drug itself. Dr. Chabner also noted another effect of the drug is that it prevents the export of packaged certicosteroids from adrenal cells in culture.

Clinical Development Plan

The clinical development plan for taxol is changing rapidly, Dr. Chabner stated. Broad Phase 2 trials are being conducted. Two major problems with taxol are that it is in short supply and there is a tremendous investment required in obtaining the drug and bringing it to the clinic. A number of trials, however, for all the major solid tumors are on-going in Cancer Centers and in the cooperative groups.

At NCI, Dr. Chabner said, intramural researchers are completing a protocol with colony-stimulating factor for rescue. Dr. Chabner said that he is confident that the drug could be combined with cisplatin in high doses with G-CSF rescue, and this would make for a very interesting regimen. There is currently a cooperative group trial comparing the standard regimen of cisplatin and cytoxan with taxol and cisplatin.

For breast cancer, Dr. Chabner continued, a major focus is to combine taxol with the standard drugs, particularly adriamycin. A protocol of this type has been written and will be activated shortly in the clinical center.

Drug Development and Supply

A novel approach is being used for development of this drug. Since no patent protected taxol, a collaborative research and development arrangement was prepared in which clinical data and background experience of the Institute in producing the drug is provided to a commercial firm in return for their promise to undertake the clinical development of the drug. This was competed last summer, and an agreement with Bristol-Myers-Squibb has just been signed. The job of developing taxol has not been totally left to Bristol-Myers-Squibb; NCI will continue to try and make sure that supplies are made available. A new RFA was issued that supports grants for taxol semi-synthesis or other aspects of the supply problem.

A major limitation with taxol in terms of further development is supply. NCI will continue to work for access to taxol through cooperation with other Federal agencies such as

U.S.D.A. This has become an important component because of new legislation that has made it difficult for U.S.D.A. to sell even common timber, let alone an unusual plant like *Taxus* to a commercial user. And there are concerns that large scale use of *Taxus* for drug development will destroy some natural habitats. In the case of *Taxus*, it grows in conjunction with the large Douglas firs and spruce trees that are harvested in timber sales and that are part of a large controversy concerning the spotted owl.

Recently, a petition to place *Taxus* on the endangered species list was rejected. However, with the wholesale harvesting of *Taxus* may come the possibility that timber supplies will be sequestered by people who feel they can make a profit by holding on to it. Dr. Chabner said that it was his feeling that for the near future the major source of drug will come from the trees themselves and that they will get permission from U.S.D.A. for an expanded harvest of *Taxus* for this purpose. In the long run, he said, semi-synthesis and cultivation or plant hedging will provide the needed supplies. Further, the nursery industry is interested in this and is going to make available their plant cuttings for testing and possibly for large scale extraction. Other, more exotic methods such as hydroponic culture and genetic engineering are also being studied.

In closing, Dr. Chabner stated that with regard to supplies at the current usage rate NCI will be able to keep up with its Phase 2 needs. It is NCI's hope that it will be able to expand the use of taxol to patients with refractory ovarian cancer on a compassionate basis later this year. He reminded the audience, however, that there is no short term solution to the large scale need for taxol. Dr. Chabner added that there is a taxol analog called taxotere, which is being tested by Rhone-Polanc in Europe and in the United States; however, there is no information yet as to the clinical activity of this analog.

Questioned about the possibility that the neurologic toxicity seen with taxol could be from another part of the molecule other than the business part for cancer, Dr. Chabner responded that the structure-versus-activity relationship is not well understood. He answered in the affirmative when asked whether analogs of taxol will be tested *in vivo* given that minor structural changes in the vincas have brought about major differences in their profile.

Dr. Broder interjected that he believed this compound to be the most important new drug in practical terms to come along within the NCI in 10 or 15 years. He added that taxol is an important lead compound that has a number of important science spin offs because taxol in some systems mimics the activity of the $C\text{-}_{mos}$ oncogene and promotes the excessive and aberrant expression of mitosis promoting factors. For this reason it fits in with the whole cyclin and CDC2 kinase story. Dr. Broder told the Board that NCI has made the development of this drug an emergency priority. Every component of NCI has been asked to participate in solving the problem. Dr. Broder said that they need the help of the Board members to help with this problem by explaining at their institutions and back in their communities that shortages do exist. Because of this fact, Dr. Broder said, they will have to do whatever they can to make sure the drug goes to appropriate clinical trials where important knowledge is likely to be generated.

Asked what the status of the soluble analog is and whether the analog is supposed to be more potent and water soluble, Dr. Chabner said that he was not sure of the status of taxotere—the only analog that is in clinical development.

A Board member asked whether taxol was absorbed orally and also asked if taxol could be given in smaller doses in conjunction with vinca alkaloids so that less drug is needed. Dr. Chabner stated that he had no knowledge of any studies in which taxol was given orally. With respect to the second question, Dr. Chabner said that there haven't been any drug combination studies to date. He added that he thought the MDR system is not the basis of drug resistance in ovarian and breast cancer patients. In the breast cancer patients, roughly 95% had been treated with anthrocyclines and failed. The fact that half of those patients responded to taxol indicates that MDR is not the exclusive mechanism of resistance. Dr. Chabner continued by saying that in lymphomas a majority of patients are not resistant on the basis of MDR. This could mean that these people who have been treated with vinca alkaloids may be resistant on the basis of tubulin mutations, which would make them more sensitive to taxol.

A Board member asked if NCI has been in touch with the French company in reference to their extraction of the drug from the needles of the tree. Dr. Chabner responded that he had been in close contact with Rhone-Polanc. He noted that when he first spoke with these people, they were in the middle of acquiring an American pharmaceutical company. While they were in the process of merging the two companies they were not in a position to discuss collaborative efforts with NCI. Six months later in December of 1990 he met with them again and they indicated interest in cooperating with NCI in the Phase 2 evaluation of their drug. It is also likely that they will pursue development of the drug in independent protocols.

When asked if the loggers have been alerted to NCI's need for *Taxus*, Dr. Chabner said that they had been and added that there are many other problems involved, including: paying the local communities, being sure that the harvesting is done by companies that will sell to American pharmaceutical firms, and that those who harvest the trees do not sequester them or send them overseas. Furthermore, there is the problem of environmentalists contesting every timber sale through the courts. Because of the new legislation, Dr. Chabner said, any new timber contracts can be challenged in the courts.

Dr. Broder addressed this issue by saying that he is working with the Department of Agriculture, the Department of Interior, and with the specific representative for the Fish and Wildlife Service of the Department of the Interior and that the NCI has a good working relationship with these agencies.

In response to questions concerning the exclusivity of the agreement with Bristol-Myers-Squibb, Dr. Chabner explained that the agreement with Bristol-Myers-Squibb is that the NCI provides them exclusively with data and that the NCI will cooperate with them exclusively in the clinical development in this country.

Asked if the cut and burn approach to *Taxus Brevifolia* has been stopped, Dr. Chabner stated that it had. When asked if there was anything special about the dose schedule that would account for overcoming the toxicity of the drug in the presence of growth factors and also asked if there were any other tumor types in which activity was seen, Dr. Chabner answered by saying that positive results have been seen in melanoma, leukemia, ovarian cancer, and breast cancer, and that NCI was about to begin studies in lymphoma. To the other question Dr. Chabner replied that the schedule is very standard.

When a participant asked how many trees it takes to have enough drug for one patient for one year at the present dose therapy, Dr. Becker said that the figure he had was that it would take three trees to have a course of treatment for one patient. He added that that is a lot of trees for one patient and that if taxol is ever to become an effective drug, other sources will have to be found.

Dr. Chabner mentioned that there will be sources of taxol in the needles of the trees, so eventually, once the process gets worked out, they won't have to cut down the trees.

A Board member asked if anything eats the bark of this tree; Dr. Chabner said that elk and moose do. Dr. Broder explained that this is a very complicated molecule that has evolved for a purpose, and one would think it serves as a form of biological warfare against things that like to eat bark.

XV. NEW BUSINESS

Resolution in Support of a Partnership with the American Cancer Society

Dr. Lawrence, in response to yesterday's remarks by Mr. Tipping of the American Cancer Society, proposed on behalf of himself and Mrs. Helene Brown that the NCAB enact a resolution as follows:

> BE IT RESOLVED that the NCAB expresses to the American Cancer Society the recognition that the control of cancer is dependent on a partnership between the public and private sectors. We, therefore, pledge NCAB support of such a partnership whenever appropriate to the American Cancer Society and the citizens who look to both the NCI and the ACS for the eventual elimination of cancer.

Dr. Lawrence moved that the resolution be sent to the ACS. A Board member seconded the motion and it was passed unanimously.

Report of the Working Group on the NIH Financial Management Plan

Dr. Mihich was asked by Dr. Calabresi to report to the full Board on yesterday's meeting of the working group formed to recommend revisions to the NIH financial management plan. Dr. Mihich stated that he and his colleagues focused on pages eight and nine of the plan, and did not have any recommended changes to page eight; however, they asked the Board's chairman, Dr. Calabresi, to empanel an NCAB subcommittee to develop principles necessary to manage the research portfolio of the NCI in the spirit of this plan.

Dr. Mihich called the attention of Board members to a revised version of page nine of the NIH plan which had been distributed. The working group recommended the deletion of the final words "and scientific relevance" from the last sentence of the first paragraph on page nine. It was felt that the evaluation of scientific relevance was the responsibility of the primary reviewers.

The working group recommended revising the second paragraph on page nine by deleting the sentence appearing in parentheses, which indicates that all summary statements would include an estimate of total cost, including indirect costs. It was felt that the Board should not become involved in discussing specific indirect costs of institutions. Further discussion clarified that, according to the NIH plan, total costs would be made part of the summary statements, but the Board should not be asked to discuss indirect costs themselves.

Additionally, the working group recommended revising the second paragraph on page nine by replacing the phrase "of the percentile ranking" with "at the Special Actions Subcommittee" in the last sentence.

Dr. Salmon moved that the working group's recommended changes be approved by the Board and submitted to the NIH. Dr. Becker asked for further time to discuss the last paragraph on page nine concerning the issue of cofunding. He suggested revising the sentence "NIH administrative policies will need to be modified to facilitate such cofunding and to take it into account in arriving at an appropriate funding level for each project" by ending the sentence with the word "cofunding"; this would remove the implication that NIH might reduce the amount of funding for a project if other sources of funding were available.

Mrs. Bynum commented that if NIH adopts a format for summary statements that includes information on cofunding, that information would be there whether or not the Board chooses to ignore it.

Dr. Salmon moved to recommend to the NIH the revisions to the financial management plan suggested by the working group, with the addition of ending the third sentence of the last paragraph of page nine after the word "cofunding." The motion was seconded and passed without opposition.

Other New Business

Dr. Broder announced a workshop on biodiversity that will cover some of the issues and ecological implications of obtaining natural products; the workshop will be held on March 13th and 14th in Building 31, Conference Room 6. He recommended that members contact Michael Grever in the Developmental Therapeutics Program for further information.

Mrs. Bynum explained that, at the first meeting of each calendar year, the NCI must ask the Board to approve and/or leave within the purview of the program and grants management staff certain authorities to take action without consulting the Board. She stated that this is necessary to make timely awards without interruption. Three authorities are described under the "New Business" tab in the members' notebooks: one is to negotiate adjustments in awards to correct errors or inconsistencies, or to negotiate unanticipated expense changes such as salary scales. The second relates to the award of noncompeting or administrative supplements approved by the executive committee. The third relates to adjustments in funding due to administrative or organizational changes, including changes of investigator, that threaten the continuity of supported research.

Dr. Durant moved to approve the requested authority. A Board member seconded the motion, which was passed unanimously.

Dr. Temin moved that the Board request justification for MERIT application extension budget increases greater than 15 percent. Dr. Becker seconded the motion, which was passed unanimously.

Dr. Durant made a motion for adjournment, which was seconded and approved. The 77th meeting of the National Cancer Advisory Board was adjourned at 11:51 a.m.

April 3, 1991
Date

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