DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
September 23-24, 1991

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

Department of Health and Human Services
Public Health Service
National Institutes of Health
National Cancer Institute
National Cancer Advisory Board
Summary of Meeting[1]
September 23-24, 1991

The National Cancer Advisory Board (NCAB) convened for its 79th regular meeting at 8:30 a.m. September 23-24, 1991, in Building 31, C Wing, 6th Floor, Conference Room 6, National Institutes of Health (NIH).

NCAB Members

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

President's Cancer Panel

Dr. Harold P. Freeman (Chairman)
Mrs. Nancy G. Brinker (Absent)
Dr. Geza J. Jako

Alternate Ex-Officio NCAB Members

Dr. Miriam Davis, NIEHS
Captain Bimal Ghosh, DOD
Dr. Theodore Lorei, DVA
Dr. Hugh McKinnon, EPA
Dr. Lakshmi C. Mishra, CPSC
Dr. John Whalen, NIOSH

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

---

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

Liaison Representatives

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

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

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

Dr. Edward P. 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. M. W. Linehan, Head, Urologic Section, Surgery Branch, DCT, Society of Urological Oncology, representing the Society of Urological Oncology for Dr. Jerome Richie

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. Thomas J. King, Treasurer, American Association for Cancer Research, representing the American Association for Cancer Research

Ms. Linda O'Connor, President, Oncology Nursing Society, representing the Oncology Nursing Society

In addition to NCI staff members, meeting participants, and guests, a total of 36 registered members of the public attended the meeting.

TABLE OF CONTENTS

I. CALL TO ORDER, OPENING REMARKS, AND CONSIDERATION OF MINUTES OF PREVIOUS MEETING—DR. PAUL CALABRESI

Dr. Calabresi called the meeting to order and welcomed all to the 79th Meeting of the National Cancer Advisory Board (NCAB). He extended a special welcome to newly-appointed members of the Board: Mrs. Zora Brown, who succeeds Mrs. Nancy Brinker; and Mrs. Brenda Johnson, who succeeds Mr. Louis V. Gerstner, Jr.

Dr. Calabresi introduced several guests representing medical, research, and professional organizations. He welcomed members of the public and instructed those who wished to express views pertaining to items discussed to write Mrs. Barbara Bynum, Executive Secretary of the Board, within 10 days following the meeting.

Dr. Calabresi reminded participants that proceedings of the Board are conducted in accordance with the statutory provisions of the Federal Advisory Committee Act. Dr. Calabresi then quoted from the Federal Advisory Committee Act to clarify, for the record, the statutory provisions guiding the structure and proceedings of NCAB meetings. He stated that the Board is meant to "be utilized solely for an advisory function"—with the exception of the review of grant applications, in which the Board's actions can determine the disposition of grant awards. Meetings must be open to the public except when the need for confidentiality concerning grant applications requires closed sessions. A designated employee of the Federal Government must convene, approve the agenda of, and attend each meeting; Dr. Calabresi noted that in case of the NCAB that person is Mrs. Bynum. Dr. Calabresi stressed the importance of conducting these meetings in accordance with the statute and asked participants to cooperate in adhering to the agendas for the Board meetings. He also asked participants to review copies of the May minutes in their Board books by close of business Tuesday.

Dr. Calabresi continued by noting the implementation of certain changes that were requested by the Board. First, subcommittee meetings will be scheduled throughout the meeting to avoid conflicts in members' attendance and to allow as many members as possible to attend subcommittee meetings. Second, the closed session for review of grants will be held at 3:00 p.m. Monday afternoon, followed by open-ended time; this will allow for flexibility if the closed session does not last as long as anticipated.

Dr. Calabresi reviewed the schedule of subcommittee meetings for Monday and Tuesday. He emphasized the critical importance of having all Board members in attendance over the next two days to ensure the presence of a quorum should a vote be necessary.

II. FUTURE BOARD MEETING DATES—DR. PAUL CALABRESI

At this time, Dr. Calabresi discussed the previously confirmed 1991 and 1992 dates and the proposed 1993 dates for NCAB meetings. He indicated that three-day meetings have been scheduled but that unless absolutely necessary, the meetings will continue to be two days. They have been scheduled in this way to avoid announcing an extension should the meetings require three days.

The May 1992 meeting, Dr. Calabresi announced, will be scheduled for Tuesday through Thursday because of the clinical investigation meeting, but all other 1992 and 1993 meetings are scheduled for Monday through Wednesday. With no objections, the 1993 dates were confirmed.

Dr. Calabresi instructed those Board members who wished to have a grant application discussed at the afternoon's closed session to inform Mrs. Bynum. He reiterated that attendance

in the closed session is determined on a "need-to-know basis" due to the privileged and confidential nature of the discussions.

III. REPORT OF THE PRESIDENT'S CANCER PANEL—DR. HAROLD P. FREEMAN

Dr. Calabresi introduced Dr. Harold Freeman, chairman of the President's Cancer Panel. Dr. Freeman began by stating that the newly appointed panel, in office for approximately four months, recognizes the great challenge that has been given to them.

Dr. Freeman reflected on the 20-year history of the President's Cancer Panel and the 20th anniversary of the National Cancer Act, declared by President Nixon in 1971. He reported that 80 percent of the money invested in cancer research in the history of the United States has been invested during the last 20 years, primarily because of the National Cancer Act.

Dr. Freeman reviewed the first two meetings conducted by the new panel. The first, held at the NIH in July and entitled "Cancer and Poverty," was of personal interest to Dr. Freeman because of his work in Harlem as a surgeon for 25 years. Dr. Louis Sullivan, Secretary of the Department of Health and Human Services (DHHS), and Dr. Bernadine Healy, Director of the National Institutes of Health (NIH), both spoke at this meeting.

The relationship between economic status and cancer was carefully examined, and the panel learned that cancer causes poverty and poverty causes cancer. Cancer does not occur simply as a scientific disease, Dr. Freeman emphasized, but also embodies social, political, economic, physical, and cultural circumstances. These interrelationships must be understood.

The second panel meeting, entitled "The Training of the Biomedical Scientist," addressed the subject in general, but concentrated on the training of minority scientists. The panel examined the value of minority institutions, industry, and government in the training of the scientist. The panel members addressed the country's faltering educational system and the low numbers of individuals entering scientific fields.

In preparation for the meeting, Dr. Freeman met with Dr. John Ruffin, Director of the Office of Minority Programs; Mrs. Barbara Bynum, Director, Division of Extramural Activities, National Cancer Institute (NCI); Mr. Elward Bynum, Director of the Minority Access to Research Careers (MARC) Program; Mr. Sidney McNairy of the Research Centers and Minority Institutes Program; and Dr. Claudia Baquet, Associate Director, Cancer Control Science Program, NCI.

Dr. Broder spoke at this panel meeting, addressing the quality of elementary school education, the considerable time and expense involved in science education, and the need to have a diverse scientific community in the United States. Also emphasized at the meeting was the need for the educational environment to be safe, comfortable, and supportive. The lack of American students with good preparation for or an interest in a career in science was also addressed.

Dr. Freeman stated that these first two meetings reflect his own personal philosophy that the fight against cancer, as it relates to poverty, is a human fight, irrespective of race. Affirmative action, he continued, is a critical issue in education, but with respect to poverty, one must take into account all who are affected.

Dr. Freeman discussed a letter he received from Vice President Quayle in which the Vice President asks the President's Cancer Panel to form a subpanel chaired by Mrs. Nancy Brinker to address breast cancer in America. Some key issues that the Vice President suggested for

subpanel analysis are: current research into the cause of breast cancer; improved treatment possibilities; new prognosis techniques; integration of the latest advances into mainstream medicine; training and career development in this field; potential early detection methods that do not involve radiation; the role of biotechnology; rapid approval of safe and effective new treatments; quality control and safety for mammography screening; improved communication about new developments; promotion of early screening and detection; and the needs of poor and minority women.

Dr. Freeman responded to Vice President Quayle and indicated that he would create a subpanel of top experts to study breast cancer, and that the panel expects to report to the Vice President in approximately 18 months.

The next two President's Cancer Panel meetings have been planned, Dr. Freeman noted. On December 9, a meeting in Houston, Texas will be devoted to breast cancer. The second meeting, to be in San Francisco on February 21, 1992, will address technology transfer, particularly the role of cancer centers in applying research findings in American communities. A third panel on lifestyle considerations, is anticipated to take place in New York in the spring.

Dr. Freeman concluded by emphasizing his belief that a strong cancer research program is critical, but that health care is also a vital dimension that must be addressed by the Executive Branch of the Government and Congress. He views the charge of the President's Cancer Panel as comprehensive. Dr. Freeman emphasized that the war against cancer, primarily a research war for the last 20 years, must be refocused to include technology transfer to the communities and improved access to health care.

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

Introduction of New Board Members

Dr. Broder began his report by welcoming and introducing two new members of the NCAB—Mrs. Zora Brown and Mrs. Brenda Johnson.

Mrs. Zora Brown serves as President of the District of Columbia Breast Cancer Resource Committee and is a member of both the District of Columbia Cancer Consortia and the Breast Cancer Foundation. Currently, she is the Director of Administration and Public Relations for Broadcast Capital Fund—a nonprofit investment company.

Mrs. Brenda Johnson serves as Chair of the American Cancer Society Youth Against Cancer program and is on the Board of Directors of the American Health Foundation. She has served on the Board of Directors of the American Cancer Society. Ms. Johnson is a partner in BrenMer Industries—an importing and marketing company. She was formerly a teacher and supervised a Head Start program.

New Developments Within the NCI

Dr. Broder lauded the success of the first meeting of the President's Cancer Panel under the leadership of Dr. Harold P. Freeman. The subject of the July 9, 1991, meeting was "Poverty and Cancer." A meeting was subsequently held at Morehouse College on "Training in Science and Medicine." Dr. Broder commented that the United States faces significant problems related to scientific and medical education and its financing, especially among minority groups and underserved populations. In light of this problem, Dr. Broder announced that a presentation would be given on day two of the meeting reporting on the second year of a program initiated by the NCI to encourage students to enter scientific careers and efforts to regionalize this program.

Honors, Awards, and Staff Changes Within NCI

Dr. Broder announced that Dr. Frederick Becker, a member of the NCAB, was appointed to the Herbert L. and Olive Stringer Chair in Basic Sciences at the University of Texas. He extended his congratulations to Dr. Becker.

Dr. Broder then announced that, due to the large number of awards and honors to NCI staff, he would present slides of the following awards and their recipients: Public Health Service (PHS) Commendation Medal; PHS Unit Commendation; PHS United Commendation in the Division of Cancer Etiology; National Institutes of Health MERIT Award; PHS Special Recognition Award; PHS Superior Service Award; DHHS Distinguished Service Award; PHS Outstanding Service Medal; NIH Director's Award; Equal Opportunity Special Achievement Award; DHHS Secretary's Award for Exceptional Achievement; Young Investigator's Award (awarded by the American Society of Pediatric Hematology/Oncology); Barbara Bohen Pfeiffer Award for Scientific Excellence; Fox Chase Cancer Center Communication Award; Special Technology Transfer Award; George H. Scott Award; and the Antoine Bourée Latorer Health Prize. In particular, Dr. Broder mentioned that Dr. Steven Rosenberg received three awards—the Scientist of the Year Award for 1990, the Sheen Award, and the Gottlieb Award. Also, one of the first Rose Kushner Awards from the American Medical Writers Association was awarded to the Women's Leadership Summit for a kit developed by Corrinne Vanchieri and Miriam Adams. Rose Kushner was a member of the NCAB from 1980 to 1986.

Dr. Broder announced that Dr. John Minna, one of the recipients of the Public Health Service Unit Commendation Award and Chief of the Navy Medical Oncology Branch, has retired to assume the position of Director of the Cancer Center and Division Chief for Hematology/Oncology at the Southwestern Medical Center at the University of Texas at Dallas. Dr. Broder then announced the following NCI staff changes: Dr. Fred Li, Chief of the Clinical Study Section of the Clinical Epidemiology Branch in the Division of Cancer Etiology, retired in June; Dr. John Gart, Chief of the Mathematical Statistics and Applied Mathematics Section of the Biostatistics Branch, retired in August; Dr. Mike Grever began serving as Acting Associate Director for the Developmental Therapeutics Program in February; Dr. Dwight Kaufman, recipient of the NIH Commendation Medal, began serving as the Acting Deputy Director in July; Dr. Mike Friedman, Acting Associate Director of the Radiation Research Program, returned to being Associate Director of the Cancer Therapy Evaluation Program; and Dr. Eli Glatstein assumed the position of Acting Associate Director of the Radiation Research Program in August.

In the Division of Cancer Prevention and Control, Dr. Thomas Glynn has been appointed Chief of the Prevention and Control Extramural Research Branch. Dr. Carolyn Clifford has been appointed Chief, Diet and Cancer Branch, of the Cancer Prevention Research Program.

There have been two departures in the Division of Cancer Treatment (DCT): in the Office of the Director, Dr. Mace Rothenberg, Special Assistant of Clinical Affairs, resigned in June and is now the Executive Director of the Southwest Oncology Group in San Antonio; and in the DCT Radiation Research Program, Dr. John Antoine, Associate Director, Radiation Research, DCT, joined the Loma Linda Cancer Institute as Director for Research and Professor in the Department of Radiation Medicine.

Dr. Broder expressed his sorrow over the loss of Drs. Robert Moore and David Byar who died on July 31, 1991, and August 8, 1991, respectively.

The Biomarkers and Prevention Research Branch and the Preventive Oncology Branch have been reorganized and established in the Early Detection and Community Oncology Program.

New Scientific Developments Within the NCI

Dr. Broder reported that the NCI held a breast-imaging workshop September 4th through 7th, which was sponsored by the Division of Cancer Treatment and the Division of Cancer Prevention and Control with input from the Division of Cancer Biology, Diagnosis, and Centers. The workshop included discussion of new technology and a review of quality assurance issues; a report is expected soon. On September 12th in Bethesda, Maryland, the NCI also held a workshop on cancer epidemiology in Latin America and the Caribbean.

Dr. Broder informed the Board that the NCI installed an eight-processor Cray Y-MP supercomputer at the Frederick Cancer Research and Development Center in Frederick, Maryland. He added that this computer will be considered a national resource to be used for computational chemistry and research in pursuit of new drug designs and to search for cures for cancer, AIDS, and other diseases. Dr. Broder commented that the NCI feels that the addition of this computer will allow the Institute to do "cutting edge" research.

Dr. Broder stated that 1991 marks the twentieth anniversary of the National Cancer Act, which was passed on December 23, 1971, and it is an appropriate time to commemorate this Act in Congress. He explained that Congressman Henry Waxman is holding a hearing on the achievements of the National Cancer Program at which Dr. Broder and Dr. Harold Freeman will testify. The American Cancer Society has planned a number of events in conjunction with the hearing, with an emphasis on patients who have survived cancer. A cancer survivor from each of the Cancer Society's divisions nationwide has been invited. There are plans for these attendees to have lunch with their respective Senators and Congressmen and attend a reception given by Vice President and Mrs. Quayle.

Dr. Broder referred to an article in the August 21st issue of the *Journal of the National Cancer Institute* (JNCI) on smoking-attributable cancer mortality in 1991 and explained that the lung cancer risk for men has doubled, while the risk for women has increased more than four-fold. NCI, Dr. Broder stated, will introduce its new American Stop Smoking Intervention Study for Cancer Prevention (ASSIST) Program on October 4th. ASSIST is a collaboration between NCI and the American Cancer Society, as well as State and local health departments, that is expected to reach 90 million Americans in an effort to accelerate the current downward trend in smoking. There will be a particular focus on smoking cessation among heavy smokers, women, medically underserved and less-educated groups, and minorities.

Trans-NIH Strategic Plan

Dr. Broder explained that Dr. Bernadine Healy, in her first year as NIH Director, has initiated the first trans-NIH strategic plan. The NCI is in the process of developing a document that can map out scientific policy strategies for the 1990s and beyond. In the development of this plan, a mission statement for the NIH has evolved: "Science and the pursuit of knowledge to extend healthy life and reduce the burden of illness." Also part of this plan are four goals: 1) to foster innovative research strategies designed to advance the nation's capacity to improve health; 2) to provide a scientific base that will strengthen the nation's capability to deliver more health care to enhance the quality of life for its citizens; 3) to provide a scientific base that will strengthen the nation's economic competitiveness and ensure a continued high return on the public's investment; and 4) to become and continue to be a model for public accountability, scientific integrity, and social responsibility.

Other priorities regarding basic biomedical and behavioral research, clinical research, as well as scientific career development, women and minority scientific research participation, and research infrastructure are included in the planning effort. Each of the Institutes, Centers, and Divisions (ICDs) at NIH participated in developing initiatives; Ms. Judy Whalen led NCI's

participation. Eleven science panels were set up with representatives from all of the categorical Institutes, intending to provide a trans-NIH perspective. Panels were also developed to address 11 policy issues facing NIH in the 1990s. As an aside, Dr. Broder mentioned that the panel on vaccine development discussed the development of cancer vaccines for primary and secondary prevention as one of its topics. Ms. Whalen will be able to provide draft reports of these panels, and Dr. Broder invited the Board's participation in drafting issues. He explained that the NCAB and other advisory groups will be asked to comment on the plan in the winter. A series of regional meetings will provide a forum for input into the plan by the scientific community and other interested parties. The goal is to present a completed plan to Congress by spring of 1992.

Shannon Awards

Dr. Bernadine Healy has announced the first round of the James A. Shannon Director's Awards, which will provide approximately $30 million to help maintain the work of those scientists whose NIH grant applications fell just below the pay line. The first recipients of the Shannon Awards are approximately 310 scientists at over 146 institutions throughout the United States—about 55 NCI grantees—who were nominated by NIH program staff with the concurrence of Institute Directors.

Discussion of the NCI Budget

Dr. Broder then moved to a discussion of the NCI budget. The NCI operated with a budget of $1.713 billion in fiscal year (FY) 1991 ($80 million more than in fiscal year 1990).

Funding for the 300 Shannon Awards (the majority of which are 24-month, $100,000 awards) supported in fiscal year 1991 comes from the NIH Director's Discretionary Fund and the 1 percent NIH Director's Transfer Authority. The NCI contributed $4.8 million through the 1 percent transfer mechanism and NCI grantees received $2.7 million in Shannon Awards. In addition, the NCI received $2.5 million from the Discretionary Fund, for a total of $5.2 million for its grantees.

Because of NCI's statutory authority to administer construction grants, NCI has become the effector arm for certain construction grants. Approximately $17 million has been transferred to NCI via an intra-agency agreement from NIH for use in administering and awarding construction grants. More than half of these funds will be administered to Jackson Laboratories for their animal production facility. The remainder of funds were used for awards to the Universities of Colorado and Kansas. NCI itself obligated $5.4 million for grant construction renovation projects.

Dr. Broder explained that he did not know the final operating budget for fiscal year 1992 because both the House and the Senate have voted on a bill for 1992, but a conference between the two chambers of Congress has not occurred. He added that if a bill is not enacted by October 1, NCI will probably begin the new fiscal year under a continuing resolution.

Dr. Broder reported on NIH and NCI in the 1992 Congressional mark-up process. In fiscal year 1991, the NIH operating level is approximately $8.3 billion and the NCI operating level is approximately $1.714 billion. The President's budget for NIH in fiscal year 1992 is approximately $8.775 billion, about a 6 percent increase. The NCI has an approximate operating level of $1.810 billion in the President's budget, about a 5.6 percent increase. In the House report, NIH received approximately $8.8 billion, a 6.6 percent increase; NCI received approximately $1.831 billion, which is about a 6.8 percent increase. Dr. Broder then presented the Senate report, which would provide NIH with just under $9 billion (8.5 percent increase) and NCI with more than $2.010 billion, representing a 17.3 percent increase.

Concerning the NCI, the House proposed an overall increase of $38 million and approximately $17 million in redirections within the bill. Specifically, a proton beam facility and equipment (about $4 million) are mentioned, as well as women's health issues, poverty and cancer, cancer vaccine research, and the maintenance of Community Clinical Oncology Programs (CCOPs). The House is providing a $30 million increase for breast, ovarian, and prostate cancer research. It is also designating a $2 million increase for pediatric AIDS. Also mentioned are requests for an aging conference; a psychosocial demonstration study project; and international collaborations in cancer prevention, information, and dissemination and training.

Included in the Senate's bill is a redirection of $27 million. The following specific appropriations are included: $40 million for women's health, ovarian, and cervical cancer; $20 million increase for basic research in breast cancer; $10 million increase for six specialized programs of research excellence (P50 program); no less than $132 million increase for breast cancer; $5 million increase for cervical cancer; and $5 million for ovarian cancer. There is a request for NCI to establish a program of research excellence and collaboration with the National Institute on Diabetes and Digestive and Kidney Diseases. Other discussions concern funding for the Community Clinical Oncology Program at $16.5 million, a retrovirus research center, a $4 million increase for pediatric AIDS, information dissemination, cancer centers, poverty and cancer, gene therapy, and cancer vaccine research. Also, a number of other activities are mentioned, involving Native Americans, Hawaiians, American Samoans, American Indians, and Alaskan Natives, as well as behavioral research, longitudinal studies of DES-exposed women, and neurofibromatosis. There is a specific requirement to establish a Matsunaga-Conte Prostate Cancer Center.

Dr. Broder stated that two issues are particularly important in regard to the Congressional appropriations: 1) Congress will periodically designate other Institutes to assume certain types of cancer-related research; and 2) the National Institute on Diabetes and Digestive and Kidney Diseases has been asked to begin programs in prostate diseases (cancer would be one component), and the Neurology Institute has been asked to begin programs in brain tumors.

Dr. Broder then focused on research project grants, noting that the total-funded research project grant pool was just under $740 million in 1990. The estimate is $790 million for 1991. In 1992, the President's budget provides approximately $846 million, and the House proposes about $840 million. A projection of the total number funded in 1990 was about 3,016; the estimate for 1991 is 3,073; approximately 3,165 are in the President's budget for 1992; and 3,215 are in the House budget in 1992. About 728 research project grants were funded in 1990, and it is estimated that 840 will be funded in 1991. Slightly less than 900 new and competing applications will be funded in 1992 according to the President's budget, and slightly less than 950 according to the House budget. Dr. Broder explained that the final estimate according to the Senate budget has not been released. The percentage of funding for the competing pool is as follows: 25 percent in 1990, an estimated 29 percent in 1991, 30 percent in the President's budget for fiscal year 1992, and 32 percent in the House.

Dr. Broder concluded his budget presentation by saying that the Program Project Grant Program has continued to move forward. He cautioned the Board that there will be continued stresses on the Program Project Grant line and expressed his hope that discussions about options for protecting investigator-initiated research that involves multiple collaborations will continue.

Twentieth Anniversary of the National Cancer Act

Dr. Broder showed some archival slides to remind the Board that, although it has been 20 years since the enactment of the National Cancer Act, the National Cancer Institute has existed since 1937 and is the oldest categorical Institute. A slide of Dr. Sarah Stewart, an NCI scientist noted for her work on the relationship between viruses and cancer, was included, as

well as slides of Dr. Henry Caplan, Dr. Vincent T. DeVita, Dr. Robert Huebner, Dr. Howard Temin, and Dr. David Baltimore, among others.

Dr. Broder announced that there would be at least two events commemorating the 20th anniversary of the National Cancer Institute. The first is a symposium on viruses and cancer on December 16th that Dr. Richard Adamson and Dr. Jack Gruber are coordinating.

Dr. Broder suggested that the NCAB should coordinate an event for the next meeting that would highlight certain aspects of the National Cancer Institute. He recommended that there not be a celebration for the 20th anniversary of the National Cancer Institute because the mission has not been accomplished, but, rather, that there be a commemoration.

Dr. Sydney Salmon proposed a resolution for the NCAB to forward to the House/Senate budget conference committee. The resolution commended the United States Senate for its recommendations for the NCI's fiscal year 1992 budget. The resolution was tabled pending revision of the language. Dr. Salmon said he would reword the resolution and propose it again at a later time during the meeting.

V. LEGISLATIVE UPDATE—MS. DOROTHY TISEVICH

Ms. Dorothy Tisevich, NCI's legislative liaison, presented a brief update on recent legislative activities related to NCI. Dr. Ihde, accompanied by Drs. Adamson, Chabner, Greenwald, Rabson, and Ford, testified at a hearing on breast cancer, chaired by Senator Brock Adams (D-WA). Senator Adams has introduced bills to authorize additional funds for breast cancer research at NCI and to improve the quality of mammography.

Regarding taxol, Dr. Chabner testified before Representative Ron Wyden (D-OR) on July 29th. Mr. Wyden is concerned that exclusive agreements between Federal agencies and Bristol-Myers Squibb are creating a monopoly on this drug. Mr. Reid Adler of the NIH Office of Technology Transfer also testified at this hearing regarding NIH policies on collaborations with industry. Other witnesses included representatives from the U.S. Department of Agriculture, U.S. Interior Department, Bristol-Myers Squibb, Hauser Chemical, and two breast cancer patients. The Departments of Interior, Agriculture, and Health and Human Services entered into a joint memorandum of understanding to facilitate the rapid development of taxol.

Dr. Martin Brown, an economist in the Division of Cancer Prevention and Control, briefed Senator David Durenberger (R-MN) on the cost and availability of high-quality screening mammography in the United States. Drs. Brian Kimes and Andrew Chiarodo, Division of Cancer Biology, Diagnosis, and Centers, briefed Senator Ted Stevens (R-AK) on NCI activities in prostate cancer. Senator Stevens, recently diagnosed with prostate cancer, is responsible for an amendment to the appropriation bill to designate NCI's prostate SPOREs as Matsunaga-Conte Prostate Cancer Research Centers.

Ms. Tisevich called the members' attention to their legislative update packages, which include information on construction funds that appeared in the Energy and Water Development Appropriation. These funds include $4.8 million for the Oncology Center at the Medical University of South Carolina for Department of Energy-funded cancer and birth defect surveillance near the Savannah River site; $10 million for a Research Institute at Loma Linda University Medical Center for proton beam therapy with monoclonal antibodies; and $10 million for the Cancer Research Center at Indiana University School of Medicine for research into the causes and treatment of cancer. The Department of Energy is also directed to review funding requirements for boron neutron capture therapy for fiscal years 1992 through 1996.

Similar to a bill introduced by Mr. Waxman in the House (D-CA), Senator Kennedy (D-MA) introduced the NIH reauthorization act of 1991 on July 22nd, which includes many of the same provisions which were included in last year's bill but were not included in the version of the reauthorization bill that was enacted. The difficulty in passing a more complete bill was due to language in the House bill concerning human fetal tissue transplantation research. This year's House bill includes a provision directing the Secretary of Health and Human Services to fund meritorious projects, thus overturning the moratorium. The Kennedy bill, in its current form, continues the moratorium, but it is expected that it will be revised and a clean bill will be introduced that would overturn the ban. The White House has threatened to veto the bill if this language is adopted.

In the House, the Committee on Energy and Commerce chaired by Representative John Dingell (D-MI) [ranking minority member is Mr. Norman Lent (R-NY)] has jurisdiction over NIH programs; the Subcommittee on Health and the Environment is chaired by Henry Waxman (D-CA) [ranking minority member is Representative William Dannemeyer, (R-CA)]. In the House bill, the total amount that would be authorized to the NCI for fiscal year 1992 would be $2 billion, and necessary sums thereafter. Of the amount appropriated, there is a requirement to spend 10 percent on cancer prevention and control programs; however, there is a special provision for fiscal year 1992 that would require the NCI to fund prevention and control at 75 percent of the amount that is identified in the bypass budget ($136.7 million of $182.3 million). Basically, the NCI would be required to redirect about $47 million into prevention and control from other programs. It also requires that $50 million be spent on basic research in breast cancer and development of a test for early detection of ovarian cancer.

The Senate Committee on Labor and Human Resources has jurisdiction over NIH programs and is chaired by Senator Kennedy (D-MA)—ranking minority member is Senator Orrin Hatch (R-UT). There is no subcommittee with jurisdiction in this area. The Senate bill authorizes the appropriation of $2.018 billion for research activities, $156.6 million for prevention and control, and $75 million for breast cancer and cancers of the female reproductive system—one-third for basic research on the causes of breast cancer; one-third for SPOREs in breast and prostate cancer, clinical research, and information and education; and one-third for ovarian and other cancers of the reproductive system. The total amount authorized by the Senate bill is $2.25 million for fiscal year 1992, with funds as necessary through fiscal year 1996—a higher level of funding for a longer time period than the House bill.

Both chambers of Congress address women's health research concerns, requiring the establishment of an Office of Research on Women's Health and the inclusion of women and minorities in NIH clinical trials.

The House bill contains several new provisions: a limitation on indirect cost expenditures; a requirement that peer review must include consideration of human subjects protection and ethical implications of research; and a requirement for data sharing on safety and effectiveness of drugs, medical devices, treatments, or other products or substances.

Ms. Tisevich pointed out the Ethics Reform Act of 1989, which imposed a total ban on the receipt of honoraria by all Federal employees and officers (except Senators, Senate employees, and special Government employees), effective January 1, 1991.

Senator John Glenn (D-OH) and Representative Barney Frank (D-MA) have introduced bills that would allow Government employees below grade 15, as well as certain career employees above grade 15, to accept payment for appearances, speeches, and articles that are unrelated to the employee's official duties. The maximum amount of the payment would be $2,000. Ms. Tisevich explained that there is concern about how standards developed by the

Office of Government Ethics will affect the interpretation of an activity in relation to an employee's official duties.

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

- The Farm Animal and Research Facilities Protection Act, which would make it a Federal crime to enter an animal facility to commit offenses (including stealing or damaging animals or property), introduced by Representative Charles Stenholm (D-TX)
- Tobacco Product Education and Health Protection Act of 1991, introduced by Senator Kennedy, in which an interagency committee on smoking and health (possibly including the NCI) would coordinate activities of Federal and private agencies.
- Legislation introduced by Representative Pete Stark (D-CA) to extend a tax credit of 50 percent for clinical testing expenses for orphan drugs and impose a windfall tax on orphan drugs if they become excessively profitable.
- The Access to Lifesaving Therapies Act, introduced by Representative Tom Campbell (R-CA), providing expedited approval of drugs or biologics for the treatment of individuals with life-threatening diseases including AIDS, Alzheimer's disease, cancer, cardiovascular diseases, and Parkinson's disease.
- Legislation introduced by Representative Morella (R-MD) and Senator Rockefeller (D-WV), that would allow Federal agencies to copyright software developed under Cooperative Research and Development Agreements (CRADAs).

Ms. Tisevich reported that during the 102nd Congress, more than 200 bills related to women's health issues have been introduced. She pointed out the section on women's health in the legislative update package, including several measures such as the Women's Health Equity Act, that would affect NIH and ADAMHA programs.

Ms. Tisevich reminded members that October 1991 is Breast Cancer Awareness Month, and several activities have been planned by the National Alliance of Breast Cancer Organizations, the Breast Cancer Coalition, the American Cancer Society, and others. On October 8th, 175,000 letters urging increased funding for breast cancer research will be delivered to Capitol Hill. Ms. Tisevich's office is working with the Office of Cancer Communications to develop an information packet to assist Congressional staff in responding to these letters. Senator Connie Mack (R-FL) plans to broadcast a one-hour live question-and-answer session on breast cancer in southern Florida on September 26th—Dr. Joyce O'Shaughnessy of the Clinical Oncology Program in the Division of Cancer Treatment, will represent NCI. Senator Mack has introduced a bill to extend a tax credit to taxpayers for certain cancer screening tests.

Dr. Calabresi expressed his concern about the "compartmentalization" of bills in the budget. Ms. Tisevich replied that some groups, particularly the advocates for women's health issues, are managing to strongly convey their messages. She explained that there was no way to avoid some of the efforts directed toward the women's health issues; the NCI is less likely to receive directive language if it is more proactive in spreading its messages. Dr. Broder responded that he acknowledges that Congress recognizes certain constituency groups and has budgetary constraints, but he is concerned about a special form of earmarking—when directive language is used to award a specific grant to a specific institution. He feels that this process nullifies peer review, and the NCI should defend its programs and interests and discourage naming a specific institution to receive a priority or grant. Dr. Broder also stated that the Institute should consider carefully language in a Congressional appropriation or authorization;

for instance, he agreed that more attention should be given to the association between DES and certain diseases, as Congress suggested.

Dr. John R. Durant asked Dr. Broder about the difference between Board members being classified as regular Government employees or special Government employees, regarding the Ethics Reform Act of 1989. Dr. Broder answered that a special Government employee is considered a full-time Government employee. He explained that, basically, the Government wants to ensure that no Government employee, regardless of status, is using his or her office for personal gain. He gave the example that even if one is acting on behalf of his or her institution, it is considered personal business—not official business. Dr. Calabresi suggested that the Board continue this conversation during the New Business session with Dr. Elliott Stonehill. Ms. Barbara Bynum added that it might be helpful to look at the "New Business" section in the notebooks, which delineates the categories of Federal employees.

VI. ONCOGENES, CELL CYCLE REGULATION, AND ANTINEOPLASTIC DRUGS—DR. GEORGE F. VANDE WOUDE

Dr. Werner Kirsten introduced Dr. Vande Woude as the Director of the Basic Research Program at the Frederick Cancer Research and Development Center. Dr. Vande Woude's primary scientific interest is in the molecular biology of cancer. Of particular interest are his studies on the structure and function of the transforming gene of the Maloney sarcoma virus and its cellular counterpart, the *mos* proto-oncogene. A significant aspect of this oncogene is its role in the regulation of meiosis. Dr. Vande Woude and his colleagues have discovered that the gene encodes a protein that acts as an initiator for oocyte maturation and is an active component of cytostatic factor (CSF), an activity responsible for metaphase arrest in vertebrate eggs. It is this activity, Dr. Kirsten stated, that makes this proto-oncogene important to cancer research and is the topic of Dr. Vande Woude's presentation.

Dr. Vande Woude began his presentation by focusing on and reviewing some of the achievements in the past five years that have led to a greater understanding of the role that genes play in cancer. For many years, Dr. Vande Woude said, there has been an interest in determining the molecular basis of the transformed phenotype, including what is responsible for morphological alteration and loss of contact inhibition. One tumor cell phenotype, genetic instability, Dr. Vande Woude said, is of specific interest because it is responsible for tumor cell progression. No reasonable explanations have been proffered. However, since so many different oncogenes can produce the transformed phenotype, it is expected that there is a common explanation involved. By understanding the molecular basis of the transformed phenotype, researchers hope to find new strategies for improving diagnostics and treatment. Dr. Vande Woude felt that understanding the normal function of the *mos* proto-oncogene has led to an understanding of how it can transform cells and this has provided a possible explanation of the transformed phenotype, including why tumor cells are genetically unstable. This same hypothesis can also explain why antineoplastic drugs work.

Dr. Vande Woude began with a brief review of the recently discovered genes that are responsible for regulating procession through the cell cycle. Referring to Dr. Yoshio Masui's experiments 20 years ago, Dr. Vande Woude said that Dr. Masui showed that there was an activity present in maturing oocytes that promoted meiotic maturation. Dr. Masui called this activity maturation promoting factor, or MPF. Since that time, it has become clear, Dr. Vande Woude said, that MPF is a universal regulator of M-phase (either meiosis or mitosis) and has maintained its function in organisms through one billion years of evolution from yeast through man, which emphasizes the importance of these regulators of cell division to this fundamental biological process. MPF consists of two proteins, $p34^{cdc2}$ plus B cyclins. MPF is a kinase that is active during M-phase and is believed to be responsible for nuclear envelope breakdown, chromosome condensation, and formation of the spindle. During the past several years, cyclins have been shown to regulate the start of DNA synthesis and entry into mitosis. Moreover,

several have been implicated as possible oncogenes in human cancers thereby showing a direct connection between cell cycle regulators and tumor cell progression.

Dr. Vande Woude explained that 11 years ago his laboratory showed that when the *mos* proto-oncogene is constitutively expressed in somatic cells, the cells become morphologically transformed, demonstrating that the normal product induces the transformed phenotype. In 1985, it was discovered that the *mos* gene is expressed in high levels in germ cells. Dr. Vande Woude stated that *mos* is required for oocyte maturation in vertebrates and is the active component of CSF, an activity discovered 20 years ago by Dr. Masui and believed to be responsible for arresting oocyte maturation at metaphase II of meiosis, which corresponds to a mature unfertilized egg. To demonstrate the presence of CSF, the activity responsible for M-phase arrest, Dr. Masui took a cytoplasmic extract from unfertilized eggs and injected it into one blastomere of a two-cell embryo. The injected blastomere was arrested in cleavage, while the uninjected blastomere continued to cleave. It was discovered that the *mos* product has the same activity and also arrested blastomeres from cleaving. This and other experiments led to the conclusion that *mos* is an active component of CSF. Since CSF is believed to arrest M-phase by stabilizing MPF, this meant that the proto-oncogene directly or indirectly influences the cell cycle regulator MPF. Also important, this discovery showed that *mos* functions at metaphase, the last stage of the cell cycle. Thus, the *mos* product is expressed immediately when oocytes are induced to mature and stays at high levels in the unfertilized egg. The product is, however, rapidly and specifically degraded upon fertilization. This led to the question of how a gene that normally functions at the last stage of the cell cycle could be responsible for transformation. The proposed answer, said Dr. Vande Woude, is that it is the expression of M-phase activities throughout the cell cycle that is responsible for the transformed phenotype and converting the cell into a transformed cell.

Dr. Vande Woude then described studies that suggested that the *mos* product is involved in microtubule modification. He presented slides showing that *mos* colocalizes with tubulin, both in the spindle pole region of cells in mitosis and in the mid-body aster regions of cells in early telophase. The most convincing evidence that *mos* is associated with tubulin has been obtained from experiments with cells treated with nocodazole, which destroys microtubule structures and leaves residual tubulin oligomers. These experiments have revealed that the *mos* cytoskeletal distribution is also disrupted by the drug and that the product colocalizes with the residual tubulin oligomers. Dr. Vande Woude said his laboratory's working model is that the normal function of *mos* is to contribute to the formation of the spindle pole in maturing eggs.

Taxol, a microtubule-stabilizing drug, was found a number of years ago to display CSF activity, indicating a connection between taxol and *mos* proto-oncogene function. Moreover, Dr. Vande Woude discussed similar experiments in mouse eggs. He showed slides of normal, matured mouse eggs compared to mouse eggs in which the endogenous *mos* had been destroyed. In the latter eggs, the maturation process had been arrested. Dr. Vande Woude then compared this slide with one that showed a mouse oocyte treated with taxol at approximately the same stage. The two slides showed striking similarities in morphology, further suggesting a connection between *mos* function and the effect of taxol on microtubules.

Dr. Vande Woude stated that M-phase tubulin modification by mos during interphase of the somatic cell cycle could provide the first explanation of the transformed phenotype. Thus, the altered cell morphology and loss of contact inhibition of tumor cells may represent an activity normally displayed by daughter cells during M-phase of cytokinesis. Further, it is not only *mos* that has M-phase, but the products of other oncogenes, such as *src* and *ras*, also have M-phase function and may transform cells by displaying this activity in somatic cells during interphase. Dr. Vande Woude proposed that the molecular basis of morphological transformation may be due, in general, to the expression of M-phase activities during interphase. The cooperation of oncogenes has been proposed as a model for tumor progression. Dr. Vande Woude said that this cooperation can be explained by oncogenes that influence the two major cell cycle control

points. Thus, one of the oncogenes promotes entry into DNA synthesis, while the other contributes M-phase activity to interphase of the cell cycle. Alterations in tumor cell morphology and changes in nucleus structure are two properties of transformed cells that can be attributed to oncogenes with M-phase activity.

Genetic instability is perhaps the most important property of tumor cells, since it is responsible for this malignant progression. Since *mos* normally functions downstream in the cell cycle, and because it directly or indirectly stabilizes MPF p34 kinase activity, it may compromise the ability of cells to arrest at "checkpoints." Checkpoint genes were discovered in yeast and represent genes that cause progression in the cell cycle to pause while the fidelity of the process to that point is checked. Dr. Vande Woude believes that genetic instability in tumor cells is also due to the expression of oncogene M-phase activity during interphase of the cell cycle. He proposed that because certain oncogenes have downstream M-phase activity, they promote the cell to override the checkpoint function, which therefore makes the cell vulnerable to damage. Compromised checkpoint functions could explain how point mutations, gene amplifications, deletions, and chromosome translocations can contribute to tumor progression in a single tumor lineage.

If oncogenes and tumor suppressor genes are responsible for malignant disease, then they must render tumor cells vulnerable to antineoplastic drugs. Dr. Vande Woude proposes that genetic instability that leads to tumor progression, is caused by oncogenes compromising of checkpoint function. The same mechanism could account for how antineoplastic drugs preferentially target tumor cells over normal cells. His theory is that "the ability to recognize the damage done by antineoplastic drugs like taxol is compromised in the transformed cells, but not in the non-transformed cells, and therefore allows the tumor cells to grow," thereby specifically targeting the transformed cells.

In an example of how this works, Dr. Vande Woude said that if transformed cells are mixed with nontransformed cells at the ratio of 1:100, 1:1,000, or 1:10,000, the expected decrease is seen in the number of colonies representing the overgrowth of the transformed cells. However, if this is done in the presence of taxol, transformed cells have been either destroyed or prevented from growing. An assay has been developed to determine whether a similar effect can be achieved with different drugs.

Dr. Vande Woude concluded his presentation by expressing his belief that experiments on checkpoint genes to determine whether they are compromised in tumor cells will be an important area of research.

Dr. Temin asked under what earmarked program this research would fall. Dr. Vande Woude responded that it would fall under the category of basic fundamental research on the cell cycle. He added that he thought it was nonproductive to try to segregate the various disciplines.

Dr. Broder asked what role *mos* plays in the alignment of chromosomes during meiosis and in the recognition of maternal and paternal chromosomes. Dr. Vande Woude stated that the answer to this question was not known; however, he believes that it may have something to do with the spindle pole.

Dr. Chabner asked whether *mos* had any effect on tubulin polymerization. Dr. Vande Woude responded that his laboratory was investigating this possibility. It is a high priority and can now be tested, since they have just succeeded in making pure soluble *mos* protein.

Dr. Salmon then re-introduced a resolution to urge the House/Senate Conference Committee to reach agreement on the NCI's FY 1992 budget as outlined in the NCI Bypass Budget. The resolution was passed unanimously.

VII. TAXOL: AN UPDATE—DR. BRUCE CHABNER

Dr. Chabner discussed the current status of taxol as an update of his presentation at the May 1991 Board meeting. He commented that it was appropriate that his discussion followed the presentation on the *mos* oncogene, since taxol's actions are similar—small molecules that can mimic the function of proteins.

Dr. Chabner reminded the audience that taxol is a drug developed at NCI that went into clinical trials approximately eight years ago. Until it was discovered in 1989 that taxol had activity in ovarian cancer, particularly in relapsed patients, its clinical development was slow. Three studies have been conducted since that time which confirm activity on patients who have failed cisplatinum therapy. Taxol is unique in that it promotes the assembly of microtubules, similar to the effects of the *mos* oncogene.

Two years ago, NCI advertised for a commercial sponsor for the drug under a Collaborative Research and Development Agreement. Bristol-Myers Squibb, a major pharmaceutical firm, was the best of four applicants. In January 1991, an agreement was signed with this company. Dr. Chabner explained that Dr. Broder's public recognition of the supply problem with taxol has led to several memoranda of understanding, which will allow Bristol-Myers Squibb to have access to trees on United States forestry lands.

Dr. Chabner presented a slide of *Taxus brevifolia*, a small shrub that grows in the Northwest. Related species are found worldwide, but it is particularly abundant in forests in Oregon, Washington, and British Columbia. It primarily grows among the larger trees used for lumber and, thus, is ordinarily cut as part of the lumbering process. In the past, it has also been disposed of by burning because it had little commercial value.

Since the signing of the CRADA in January, Bristol-Myers Squibb has actively pursued the procurement of taxol and an increase in supplies. The current goal is to harvest 750,000 pounds of taxol bark.

Dr. Chabner presented his next slides, depicting the harvesting process in which the logs are cut, trimmed, and stripped of bark. The bark is rolled off as a sheet, pulverized, bagged, and shipped to the processing center. Drug extraction occurs at the processing center, where the bark is further pulverized to extract a gum or paste, which is fractioned by column chromatography and purified.

Each year, approximately 5,000 ovarian cancer patients die. The projected 750,000 pounds of bark will yield about 25 kilograms of taxol—enough to treat about 10,000 to 15,000 patients. Taxol is also active in breast cancer. Dr. Chabner explained that there is an even greater need for taxol since 50,000 breast cancer patients die each year who would be eligible to receive the drug.

As a result of meetings held earlier this year, the Department of Interior and the Department of Agriculture agreed to provide members of the CRADA access to trees on Federal lands. A memorandum of understanding was signed among the agencies, and a separate memorandum between those agencies and Bristol-Myers Squibb was signed to allow exclusive access to the *Taxus brevifolia* that would be harvested as part of the normal harvesting of trees on Federal land. Dr. Chabner reported that the CRADA is halfway toward its goal of harvesting 750,000 pounds of bark a year. The drug will be released for compassionate use for ovarian cancer through the cancer centers in October 1991.

Because of the complex harvesting process, supply limitations, poor and environmental opposition, alternative sources for the drug are being investigated. The supply of *Taxus*

brevifolia on Federal lands is estimated to be between 20 to 30 million trees, and the CRADA is harvesting 35,000 trees a year.

A Request for Application (RFA) was issued in 1990. Of 61 applications, 13 have received funding. Three applications were received Shannon Awards of $100,000 over the next two years. The NCI obligated $2 million toward these awards and the NIH, $150,000. Applications addressed semisynthesis of the drug from precursors, plant culture, alternative plant sources, formulation, taxol metabolism, and taxol's mechanism of action.

Dr. Chabner then highlighted issues raised at the July 29th Congressional hearing on taxol that Ms. Tisevich mentioned. In answer to questions about public protection regarding the price of taxol and how this will be enforced, Dr. Chabner explained that there is a unique fair pricing clause in the CRADA, but there is no mechanism for enforcement of fair pricing at this time. It was asked if Bristol-Myers Squibb has a monopoly on taxol-related research. Dr. Chabner answered that the company does not have a monopoly and the drug is not patented; however, it does have exclusive access to NCI data and exclusive cooperation with the NCI. Dr. Chabner stressed the difficulty of attracting a commercial sponsor to participate in the development of a product if they do not have some guarantee to market exclusivity. A French pharmaceutical firm currently is testing an analog of taxol called taxotere. The NCI is cooperating with this company to set up clinical trials, and is encouraging research activities that could lead to analogs or related compounds through the NCI grants program. It was questioned if the CRADA discouraged competition. Dr. Chabner replied that the CRADA includes a provision to provide other companies with small amounts of yew bark to use for their own commercial or scientific investigations. The agreement obliged Bristol-Myers Squibb to conduct a survey of yew trees on Federal lands to obtain supply information.

Dr. Chabner interpreted the CRADA as an implementation of the Federal Technology Transfer Act and as a test case for how an unpatented compound can be developed with a commercial partner. The first phase of the agreement is going well, especially now that the supply problem has been alleviated.

Clinical Trials

Four studies on breast cancer are being conducted at the present time. One was completed at M.D. Anderson in which 25 patients were entered who had failed primary therapy for metastatic disease. There were 14 responses—three complete responses and 11 partial responses—with an overall response rate of 56 percent. A trial is being conducted to confirm this single-agent activity in metastatic breast cancer at Memorial Sloan-Kettering. This study has reported six responses of 12 evaluable patients for a 50 percent response rate. NCI has begun a study of primary therapy with G-CSF to reverse the leukopenia associated with taxol and adriamycin in patients previously untreated who have metastatic diseases. Only four patients are evaluable—two responses, and two are still on treatment. A similar study that began in August is being conducted at M.D. Anderson.

Other Phase II taxol clinical trials are underway in several tumors: colon; nonsmall-cell lung; small-cell colon; prostate; upper GI; and pediatric solid tumors. Responses have been noted in both nonsmall-cell and small-cell lung cancer. Dr. Chabner predicted that results seen in the breast cancer studies alone will escalate the need for the drug tenfold.

There is an approved protocol at Ohio State University to initiate the compassionate release of taxol. One kilogram of taxol will be released this year, which is enough to treat at least 500 patients. Dr. Chabner stated that there is a wait for the cancer centers to submit their protocols and they have been urged to facilitate their processes of approval. The Ohio State study will begin in the first or second week of October, and UCLA and the University of Pennsylvania are close to beginning their studies.

Dr. Chabner mentioned that an important innovation of the CRADA is that it maintains a treatment referral center which provides information and alternatives for patients who are not eligible for these protocols and are patients with ovarian cancer who have failed other therapies.

Referring to Dr. Chabner's notes that suggest taxol is located in the heartwood, Dr. Erwin Bettinghaus asked if it is located lower or higher in the trunk, and if the root system has been examined. Dr. Chabner replied that some of the plant culture methods actually use cells from the roots, and they do produce taxol.

Responding to Dr. Howard Temin's questions, Dr. Chabner stated that taxol was originally discovered in the Natural Product Contract Program in Developmental Therapeutics. In answer to a second question by Dr. Temin regarding protection of the old growth forests, Dr. Chabner explained that the lumbering industry has not been active in environmental protection of this sort. Although the Environmental Defense Fund has been active in protecting species such as the spotted owl, it has favored and supported the yew harvesting program. In general, the environmentalists have been supportive.

Dr. Becker expressed his concern that taxol is rarely described as a toxic agent. He feels that people will believe that taxol is a panacea when, in fact, there are few complete remissions. Dr. Chabner explained that one rarely sees complete remissions with single agents in patients who have failed therapies. Dr. Becker continued to explain that the current information, based on tests, could render misinformed connotations. He believes that efforts should be made to grow other forms of *Taxus*. Specifically, Dr. Becker suggested that the Department of Agriculture should be persuaded to urge tobacco farmers to grow *Taxus* instead.

In response to Dr. Becker's idea, Dr. Broder first explained that the issue of altering tobacco plants so that they produce medicinal products has been raised in the past, but the tobacco growers are only a small percentage of the tobacco industry problem and are not in the "loop of profitability." Secondly, Dr. Broder reminded the Board that the Drug Development Program is usually concerned with the safety and efficacy of a drug and regulatory issues, not supply limitations. The limited supply of taxol is a relatively unique and serious problem that will emerge more frequently as research expands into biologicals. Dr. Broder then acknowledged Dr. Becker's warnings about the side effects of taxol, but stated that based on results thus far, he believes that taxol can be approved for use in refractory ovarian cancer. Dr. Broder praised Dr. Chabner and his group for the rapid response to initiating the use of this drug, which required multiple governmental agencies—the Department of Agriculture, the Forest Service, the Department of Interior, The Fish and Wildlife Service, and NCI—to work together. NCI is serving as the catalyst for competition to develop alternative resources. Dr. Broder stated that he believes total synthesis—optically and isomerically correct synthesis—of taxol is a practical possibility. He expressed his hope that every comprehensive center that receives NCI funding will participate in the distribution of taxol to increase efficiency that would be difficult for one Government authority to accomplish.

Dr. Durant asked Dr. Broder if Bristol-Myers Squibb would own the rights to a successful synthesis. Dr. Broder explained that this would not happen because when a grantee receives funding under an R01 or P01, a program is established to give a royalty to the inventor-employee of a product and the institution takes the title of the invention. The Government has certain emergency mark-in rights and can practice the invention royalty-free, but the invention would still belong to the institution that could, therefore, license the product to anyone.

Dr. Salmon commended Dr. Chabner and his staff at NCI for their work and asked if Phase II trials will be conducted on all major forms of human cancer. Dr. Chabner replied that the immediate plan is to test taxol in the most common tumors and, ultimately, test every tumor that exists.

VIII. NCI HUMAN TISSUE RESOURCES—DR. SHEILA TAUBE

Dr. Rabson began explaining that the Institute's interest in the issue of obtaining human tissue for investigators was a direct outgrowth of a concern expressed by the NCAB. He then introduced Dr. Sheila Taube.

Dr. Taube noted that technical advances in molecular biology, immunology, and genetics have made direct analysis of human tissues more feasible and desirable for the study of basic cancer biology as well as for the search for new markers for diagnosis and prognosis. In addition to concern expressed at meetings of the NCAB and the President's Cancer Panel, questions on access to human tissues have been expressed directly to the Cancer Diagnosis Branch (CDB) by researchers themselves, and comments made at peer review sessions have also focused on this need.

In the early 1980s, the CDB surveyed various NCI programs to determine what resources were available and tried to determine how tissue procurement operations were functioning in major research institutions. Some cancer centers and research institutions had tissue procurement and banking operations, but these usually had resources to serve only the investigators at those locations; only a couple of banked collections were available to the scientific community at large. The survey also found that a great deal of tissue that could be used for research was being discarded.

In 1984, the CDB convened a working group to evaluate existing resources. An important conclusion reached by the working group was that the need for additional tissue resources was unlikely to be met by existing resources or by the scientific community without NCI support. They suggested that the NCI establish a network of tissue resources; that tissues be supplied in response to users' requests rather than through tissue banks; that a limited number of standard tissue preparation methods be offered; and that only minimal patient data be provided on a routine basis.

Dr. Taube explained that banking involves collection of all available tissues and storage for an indefinite period, whereas procurement refers to the collection of specific tissues as needed and requested at a particular time. Banking without information on tissues and preparation methods needed can result in inefficient use of resources and storage space. Procurement on an as-needed basis is more efficient, but can result in waiting periods for researchers, especially when dealing with rare tumor types.

Following the working group's recommendations, the CDB issued an RFA to set up a network to procure and distribute tissues. Three institutions were funded to form the Cooperative Human Tissue Network in January 1987: the University of Alabama at Birmingham; Ohio State University, with a subcontract to the Children's Cancer Study Group to provide rare childhood tumors; and the University of Pennsylvania, in collaboration with the National Disease Research Interchange. The Network has been very successful in meeting the needs of a large number of researchers. While the major activity of the Network is to procure specimens as needed, the centers also bank rare and difficult-to-obtain tumors. Tissues are kept in this relatively small banking operation for only one or two years, following the recommendation of the working group.

After two and one-half years of operation, the CDB presented data on distribution activities to the Division of Cancer Biology, Diagnosis, and Centers (DCBDC) Board of Scientific Counselors, which supported the continuation and expansion of the Network. In 1991, five awards were made, including new awards to the three original centers. New awards were made to the Children's Cancer Study Group, which submitted a separate application in this round, and to Case Western Reserve University.

Calling attention to information in the members' notebooks on distribution of tissues through the Network, Dr. Taube showed a slide presenting updated information based on a recent meeting of the Cooperative Human Tissue Network Coordinating Committee. In 1990 the Network distributed approximately 6,000 tissues; since the renewed funding in January, there has been a dramatic increase in distribution.

Specimens provided by the Network are examined by a pathologist, and the pathology report, along with minimal demographic data, is provided to the user. Patient follow-up data are not usually available, since specimens come primarily from private practitioners rather than experimental protocols, and human subject protection concerns prevent extracting information from patient records.

This program has been enormously valuable for studies involving: correlations between specific markers, such as gene mutations and particular tumor types; the classification of tumors; definition of important genetic alterations; and the search for new oncogenes, suppressor genes, and novel tumor antigens.

There is an increasing emphasis, Dr. Taube continued, on the need for better indicators to predict which patients will benefit from specific therapeutic and preventive interventions. While basic research has defined genetic alterations associated with tumor progression, spread, and metastasis, data are not yet available to make clinical decisions based on these observations. Collection of tumor specimens with clinical follow-up data would make it possible to define and evaluate new prognostic markers. In recent years the CDB has been exploring ways to develop such tissue collections; it has become apparent that the most efficient method would be to take advantage of the careful follow-up and monitoring that is done in the context of clinical trials.

Slides prepared for biopsy or surgical specimens in clinical trials are submitted for pathological review and confirmation of diagnosis. Paraffin blocks are prepared, but are not routinely available for large studies. Frozen specimens are not generally collected. Reasons for this difficulty include the fact that patients often have their initial biopsy and surgery at hospitals that are not equipped to provide special handling of tissues. There is a reluctance to release paraffin blocks, and pathologists often do not have time to return to samples to cut additional sections. Specimens collected by research institutions are often reserved for local research priorities; clinical trial groups also depend on the tissues they collect to conduct their own research. All of these factors work against the creation of repositories of tumor samples with clinical data that could be made available for large-scale evaluation of prognostic indicators.

To be useful for studies of prognostic indicators, collections have to mature; tissues must be collected in an unbiased fashion and maintained until sufficient follow-up time has passed to detect significant differences among patients. The banking required for such a collection would be focused; only specimens from patients entered onto protocols with careful clinical follow-up and data collection would be banked. The problem of the effects of freezing on samples would also have to be addressed.

The CDB recently worked with one of the clinical cooperative groups and the Cooperative Human Tissue Network grantees to develop a proposal for collection of ovarian tumor tissues with clinical data, as well as to increase availability of ovarian tissue through the Network. The NCAB concurred with the review of this application, and it is hoped that it will serve as a model for future tumor collections.

In June of 1990, the Consensus Development Conference on Treatment of Early Stage Breast Cancer indicated that refinement of prognostic factors would depend on the effective development and use of tissue and clinical data banks. Discussions with groups involved in breast cancer trials have begun; however, the complications of setting up such a repository appear to be many. One of the biggest problems is the small size of the early stage tumors that

are of greatest interest. Another major issue is control over these limited resources. Investigators who collect tissues want control over them or at least priority access. However, since no single group can collect sufficient numbers of samples to perform definitive studies, some agreement will have to be reached.

Dr. Taube noted that it may not be feasible to pursue the more lengthy process of developing initiatives to solve these problems, and that the Institute may have to resort to administrative actions. Dr. Broder, she added, has assigned CDB the task of tracking tissue collections so that it is known what collections are available and the numbers of samples they contain. The Branch expects to have a tracking system in place within a year, and will track NCI-supported resources available to the scientific community at large. It is unlikely, she said, that the Branch will be able to track all collections developed by individual investigators, most of which are not generally available to the larger community. However, the tracking system should help avoid extensive duplication of effort and serve as an information resource for researchers.

Dr. Becker asked for clarification on the difficulty of getting paraffin sections. Dr. Taube explained that while hospitals do retain paraffin blocks, they usually do not have the staff resources for the painstaking and time-consuming work of cutting new sections for researchers. Dr. Becker added that imposing a limit on long-term banking limits the availability of specimens since few centers can aggregate any significant number, particularly of the rarer tumors. Dr. Taube answered that the CHTN is banking rare tumors, preferring to focus banking activities on specialized resources rather than inefficiently banking all tumors. She added that rare tumors, which are not associated with long-term clinical follow-up, are not retained more than one or two years if not requested, due to deterioration of tissues.

Dr. Salmon and Dr. Becker took exception to the idea that tumors cannot be kept in a usable state for long periods of time; Dr. Becker noted that freezer burn should not be an impediment to modern molecular analysis.

IX. 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. A total of 1,198 applications were received, requesting support in the amount of $276,416,755. Of these, 1,075 were recommended for funding at a total cost of $224,375,061.

X. NIH FINANCIAL MANAGEMENT PLAN—AN UPDATE—DR. JOHN DIGGS

Mrs. Barbara Bynum explained for the benefit of new Board members that the NCAB and all of the other advisory councils to NIH had been informed about NIH's plan to address Congressional concerns regarding cost containment. Part of the plan involved changes in the way extramural business is conducted and specifically in the peer review process. She noted that the Board members' notebooks contained a copy of the NIH plan. Mrs. Bynum then introduced Dr. John Diggs, Deputy Director of the NIH Office of Extramural Research, to further discuss the plan.

Dr. Diggs recalled that the Congress, in the process of making appropriations for fiscal year 1991, asked NIH to develop a financial management plan to contain the costs of biomedical research while ensuring the predictability, stability, and viability of research funding. Ten points were included in the Congressional language; a primary concern was that annual increments in the cost of research project grants had exceeded all accepted indices of inflation. Other concerns included the average duration of grant awards and the 95 percent approval rate, which was seen as eroding confidence in the peer review process.

NIH developed a financial management plan with the guiding principle that NIH is committed to supporting high-quality research relevant to the improvement of human health. Senior staff spent about six months developing a draft of the plan, which was presented to about 10 outside reviewers. After some modifications based on this review, the plan was presented to the biomedical community in a public forum on December 17. On the following day, the plan was presented to the Advisory Committee of the NIH Director.

Copies were also sent to a number of scientific societies, and the plan was discussed in many of the council meetings. In late May the plan was submitted to the Department of Health and Human Services. Changes were recommended by DHHS and by the Office of Management and Budget (OMB). The final version of the plan was submitted to the Congress in early June and was well received by the appropriation committees.

Dr. Diggs explained that he intended to provide a brief overview, using slides, of the NIH plan and then an update on activities in recent months and plans for Phase II of the plan. The concern of the Congressional appropriations committees stemmed from the large amount of mail they were receiving from the scientific community. The mail focused on the reduction in the total number of awards, which dropped from more than 6,000 in FY82 to 4,845 in FY90. The award rate dropped from 35 percent in FY88 to 25 percent in FY90, while across-the-board cuts had increased to 15 percent. Concern was also expressed about the fact that the average duration of research grants increased from 3.3 years in FY83 to 4.3 years in FY90. And, as noted earlier, concern was expressed about the rise in the average cost of awards and the 95 percent approval rate.

One suggestion made by the Congress was that the NIH maintain a stable 6,000 competing awards starting in FY91, with an average duration of four years; limit the annual increase in average cost to the Biomedical Research and Development Price Index; and eliminate downward negotiations. Dr. Diggs noted that, while the NIH has eliminated across-the-board cuts, some cuts between initial review and the actual awards have been necessary to reach the level of 6,000 awards.

Another suggestion of the Congress was to have peer reviewers look carefully at budgets and assess the appropriateness of indirect costs. Dr. Diggs noted that the NIH did not adopt this suggestion because of its strong belief that priority scores should not be influenced by concern about indirect costs.

Dr. Diggs stated that the NIH plan eliminated the use of the approval rate, using instead the award rate, which is based on the number of applications funded compared with the number reviewed, not the number approved. He observed that letters going to many applicants with the message that the application was approved but funding was not available were causing anger in the scientific community.

Another suggestion of the Congress was to set the average award duration at four years; in the first NIH plan, this was attempted, but the NIH is backing away from that commitment, and the Congress is believed to have accepted the fact that this is necessary.

The plan states that the NIH will try to limit the aggregate growth of outyear costs to 4 percent. For every award that increases at a greater rate than 4 percent, other awards will have to be held at less than 4 percent. While this rate of increase is less than the rate of inflation, Dr. Diggs noted that in the past, awards were not even being increased at 4 percent and, in fact,

sometimes faced across-the-board downward negotiations in the outyears; these across-the-board reductions, as previously stated, are being eliminated.

The NIH is asking the ICDs to limit average growth in competing awards to the Biomedical Research and Development Price Index. Dr. Diggs again noted that peer review applies only to direct costs.

Dr. Diggs continued by stating that now that implementation of the financial management plan has begun, the NIH is entering into Phase II of the plan, which involves cost management. The definition of cost management being used, he said, is "the prudent and effective management of finite resources to support an array of research programs and activities." This phase of the plan focuses on both the macro and micro levels.

The macro level involves the entire portfolio of competing awards. Consideration should be given to the mix of competing new awards, competing renewals, and Type 5s; this mix has a major impact on outyear costs. Dr. Diggs added that it is also important that each Institute, both in advisory council meetings and high-level staff meetings, look at the mix of regular research awards, program projects, FIRST awards, and MERIT awards, as well as the growth in average costs and length of research project grants. He repeated that he did not believe the NIH will be held to the requirement of trying to focus on the four-year average.

In addition to the overall portfolio, it is also important to look at the appropriate project costs of an individual grant. Each Institute will be asked to look at individual budgetary adjustments before the initial award rather than through across-the-board reductions after the awards. Attention will also be given to the impact of these budget reductions on future-year commitments, particularly when looking at the growth of a renewal award over the previous Type 5 award, or the last year of the previous award. The tentative approach to indirect costs is to lock in the indirect costs at the first year of award throughout the award's lifetime.

Dr. Diggs stated that he would continue by discussing four major efforts: a working group on the costs of research; a cost/price analysis study; an OMB study on staffing patterns and costs of NIH research grants; and further discussion of the NIH management plan.

The Department-wide working group on the cost of research is made up of Dr. Healy, NIH Director; Kevin Molley, Assistant Secretary for Management and Budget; and Dick Kusserow, Inspector General. Phase I of the group's work, characterization of the current system and formulation of definitions of the components of indirect costs, has been completed. In Phase II, the group has developed four alternative models and is in the process of evaluating these models. The impact of the current model and the alternative models will be evaluated using sample institutions, including large and middle-sized institutions and some historically Black colleges and universities.

At the completion of Phase II of the working group, a task force will be convened, composed of industry executives, university leaders, principal investigators, research administrators, and auditors. A comprehensive set of options will be presented to the scientific community at a public forum sometime around mid-December.

Dr. Diggs moved to the topic of the cost/price analysis, which, he stated, is a larger undertaking than the term implies. The first sample will be small, but will include regular research grants and program projects for which the first year's direct costs are over $500,000. The study will examine a number of methods for adjusting the costs of grants, focusing on the

reductions made by the study sections or the initial review groups. Factors to be studied will include savings from the elimination of unallowable costs, such as salaries over $120,000, and council and staff adjustments based on determination of unreasonable or unnecessary resources.

Grants Management staff will be asked to look at cost/price verification, which involves the appropriateness of costs being charged to a grant in the application. A determination will be made concerning what kind of staff resources would be necessary to do this on a routine basis rather than with a sample.

The OMB, Dr. Diggs continued, is looking at a sample of NIH grants awarded between FY85 and FY90 to closely analyze staffing patterns, particularly the pre- and postdoctoral position. Some have suggested that the NIH is supporting more trainees than under the National Research Service Awards. The OMB also wants to assess how changing staffing patterns affect the cost of NIH grants.

Dr. Diggs then moved to a consideration of major problem areas associated with the NIH financial management plan. One factor that is causing many problems is the need to award the specified number of grants required by the appropriation with finite resources.

Another problem is the misunderstanding of what is termed as "downward negotiation." During appropriation hearings, Dr. Diggs had stated that downward negotiation had been eliminated, but he was later challenged by the appropriations committees because members of the scientific community had argued that downward negotiation was continuing. The problem, he noted, is confusion over the term; what the NIH called downward negotiation has never really been downward negotiation. What have really been eliminated are across-the-board arbitrary cuts.

Dr. Diggs stated that if grants were funded straight down the line with no budgetary reductions, whether downward negotiation or cuts of another sort, the NIH would run out of money before reaching the targeted number of grants and would have a reduced success rate.

Another problem is the growth in the average cost of biomedical research grants, based on the costs of sophisticated equipment and other factors. There is also a lack of understanding of the Biomedical Research and Development Price Index.

Dr. Diggs argued that the unlikeliness of significant increases in funding, combined with changes in the nature of research, will increase pressure on NIH to focus on costs. Larger numbers of applications are being received from a larger number of investigators and institutions, and there are smaller differences in merit among the applications. One strategy is to determine the appropriate amount of indirect costs. The four models previously mentioned for determining indirect costs include:

1) The current system, which has not been working as well as it should

2) A model using part of the current system modified by introducing some of the add-ons proposed by the OMB, looking at the impact on institutions in the study

3) Another modification using a short form approach, which is now allowable for institutions receiving less than three million Federal dollars annually

4) A model using a formula rate based on geographic location, type of institution, and amount of dollars received.

Public hearings will be held after an investigation of these models.

Dr. Diggs added that computer templates are being developed to examine the ratio of equipment dollars to supplies, the ratio of personnel to other factors, etc.; these will be made available to all Institutes so that they can project and model their future portfolios.

Efforts will also be made to eliminate duplication of effort across NIH; in some cases, investigators are supported by different Institutes and equipment costs are duplicated.

Methods of forecasting are being explored to examine how decisions will impact the budget down the line. Forecasting will be used in reporting to the Congress, evaluating the impact of the NIH financial management plan, and assessing the applicability of the Biomedical Research and Development Price Index. There will be an effort to focus away from looking at the costs of funding research grants to looking at the costs of funding certain types of research.

Dr. Diggs stated that while the appropriations committees do not need an education on the costs of research, there is a need to educate other members of Congress about the real costs of biomedical research. He said that there is also a need to educate the scientific community about budget formulation.

Dr. Diggs closed by stating that the NIH financial management plan could be a great tool for the NIH to use in giving the public and the Congress the feeling that the investment in biomedical research, which is growing close to $10 billion, is one of the best investments in the nation.

Dr. Temin agreed on the problems caused by the fact that there are more competent people coming into the system, more institutions capable of doing good research, and more research problems that are approachable, but not enough money to support all of them. He expressed concern that the NIH plan would result in more money being spent on administrative costs without solving the fundamental problems, and a greater burden being placed on institutions which do not have resources to pay more of the costs of research.

Dr. Diggs acknowledged Dr. Temin's concerns and noted that alternative models to the NIH plan had been discussed which would have been much less to everyone's liking than the current plan. He added that additional questions are being raised concerning whether the nation can continue to support the research enterprise on the level to which it has developed.

Dr. Kimes observed that the NIH has "gotten caught in the numbers game" and perhaps should put more effort in talking with the Congress about numbers and what they really mean. He said that while the R01 has been held up as the ideal mechanism to meet numbers, economies in cost might be better realized where there are more interactive kinds of science going on, such as in P01s. It seems, he said, that the numbers game is pushing the NIH into a mode that is not the most beneficial to funding science in the future.

Dr. Diggs replied that the current budgeting process does lock the NIH into a numbers game and that the R01 is the basis of most of its work. He said that many people feel that

funding program projects is supporting weak science, but the cost/price analysis shows that some program projects are very cost-effective.

Dr. Stonehill asked whether it would be proper for the NIH to have workshops for the Congressional appropriations committee staffs throughout the year prior to budget time to discuss some of the issues alluded to by Dr. Kimes. Dr. Diggs said that he didn't know whether workshops had been tried, but that individual committee members had been invited to meetings at NIH.

Dr. Calabresi asked what Dr. Diggs thought was going to happen to indirect costs. Dr. Diggs replied that he believed that indirect costs "as we have seen it" will cease to exist, and that one of the four models discussed will be adopted by the end of the fiscal year. He added that once all the data have been analyzed, information on the impact of each of the models on indirect costs will be presented to the scientific community. He said he did not know whether locking in the indirect costs for the duration of the grants would be the wave of the future, but that the NIH would put the lock on "until we can see what the situation is." Dr. Diggs added that some scientists should be involved in looking at indirect costs because some feel that many of the dollars being used for indirect costs are not going to support biomedical research.

Dr. Jako asked the approximate cost, within the NIH budget, of administering the DRG Program and the Extramural Staff Program. Dr. Diggs consulted with Mr. Amoruso, who answered that 5 percent is for research management and support. Dr. Jako asked what the budget of the DRG Program is, and Mrs. Bynum said she could get that information. Asked by Dr. Jako what the cost of administering the extramural program is, Mrs. Bynum said that she could find out the cost of running DRG in terms of its line budget. She added that the question of administrative costs runs across Institute lines for two reasons: all review of grants and contracts is not done within the Division of Research Grants, and the program costs of administering grants would have to be added in. She said that rough approximations could be produced after the meeting if needed.

Dr. Diggs added that if the study sections are reducing the budgets to the level they think is necessary, additional resources will be necessary to reduce those budgets even further. It would be inappropriate, he stated, for a single program person to use "arbitrary means" for reducing the budgets. A grant-by-grant cost/price analysis would require a significant level of effort. The appropriation committees have suggested that the initial review groups are not reducing budgets enough; they have in fact suggested, he said, that when across-the-board cuts were started, review boards cut budgets proportionately less.

Dr. Becker argued that it is not appropriate to ask scientists who are reviewing grants on their scientific merit to conduct price analyses and juggle grants to make sure that the right number can be funded. He stated that this is an administrative function. Dr. Diggs repeated that he was merely reporting on what the Congress had asked for; he also noted that many scientists had expressed the feeling that it is better that study sections make the cuts and that they are nervous about administrators making those decisions.

XI. THE NATIONAL INSTITUTE ON AGING'S ACTIVITIES AS RELATED TO CANCER—DR. GENE COHEN

Dr. Ihde introduced Dr. Gene Cohen, the acting Director of the National Institute on Aging (NIA). In his introduction, Dr. Ihde noted that while persons over age 65 make up only 12 percent of the population, they develop 58 percent of all new cancers and account for two-thirds of all cancer deaths.

Dr. Cohen opened his presentation by telling the story of the myth of Tithonus. Eos, the goddess of dawn wanted to marry the mortal Tithonus, but she was concerned that she would outlive him. Eos went to Zeus to plead for immortality for Tithonus. Zeus granted Eos her wish, however he omitted one essential ingredient—eternal youth. This myth, Dr. Cohen said, points out a growing concern today—that the research on the quantity of life will outpace the research on the quality of life.

The mission of the NIA, Dr. Cohen said, is to conduct and support biomedical, social, and behavioral research and training related to the aging process, diseases, and other special needs of the aged. Dr. Cohen then showed a slide of the organizational structure of NIA and described the two intramural programs and four extramural programs that comprise the NIA. Dr. Cohen pointed out that NIA really has two focal points—older adults and aging. He explained that studying aging offers a new window to view problems relevant to all age groups. In this way, it allows the NIA to look into many of the same problems that people are looking at in other areas, from the vantage point of aging. One example is senescence of aging cells and its relationship to cancer. One of the basic questions in aging research is why senescent cells slow down and stop proliferating. In looking at why cellular proliferation slows down, new insights into cancer—where cellular proliferation increases—can be found.

Dr. Cohen then presented a slide showing the demographics of the U.S. population over 65 years of age, which is larger than the entire population of Canada—an entire nation of older adults within our nation. Within 40 years, this will double to more than 65 million people over 65 years old.

With this in mind, Dr. Cohen said that as persons age, the risk of cancer greatly increases. Surveillance, Epidemiology, and End Results (SEER) data show that people in the age group 65 and over account for 60 to 70 percent of the major cancers of the colon, rectum, pancreas, urinary bladder, and stomach. For prostate and lung and bronchus cancers, the numbers are even higher. In women, breast and ovarian cancers are especially severe in those over 65 years of age, making up nearly half of all cases. Women 65 years and older constitute 57 percent of lung and bronchus cancers. Dr. Cohen then showed a series of slides describing the rise in cancer rates for each type of cancer as a function of age. Yet, he said, there is still a dearth of information on early detection and treatment of cancer in the elderly. The magnitude of the problems of cancer in the aging population is likely to increase as the nation experiences the phenomenal growth in the elderly population in the next few decades.

Turning his remarks to the biology of aging, Dr. Cohen said that there is a strong link between cellular senescence and cancer. Recent studies have shown that some biochemical processes known to be essential to cell proliferation are inhibited or absent in senescent cells. It has also been shown that senescent cells produce proteins that inhibit the continued proliferation of tumor cells.

Dr. Cohen then reviewed some of the research goals of the NIA, including: cancer detection and treatment focusing on the influence of old age on cancer incidence; research on early diagnosis; research on management; and research on survival.

Returning to the research of the biology of aging, Dr. Cohen said that caloric restriction in laboratory animals has a dramatic effect in delaying the onset of all major diseases in later life, including tumors. Understanding the mechanism by which caloric restriction produces a 35 percent increase in life expectancy and major changes in tumor incidence and severity is likely to be an important step in understanding the relationship between cancers and aging.

Dr. Cohen then turned his presentation to the collaborative initiatives between the NIA and the NCI. NIA staff have been working with the NCI program divisions that deal with tumor

biology, cancer prevention and control, cancer etiology, and cancer treatment to organize workshops and research initiatives and to conduct analyses on aging and cancer. This collaboration has been going on for several years, however it has increased lately with the addition of a newly-established liaison. Some examples of recent collaborations are a planning meeting held last October among the NIA, NCI, and Association of American Cancer Institutes to explore the role of cancer centers and aging cancer research; and a working conference entitled "Perspectives on Prevention and Treatment of Cancer in the Elderly," held several years ago that brought together leaders in geriatric medicine and clinical oncology. An NIA/NCI collaborative study to augment the routine data collected in the SEER Program is underway to look at illness behavior and comorbidity factors. A new initiative is the working conference entitled "Perspectives on Ovarian Cancer in Older Age Women: Current Knowledge and Recommendations for Research." Another collaborative effort involves a pilot study on surgical evaluation of the older-age cancer patient. This pilot study will aid in the development of protocols for research initiatives to examine the impact of aging on treatment of older patients with cancer.

Concluding his remarks, Dr. Cohen stated that there is an obligation to contribute to the application of advanced scientific knowledge for the best interests of the older population. The NIA is committed, he said, to developing new information in clinical medicine and the basic sciences applicable to the aging/cancer interface. This is a complex problem that will require a comprehensive approach to overcome.

Responding to a question on whether nutritional education is being disseminated to young people, Dr. Cohen answered in the affirmative and said that they are working with the National Institute of Child Health and Development. Dr. Cohen also mentioned that a major scientific benefit from aging research is that, often, findings are also applicable to other age groups. An example he shared is the finding that an increased frequency of Down's syndrome is seen in families with a history of Alzheimer's disease, findings from research on Alzheimer's disease will in turn help with Down's Syndrome.

Dr. Cohen was asked how it is decided which institute will fund a grant if it relates to cancer and aging, and what percentage of grants at NIA relate to cancer. He answered that it is difficult to give a percentage since some research overlaps so much between the two disciplines. As to how it is decided who funds the research, Dr. Cohen said that he thought the decisions were made through an interactive collaboration among institute staff.

Dr. Cohen was then asked about the 35 percent growth in NIA's budget, and if it was a function of Congress' interest in aging. He answered that two areas of their research, Alzheimer's disease and severe mental and physical frailty, are driving factors for long-term health care. Congress, he said, can see the staggering cost of long-term care and recognizes that while struggling with how to approach long-term care insurance, it was at the same time critical to support research to reduce risk factors for long-term care.

In response to a question on the funding rate of the grants, Dr. Cohen said that the funding rate was 17 percent last year, prior to the 35% growth in NIA's budget.

There was then some discussion about having staff of NIA come to the Subcommittee on Aging and Cancer meeting when it convenes.

XII. DEVELOPMENT OF ANGIOGENESIS INHIBITORS FOR CANCER THERAPY—DR. M. JUDAH FOLKMAN

Dr. Chabner introduced Dr. Folkman, Andrus Professor of Pediatric Surgery and Professor of Anatomy and Cellular Biology at Harvard Medical School, noting that his work is

very well known and that his efforts in using biological approaches for the treatment of cancer fit in well with what the NCI is doing.

Dr. Folkman began his presentation by explaining that the field of angiogenesis has been around since 1962. Early experiments led researchers to ask: What would happen to a tumor population if it were forced to live only on existing host blood vessels and could not induce new capillaries or neovascularize? What is the limit of new tissue mass that can be grown without new blood vessels? What would happen if all biochemical conversation between tumor cells and vascular endothelial cells could be interrupted?

This field has now reached the stage where the answers to some of these questions garnered from laboratory findings are being tested in clinical trials in three areas. One area is diagnosis, in which they are using biopsy specimens to predict metastatic risk. Another area is stimulation of local angiogenesis to increase the healing in chronic wounds and burns. In the third area, inhibition of angiogenesis, there is a study being conducted using alpha-interferon in the treatment of life-threatening hemangiomas in newborn babies.

Dr. Folkman then explained the rationale for using angiogenesis as a therapeutic approach. He said that virtually all solid tumors are vascularized by the time they are diagnosed. In the absence of neovascularization, tumor growth is severely restricted. Dr. Folkman then briefly reviewed, with the aid of slides, how tumors grow by vascularizing. He explained that not only do the capillaries bring nutrients, but also growth factors. All vascular endothelial cells, the cells from which new capillaries are formed, make potent basic fibroblast growth factors which stimulate many tumors.

Dr. Folkman then showed what capillaries look like in normal histologic specimens. Since they are very difficult to see, he explained that a new method for staining the capillaries had been devised that clearly showed all the capillaries that had formed. A retrospective study using this new method looked back 10 years at breast cancer patients and revealed that only after a combination of angiogenesis and invasion of the duct did large masses become apparent.

Moving to a discussion of antiangiogenic therapy, Dr. Folkman said the endothelial cells are what the therapy is directed against. He then showed a slide of an invasive breast cancer under a high-power microscopic field. When there are more than 100 capillaries per high-power field, there is virtually a 100 percent metastatic risk. Confirmatory studies have shown that this is a very accurate predictor. Two prospective studies are ongoing to determine what happens in node-negative women.

Normally, capillary endothelial cell growth is suppressed and the cells grow at a very slow rate, Dr. Folkman explained. Vascular endothelium has a turnover rate of 3,000 to 10,000 days compared with bone marrow, which is entirely replicated in five days, and gut, which is entirely replicated in two to three days. These suppressed endothelial cells, once stimulated by angiogenic factors, can replicate in five days. The implication from this, he said, is that angiogenic inhibitors that are pure endothelial cell inhibitors have essentially no toxicity.

Research in humans, as well as animal research, has shown that many tumors make angiogenic factors. One of the first angiogenic factors discovered, which has since been sequenced and cloned, is fibroblast growth factor (FGF). This turns out to be the most potent and ubiquitous of the angiogenic factors. FGF has not been found in normal people; however, in patients with breast cancer, leukemia, non-Hodgkin's leukemia, lung cancer, myeloma, testicular cancer, and head and neck cancers, high levels of FGF are found. In patients with FGF, Dr. Folkman said, they are finding explosive synchronous metastasis. In 85 percent of the cancer patients they tested, they found FGF in their urine, and no normal patients have been found with FGF in their urine. This angiogenic factor gives evidence of the switch to the angiogenic state.

Describing experiments with fibroblasts transfected with FGF alone, Dr. Folkman noted that this factor is not secreted because it needs a signal peptide. No change occurs and there is no tumor. If the signal peptide is added so that FGF is secreted, the cell growth rate does not increase *in vitro*, but the cells are highly angiogenic. The results are very slow-growing, large, vascularized sarcomas. If an FGF-specific antibody is added, the tumor can be reduced substantially. In humans, Dr. Folkman informed the audience, tumors do not make just a single angiogenic factor, but many. Because of this fact, the inhibitors that have been developed aim at turning off the endothelial cell response to any factor.

Currently, there are 11 angiogenic factors under study, and all have been found, basically, by accident. Dr. Folkman then related a story of how one had been discovered in his laboratory by one of his students whose endothelial cell culture had become infected with a fungus. Normally, the fungus causes the cells to come off the plate. However, with this fungus, the cells were not only stopping their growth, but moving backwards, showing signs of reverse chemotaxis. When the fungus was isolated it was found to be *Aspergillus fresenius*, a rare fungus that grows in lacquer. The parent compound isolated was *fumagillin*. Synthetic analogs were formed that were a thousand times as potent as an angiogenesis inhibitor, and they were still not toxic. Experiments with mice showed that the inhibitor worked to reduce the tumors dramatically and this was shown in many different types of tumors in mice, rats, and humans. This treatment also seems to be synergistic with conventional chemotherapeutic agents.

In conclusion, Dr. Folkman showed slides of some newborn infants with hemangiomas. Usually, these tumors regress and disappear completely in five or six years, except in a subgroup in which they keep growing. In this group, they can spread into the eye, throat, and lung. In some of the worst cases, the tumors grow down the trachea and into the liver, and the mortality rate is between 68 and 70 percent. Dr. Folkman described a case of a child who, in 1988, was dying from pulmonary hemangiomatosis. The mother requested that they call Boston to find out what angiogenesis inhibitors the FDA had approved. The answer was alpha-interferon, but it had never been tried. Pulmonary hemangiomatosis is 100 percent fatal, and there had never been a success. They started treatment with alpha-interferon and within three months, the child was home on full activity. Since that time, the mortality rate for pulmonary hemangiomatosis has dropped from 100 percent to 3 percent. The average length of treatment duration with the angiogenesis inhibitor is one year.

The lessons learned from all of this, Dr. Folkman said, are that the treatment is long term—possibly up to 10 years; there is little or no toxicity from the antiangiogenic treatment; there are few or no side effects, with the possible exception of interfering with wound healing; and, lastly, there is no drug resistance.

XIII. ACTIVITIES TO RECRUIT MINORITY STUDENTS TO SCIENTIFIC CAREERS—DR. MICHELE EVANS

Dr. Ihde introduced Dr. Michele Evans and gave an overview of her efforts and accomplishments as Special Assistant to the NCI Director for Minority Initiatives since June 1989. He highlighted her involvement in the Adopt-A-School program, her influence on young minority students, and her role in minority recruitment and relations within the NCI. Recently, Dr. Ihde mentioned, she chaired a panel on malignancies in women and worked with Dr. Freeman on developing a President's Cancer Panel meeting. He stated that her presence would be missed in the Office of the Director, as she will return on January 1, 1992, to the Laboratory of Molecular Pharmacology as an Investigator.

Dr. Evans expressed her appreciation for the opportunity to speak about her activities as Special Assistant to the Director. She reviewed the issues that were instrumental to Dr. Broder in creating her position: the disproportionate rate of cancer among minorities and underserved

populations; the need for recruitment and training of students from disadvantaged and minority backgrounds; and the difficulties for women in the science and academic medicine fields.

Dr. Evans first addressed the relationship of poverty to disproportionate rates of cancer. Cancer incidence and mortality among African Americans is substantially higher. Hispanic Americans, Native Americans, Alaskan Natives, and Native Hawaiians are also disproportionately burdened by certain malignancies. These figures, Dr. Evans stated, indicate a direct link between poverty and cancer, a correlation that Dr. Freeman demonstrated while President of the American Cancer Society.

Poverty, Dr. Evans continued, embodies low income, low educational levels, substandard living conditions, risk-promoting behavior, unemployment, and diminished access to health care. Dr. Broder and Dr. Evans believe that inferior education, particularly in science and technology, is a major contributor to poor health among minority Americans. Improving science education and encouraging the pursuit of science and medical careers may lead to reduced cancer incidence and mortality, improved health, and improved economic status.

Dr. Evans discussed the implications of effective recruiting, training, and retention of students in science and biomedical research, as well as the slow decline in the number of American students pursuing science and engineering degrees. The number of minorities earning degrees in these fields is particularly scarce. There is also some evidence, she reported, of a decline in science and engineering degrees earned by White American students.

A shortage of minorities is also apparent in the medical field, Dr. Evans added. African Americans comprise approximately 2.7 percent - 3.0 percent of the country's physicians; Hispanic Americans and Native Americans comprise an even smaller percent. Dr. Evans reported that despite gains made since the 1970s in medical graduations among minorities, the overall percentage of minority physicians has not increased enough to effect change in health care for poor and minority populations.

Dr. Broder's and Dr. Evans' goal has been to increase the number of students, minorities in particular, involved in cancer-related research and medicine. Several reports have demonstrated the poor standing of American students—primary, intermediate, and secondary—in science and mathematics. These educational deficiencies, Dr. Evans emphasized, point to the need for early educational intervention.

In response, Dr. Evans explained, NCI's and NIH's recruitment and training efforts have expanded beyond college and graduate students to reach a broader group—high school students. In 1989, a committee of the Equal Employment Opportunity Advisory Group implemented the NCI's Adopt-A-School Program. Through this program, NCI has worked with the District of Columbia's McKinley High School toward enriching the school's science curriculum and motivating students to pursue science careers. The program—developed by Mrs. Maxine Richardson and Dr. Susan Garges—includes seminars given by NCI scientists, small laboratory group instruction supervised by volunteer NCI staff, NCI laboratory training during the summer for selected students, and in-service science retraining for the science faculty. Dr. Evans believes that the one-to-one contact between the scientist and the student has been an important benefit of this program.

Each year, Dr. Evans continued, Mrs. Richardson and the committee further define the program by designing educational science themes in conjunction with the school's curriculum and the needs of the students. Lecture topics have included cell survival, DNA damaging agents, and AIDS. As the program enters its third year, its success demonstrates the effectiveness of implementing interventions at an earlier stage in education.

Dr. Evans explained further that NCI uses a two-tier approach to science and health education, targeting not only the academically proficient students who are already interested in science, but also stimulating in all students an interest in science. Larger plenary sessions, for example, present basic information on the topic, while another lecture presents more advanced, technical information.

This approach has been utilized in the Adopt-A-School Program, and has proven useful in the Montgomery County, Maryland, school system. Dr. Evans has taught science or presented talks at several Montgomery County high schools as well as in nontraditional classrooms for students at risk for delinquency or dropping out. She reported that since a significant proportion of science and math teachers do not hold degrees in these subjects, the teachers seem to benefit as much as students from the opportunity to become better acquainted with and inspired by science.

Although educational interventions have not yet been implemented in elementary schools, Dr. Evans believes—based upon her research in the District of Columbia and Montgomery County—that the best time to begin science-related intervention may be between grades three and five. To ensure the development of a solid, stable biomedical research field for the 21st century, students must be trained and equipped for the science track in elementary school.

Dr. Evans also stressed the value and effectiveness of the one-to-one mentoring relationship and its necessity in all aspects of recruitment, training, and retention in science careers.

Dr. Evans highlighted NCI's interaction with professional organizations, through which NCI staff have provided and gained useful information and expertise. NCI has recently initiated activities with the Student National Medical Association, the largest organization of minority medical students. Interacting with medical students, particularly minority students, may allow NCI staff to influence their chosen career paths.

In support of this notion, Dr. Evans reported that 4.8 percent of all U.S. house officers in 1987 were Black, up only 0.1 percent from 1982, according to Nager and Saadatmond in the *Journal of the National Medical Association.*

Dr. Evans continued with a discussion of trends among medical students. Among nonminority students, there has been a trend away from internal medicine and primary care toward specialties. Among minority students, internal medicine numbers are down, but the number of those considering and entering public health/preventive medicine has soared. Dr. Evans attributed this increase to several major city and State health department commissioners who have provided excellent role models.

The shortage of minority oncologists in the U.S., according to Dr. Evans, is of concern to the NCI, especially with the disproportionate cancer incidence and mortality among minorities. The National Medical Association reports only 85 oncologists among its 16,000 Black physicians. In efforts to encourage an increase in minority oncologists, Dr. Evans reported, NCI staff have provided cancer facts and information to leadership and membership of the Student National Medical Association, submitted articles on oncology to their journal, and followed-up individual students who exhibit any interest in this area.

NCI has worked with the Committee on Minority Affairs for the American Association for Cancer Research (AACR) in developing AACR's Mentorship Program. The program will provide young investigators and students with research opportunities and an advice network. Dr. Evans has worked with Ms. Margaret Foti, Dr. Francis Ali-Osman, Dr. Carol Wood Moore, and Mrs. Bynum on this and other efforts of the committee targeted toward minority scientists.

NCI has also developed ties with the National Medical Association, the Association of Minority Health Profession Schools, the Society for the Advancement of Chicanos and Native Americans in Science, and the Association for Academic Minority Physicians.

Dr. Evans moved on to a discussion of women in science. She expressed Dr. Broder's concern about the shortage of women in both science and academia. Women constitute about 50 percent of the total work force, but only 15 percent of working scientists in the U.S. Among full professors of the natural sciences and engineering in the U.S., only 2,600 out of approximately 54,000 are women. Although approximately 19 percent of medical school faculty are women, 67 percent of them hold an entry-level rank.

Dr. Evans reported that despite dramatic increases in the number of women in science, medicine, and engineering over the past 20 years, these increases have not consistently lead to positions of high stature in medicine or science.

According to Dr. Evans, minority women have pursued degrees in science, medicine, and engineering at similar rates to nonminority women. In fact, she reported, African American women have increased their participation and representation in medical schools since 1971 faster than all other observed groups. Participation in medical school has increased among all ethnic groups of women, but women of color are still underrepresented among science and medical faculty.

According to *Women in the Intramural Program*, a draft document to be reviewed this fall, the NCI has employed and promoted women at a rate comparable to the NIH as a whole. However, Dr. Evans stated, the NCI wants to increase participation of women in senior scientific positions. The key, Dr. Evans emphasized, is not just to employ and promote women, but to maintain the quality and ensure the diversity of the Intramural Program.

Dr. Evans mentioned several areas to which the NCI might direct efforts to increase participation, such as the promotion and tenure process, issues of productivity, clarification of leave policies, flexible work schedules, and mentoring.

Dr. Evans has participated in the Women's Leadership Seminar Series, sponsored by Manufacturers Hanover and the NIH's Visiting Professor Program—teaching science courses and interacting with faculty members at women's colleges throughout the country. Faculty members have expressed their concerns about how to keep women in science, specifically regarding the flexibility of careers in science, the likelihood of success in obtaining funds, tenure, and the impact and need for research on women's health issues.

In efforts to reach all women, Dr. Evans continued, NCI has collaborated with the National Network of Minority Women in Science, a nationwide organization of women from all ethnic groups. Additionally, Dr. Evans has worked with the Task Force for the Office for Research on Women's Health (ORWH), collaborating with Dr. Ruth Kirschstein, former Director of the ORWH. This office recently brought together panels of experts to outline the appropriate NIH research agenda for women's health over the next 10 to 15 years. Dr. Evans cochaired the Malignancy Panel with Dr. Robert Young of Fox Chase Cancer Center. This panel supported much of the ongoing NCI-supported research on breast, ovarian, cervical, endometrial, lung, and colon cancer, and also supported many prevention trials currently in progress within the Division of Cancer Prevention and Control.

Dr. Evans pointed out that there are a myriad of other ongoing recruitment and training activities within the NCI in addition to those she discussed. By working outside a specific program, Dr. Evans has had the opportunity to interact with people across NCI and NIH. She has also been able to devote time to recruitment of minority oncologists for the Intramural and

Extramural Programs, as well as mentor individual students who are applying to graduate and medical school.

Dr. Evans feels that one of her most important contributions to the NCI has been her participation in opening the channels of communication between minority investigators within the Intramural Program. She cited the people who have guided her during her time as Special Assistant: Mrs. Maxine Richardson, the NCI Equal Employment Opportunity Manager; Mrs. Barbara Bynum and her staff; the Cancer Control Science Program, led by Dr. Claudia Baquet; Dr. Vincent Cairoli and his staff and the Cancer Training Grants; Dr. Bruce Chabner, Director of the Division of Cancer Treatment; and especially Dr. Broder, who served as her mentor.

Echoing the need for minority training and recruitment, Dr. Jako commented that by year 2030, it has been estimated that African Americans will comprise 30 percent of the U.S. population.

Dr. Salmon noted that adequate science education is a concern at his university, not only in the area of cancer, but also in biological sciences and sciences in general. A program has been implemented for teaching biological sciences to medical students, which involves about 200 students every summer and provides them with individual mentoring. The grant support for this program has mushroomed markedly beyond the initial grant support.

The second program that has been implemented at Dr. Salmon's university targets high school science teachers. He commented that many are not up to date on modern molecular biology and have not had adequate hands-on experience to pass on to their students.

Dr. Salmon asked Dr. Evans if there is an effort to train high school teachers in the Office of the Director of the NIH similar to NCI's program. He feels that high school teachers require more science training than their college educations may have provided because he believes that college curriculums for teachers who are education majors typically are not strong in science areas.

Dr. Evans responded that Dr. John Ruffin, Associate Director for Minority Programs, is quite aware of this problem. She explained that the Carnegie Commission recently recommended to the Office of Education of the Department of Education that they fund scientists to provide some technical education to teachers while they are in undergraduate training as well as in the post-graduate phase at the beginning of their careers. Money has not yet been appropriated to this effort.

Dr. Becker added that the Carnegie recommendation would take between 2 and 5 percent from the research budget of the Federal Government to give to the Department of Education. Dr. Evans noted that she thought that other funds would supplement that. Dr. Becker agreed, but emphasized that the 2 to 5 percent diversion is the most crucial figure. Dr. Evans accepted this possibility as a problem, but also indicated that the inadequate science knowledge that she has seen among high school teachers is a very frightening situation. She reported that the teachers are anxious to learn, have the capability to learn, but have not had the opportunity to take updated courses during the summer.

Dr. Evans continued by noting the low level of growth of teachers' salaries for the last year. She stated that the small increase in salaries does not make up for the amount of money spent per credit to take courses at universities, particularly laboratory courses. Tuition increases in State schools is quite disproportionate to increases in teachers' salaries. Therefore, Dr. Evans concluded, we either pay for training teachers now out of the research budget and other funds, or we may enter the 21st century with poorly educated scientists. Students' dismal performances on evaluative tests and SATs are indicators of the magnitude of this problem.

Mrs. Bynum recalled that about three years ago a coalition of scientific societies sponsored a continuing education program for teachers. The scope of this type of activity clearly needs to be expanded, she added.

XIV. SUBCOMMITTEE REPORTS—DR. PAUL CALABRESI

Dr. Calabresi turned the meeting over to Mrs. Irene Pollin for a report on the Women's Health and Cancer Subcommittee.

Women's Health and Cancer Subcommittee Report

The first subcommittee meeting on women's health and cancer was held, chaired by Mrs. Pollin. Mrs. Pollin reported that Dr. Claudia Baquet, Assistant Director, Cancer Control Science Program, DCPC, spoke on current research in her program on barriers for women to cancer prevention, early detection, and treatment. Dr. Baquet described these three issues in terms of socioeconomic, cultural/ethnic, and family factors. Following are examples of each factor: 1) socioeconomic—income, education, smoking, nutrition, and health insurance; 2) cultural/ethnic—women's attitudes toward examinations by male health care personnel, attitudes toward clinical trials, beliefs about the quality of care, spiritual and religious attitudes, and language barriers; and 3) family—health care delivery in the context of family planning, women as caregivers, and women as health care decision makers of the family. The basis of Dr. Baquet's presentation was that the treatment of a woman is also treatment of a family. Mrs. Pollin informed the Board that a draft report of this research will be published and distributed to Board members.

Mrs. Pollin stated that the goal of this first meeting was to find a major focus for the group, which will be on education, prevention, and early detection. The subcommittee will be concerned with all cancers as they affect women, not just cancers that are unique to women. Mrs. Pollin reminded the members that they have copies of the topics of focus under the aforementioned categories.

Mrs. Pollin also reported that the subcommittee discussed identifying any deficiencies in current NCI activities and the possibility of stimulating new activities. Mrs. Iris Schneider will submit a brief report to the subcommittee of NCI activities in education, prevention and early detection in the near future to be used by the Subcommittee in deciding on its future activities.

Resolution

Dr. Calabresi thanked Mrs. Pollin for her initiation of this new subcommittee. He then read a modified version of the resolution proposed by Dr. Sydney Salmon and seconded by Dr. David Bragg. The Board unanimously approved the revised resolution commending the United States Congress for its support of the National Cancer Program since the signing of the National Cancer Act in 1971 and urging the Congress' approval of the Senate's recommended fiscal year 1992 appropriation for the NCI.

Dr. Salmon recommended that the subcommittee chairpersons present only the action items and major points of discussion of their meetings, and allow the Board members to read the minutes. Dr. Calabresi agreed and introduced Dr. Howard Temin for his report.

AIDS Subcommittee Report

Dr. Temin reported that the AIDS Subcommittee members discussed the current status of AIDS vaccine research at the NIH. A presentation was given by the Division of AIDS of the National Institute on Allergies and Infectious Diseases (NIAID). Also, a report was given by

Dr. Jay Berzofsky of the DCBDC about his efforts to develop a recombinant and synthetic vaccine in collaboration with the NCI intramurally, and then extramurally with the Division of AIDS at NIAID. Dr. Werner Kirsten summarized the role of the Biologic Products Laboratory in Frederick, Maryland, in creating stock viruses and conducting chimpanzee tests for the NCI.

The report of the AIDS Subcommittee was unanimously approved.

Activities and Agenda Working Group Subcommittee Report

Dr. Paul Calabresi presented the report of the Activities and Agenda Working Group Subcommittee. The major discussion of the meeting was the reorganization of Board meetings, which Dr. Calabresi felt will improve the efficiency of meetings—especially the closed session. Communications and mailings were discussed. A member suggested that ex-officio members might not want to receive grant materials; it was decided that this will be the choice of the ex-officio member. Dr. Calabresi reported that the subcommittee would like to strike a balance between intramural and extramural presentations at meetings to gain a broader perspective on the National Cancer Program. No decisions were made regarding meetings in out-of-town (outside Bethesda, Maryland) locations, although members expressed an interest in holding meetings at a major center or in a city that would receive media attention.

Items of discussion for future subcommittee meetings were: interactions between the National Cancer Program and the Food and Drug Administration; program project grants and the endangerment of clinical research; discussions with Dr. Bernadine Healy; and issues with the Office of Scientific Integrity and the inclusion of women and minorities in clinical trials. Also, 15 major scientific topics were suggested, including angiogenesis, which was discussed at the present meeting. Dr. Calabresi reported that the subcommittee members decided that an event to commemorate the 20th anniversary of the National Cancer Act should be scheduled around the November 1991 Board meeting. Dr. Calabresi presented three optional dates: 1) the third day of the scheduled November meeting; 2) the Sunday preceding the meeting; or 3) to hold a major presentation at Masur Auditorium on Tuesday of the meeting instead of the regular program meeting. Former members of the Board and the public would be invited to a scientific presentation focusing on what has been accomplished. Dr. Calabresi then asked for feedback from the Board.

The Board favored a Tuesday presentation with room for the media, but Drs. Temin, Bragg, Bettinghaus, and Becker were concerned about finding proper speakers on short notice. Dr. Becker was especially concerned about presenting misinformation (e.g., unproven research) in the haste to prepare a program. Dr. Calabresi urged the Board to attempt to organize a successful event with the proper speakers.

Dr. Broder recommended that the agenda for this event should consist of broad items and focus on the National Cancer Program as a whole rather than specific topics, scientists, or projects. For additional flexibility, Dr. Broder added that individuals could be selected on the basis of their historical contribution rather than their current contribution. Dr. Calabresi stated that a program for this event will be compiled and faxed to each member for review. Dr. David Bragg suggested "imaging in cancer" as an addition to the agenda of scientific topics.

As an addendum to the report, Dr. Salmon suggested that agendas for the subcommittee meetings should be distributed in advance of Board meetings.

The report of the Activities and Agenda Working Group Subcommittee was unanimously approved.

Cancer Centers Subcommittee Report

Dr. John Durant presented the report of the Cancer Centers Subcommittee. The subcommittee discussed how to distribute funds among the cancer center grants in a more equitable manner. Currently, approximately 10 percent of the institutions receive about 40 percent of available funds, thus inhibiting the flexibility and expansion of the program. Dr. Durant explained that staff, in cooperation with the committee, were charged with devising several models of approaches to this problem.

Dr. Durant reported that a draft of the new guidelines for the cancer grants is available. The Board of Scientific Counselors will conduct a final review of this draft. If approved at the next Board meeting, the guidelines will be implemented with the grant cycle beginning in February. Dr. Durant informed members that minutes of this subcommittee will be distributed.

Dr. Durant concluded his report by conveying the subcommittee's suggestion to have staff deliver a report to the Board in two to two-and-a-half years about the progress of the certification process (of official comprehensive centers) and progress in centers with minimal compliance with the guidelines.

The report of the Cancer Centers Subcommittee was unanimously approved.

Environmental Carcinogenesis Subcommittee Report

Dr. Frederick Becker reported that the focus of the Environmental Carcinogenesis Subcommittee meeting was on the risk of breast implants. Reports were given by Dr. Richard Adamson of the NCI and Dr. F. Alan Anderson of the FDA.

Prostheses with a polyurethane coating were discussed for their ability to release 2, 4-diaminotoluene. Carcinogenic assays of rodents have shown that this substance produces an increased risk of carcinomas in several organs. Many in the medical field are concerned that lifetime risk could be increased by the leaching of this material from the prostheses coating. Regarding the work of the FDA, Dr. Anderson reported that leaching occurs at a low level. The FDA has estimated that, at most, 2.5 cancers would be produced by the leaching of this substance in 10 million women over a lifetime of implantation. Dr. Becker stated that in light of this information, some subcommittee members commented that the risk of surgical removal might exceed the risk of leaching 2, 4-diaminotoluene. Dr. Becker explained that there is no epidemiologic or histopathologic evidence that any carcinogenic risk exists for silicone implants.

Dr. Salmon asked if the NCI has plans to conduct an epidemiologic, hospital-based study on the outcome, or subsequent neoplasm, of women with silicone implants. Dr. Adamson explained that such plans will be discussed at the DCE Board of Scientific Counselors in October. Plans are to observe women who have silicone implants for breast augmentation. Dr. Salmon then suggested that multiple myeloma and monoclonal gammopathy should be a particular focus of study. He related an anecdotal case report of a plasmacytoma that developed around a cardiac pacemaker implant.

Dr. Becker concluded his report by restating that there is no significant risk from breast implants at this time, but breast implantation began approximately 10 years ago and outcome must be monitored.

The report of the Environmental Carcinogenesis Subcommittee was unanimously approved.

Dr. Bernard Fisher reaffirmed that women who have implants should not be encouraged to have them removed. Dr. Broder added that he believes Dr. Adamson's plan is an appropriate follow-up approach and will be approved. Dr. Bragg also added that a cohort of patients with breast augmentation should be included in a study to determine if breast augmentation hampers the ability to image a breast and detect small-sized cancers.

Report of the Subcommittee on Information and Cancer Control for the Year 2000

Dr. Erwin Bettinghaus began his report of the Subcommittee on Information and Cancer Control for the Year 2000 by congratulating the staff and reminding Board members that if they accept this subcommittee's minutes, they are approving the three concepts reviewed in the meeting and recommended for approval. Two of three concepts are renewals of current tasks: 1) to provide support to the NCI to continue providing the cancer database with materials beyond those put into Medline; and 2) an agreement with the National Library of Medicine (NLM) to support the NLM's activities for maintaining the NCI's databases—Cancer Lit and PDQ. This subcommittee approved both concepts unanimously. The third concept is a new project that will propose establishing a marketing arrangement with a payback mechanism for the information products of *JNCI*. That is, a subscriber of *JNCI* would have access to PDQ and Cancer Lit and all other materials at no extra charge. The outside contractor would provide marketing services that the Government Printing Office cannot provide. The subcommittee also approved this concept unanimously.

Dr. Bettinghaus reported that the subcommittee will ask the OCC to collect materials developed by the comprehensive clinical cancer centers to discern if the NCI can serve as a clearinghouse for this information. The subcommittee feels that it will be useful to hold a series of public forums in 1993 and 1994 and produce a progress report in 1995 with respect to the year 2000 goals. Dr. Bettinghaus invited the Board to offer any suggestions or comments regarding this idea and the subcommittee's approach to the year 2000 goals.

The report of the Subcommittee on Information and Cancer Control for the Year 2000 was unanimously approved.

Planning and Budget Subcommittee Report

Dr. Bernard Fisher presented a report on the Planning and Budget Subcommittee meeting. At this meeting, Mr. John Hartinger presented information on the 1992 appropriation for the NIH and the NCI that Dr. Broder presented to the Board in his report. This subcommittee was particularly interested in the increase of $116 million over the 1991 appropriation provided by the House.

Ms. Judith Whalen provided the subcommittee with information on the NIH strategic plan. One of the areas of scientific emphasis is molecular biology—Dr. Broder is Chairman of the Molecular Medicine Panel. She discussed the planning process and handed out copies of the Molecular Medicine Panel report. Ms. Whalen explained that the subcommittee will have another opportunity to discuss a more developed version of the plan at the January 1992 meeting.

A third item of discussion related to a biennial report which the NCAB must draft every two years by legislative mandate. Subcommittee members agreed to continue using the format of past reports. Dr. Fisher suggested that Board members review the 1989-1990 report and make suggestions relative to the content of this report to him or Ms. Whalen. The subcommittee suggested the following issues: gene therapy; chemoprevention; women's health; taxol; multiple drug resistance; and clinical perspectives on breast cancer.

Concluding his report, Dr. Fisher stated that Dr. Temin requested further discussion on funding problems in future meetings (e.g., disproportionate funding of research to a small number of labs).

The report of the Planning and Budget Subcommittee was unanimously approved .

XV. OLD BUSINESS

Approval of the May Minutes

The May 1991 NCAB summary minutes were unanimously approved with one addition. Dr. Kenneth Chan requested that the heading "Introduction of New Board Members" read "Introduction of New Board Members and Panelists" under section three of the table of contents.

XVI. NEW BUSINESS—CHAIRMAN, DR. PAUL CALABRESI

Proton Beam Therapy

Dr. Calabresi called on Dr. Salmon to begin the discussion on new business by reading a formalized preamble and motion regarding proton beam therapy as a follow-up to Dr. Salmon's previous motion. This motion proposed that the NCAB authorize the creation of a Blue Ribbon Committee to review and evaluate proton beam therapy for cancer. Dr. Bragg suggested changing a phrase of the preamble from "unsuccessful" to "limited success" regarding the NCI's efforts in the development of particle therapy. Dr. Jako expressed his support of this motion. Dr. Temin suggested that the motion to create a committee should include persons in the field of health economics. Dr. Broder suggested that the review committee should analyze the clinical delivery component as an applied element for therapy and not only research issues. Dr. Salmon agreed with Dr. Temin and, in answer to Dr. Broder, proposed adding cancer control as an issue for review. The Board unanimously approved the motion.

Dr. Samuel Wells, Jr., commented that the NCI has received two planning and design studies (R01 grants) proposing additional proton beam machines. He then directed some comments about the position of the NCI in regard to appropriations and laws to Dr. Salmon. Dr. Salmon explained that the NCI received two grant requests for a one-year design study with no commitments. He stated that it is an appropriate time to review this field and report on it. Dr. Durant added that the purpose of the motion was to provide the NCI Director with practical and scientific information about the proposal for next year's budget meeting. Dr. Becker stated his support of the intent to do an appropriate evaluation of this modality. Dr. Broder then stated that the NCI should oppose earmarking and discourage individual investigators from appealing to Congress on behalf of a specific project, but an Institute should carry out a specific task to the best of its ability at the will of Congress.

The Board unanimously approved a motion to empanel a new subcommittee on "Aging and Cancer." Mrs. Bynum reminded members that a functional statement for this subcommittee is in the notebooks. Dr. Calabresi directed the member's attention to changes in names of subcommittees on the subcommittee sheet. He then introduced Dr. Elliott Stonehill to talk about possible changes in proposed Government ethics standards.

Office of Government Ethics

Dr. Stonehill distributed copies of portions of the new Federal Government standards of conduct proposed for the Executive Branch of the Federal Government. He presented a brief background about financial ethics relative to the personnel branch within each agency of the Federal Government. According to the Ethics Reform Act of 1989 and Presidential declarations, Congress has appointed a new agency—the Office of Government Ethics—to establish a standard of conduct rule for Executive Branch employees. Dr. Stonehill concentrated his discussion on the Board's concern as special Government employees—NCAB members, President's Cancer Panel members, Boards of Scientific Counselors, and peer review groups. He explained that a special Government employee is defined as a person "working for the Government for a brief period on a specific assignment." Dr. Stonehill reminded all in attendance that members of the NCAB are not to use information (especially confidential) for personal gain or distribution.

Currently, the NCAB operates under the DHHS standards of conduct, which exclude special Government employees. The Office of Government Ethics, headed by Stephen Potts, includes special Government employees ("designated, retained, appointed, or employed to perform temporary duties, et cetera, for a period not to exceed 130 days") in its standards of conduct. Dr. Stonehill read a section of the new Office of Government Ethics document that says Executive Branch employees "shall not receive compensation from any source other than the government for teaching, speaking, or writing that relates to [their] official duties." He also explained that the definitions of official duties are broad.

Dr. Chabner asked if the new policy relates to any activity of a person's respective Department because, he explained, a regular employee has a proscription against writing or speaking about official responsibilities within his/her job and his/her agency. Dr. Stonehill pointed out specific examples of decision-making under the new standards of conduct in the new document. He mentioned that employees are not prohibited from writing or expressing themselves under this policy, but are prohibited from receiving income or honorarium for such activity.

Dr. Stonehill explained that the Government asked for feedback on the proposed rule. Comments from all the Institutes were forwarded from the NIH to the DHHS. This compilation was sent to the Office of Government Ethics for review. The DHHS indicated that "this provision will likely create a tremendous administrative burden" and that special Government employees should be eliminated from the new standards. It is expected that final rules will be established in January or February of 1992. Dr. Stonehill reminded members of the Board that they may direct any comments to the Office of Government Ethics or to the U.S. President.

Dr. Calabresi stated that this policy requires serious consideration and that most members of the Board would be disqualified under the new policy. Dr. Becker stated some of the negative effects of this policy and informed the Board that he wrote to Leslie Wilcox.

Dr. Fisher suggested that a uniform statement by NCAB members is needed. He moved that Dr. Calabresi prepare the statement with other members' help and approval. It was unanimously approved that Dr. Calabresi will prepare a statement on NCAB stationery, fax it to members, and mail it after approval. Dr. Salmon and Dr. Calabresi also urged members to write to the U.S. President about the policy.

Because of statements made by Dr. Chabner, Dr. Calabresi recommended that the statement should be broad enough to include Federal employees who are publishing or lecturing on scholarly material. Dr. Jako suggested that the statement should distinguish between the biomedical research field and other fields.

Dr. Calabresi thanked Dr. Stonehill for his presentation and turned the meeting over to Mrs. Bynum for a discussion on peer review procedures.

New Peer Review Procedures

Mrs. Bynum explained that the entire peer review system is undergoing change that will be reflected in the terminology and format of materials. Terms such as "disapproval," "pink sheet," "executive secretary," and "award rate" will no longer be used. Changes in the management procedures of the NIH's Extramural Program will be implemented to comply with either Congressional language or OMB directives. Beginning with the fall round of review meetings, "approval" and "disapproval" will not appear on the summary statements. Following primary reviews, the chairman will ask if anyone on the committee feels that no further consideration should be given to the application. The study section may still recommend deferral.

Dr. Wells asked if an application can be removed from a category if there are concerns about improprieties. Mrs. Bynum responded that an applicant institution could submit an amended application. Dr. Wells felt that it would be more sensible to defer a grant if more information is needed, rather than recommend no consideration. Mrs. Bynum stated that a study section could defer a grant if it has sufficient scientific merit and requested information has been addressed. She added that, although it has not occurred, there are policies that bar funding unless the questionable matter is resolved.

Mrs. Bynum reported that the scoring procedures will remain essentially the same. Each member votes a priority score. She explained that each application, whether accepted for consideration or not, generates a base against which a percentile ranking is calculated. Mrs. Bynum referred to the chart in the "New Business" section, which best describes scoring in terms of numbers and verbal qualifiers.

Mrs. Bynum mentioned that she hopes that the study section considers the true technical merit of an application in review and will justify budget recommendations on this basis. The study sections are asked not to consider indirect costs as part of their recommendations, but the NCAB will see the total costs recommended in the summary statement. Mrs. Bynum reminded members that it is their responsibility to consider the overall cost of various pieces of research in the recommendation and voting process.

NCAB Stationery

Dr. Calabresi announced that all Board members will receive NCAB stationery. Dr. Stonehill explained that official stationery and official Government mailing may not be used for personal interest or correspondence of a scientific nature other than the official business of the Board at the request of the Chairman.

Dr. Calabresi announced that imaging has been added to the list of future agenda items.

Dr. Jako called everyone's attention to an interview with Dr. Sam Broder in the September 20th issue of the *Cancer Letter*. He commended Dr. Broder for his work and congratulated him on the third anniversary of his directorship.

XVII. ADJOURNMENT—DR. PAUL CALABRESI

There being no further business, the 79th meeting of the National Cancer Advisory Board was adjourned at 3:13 p.m., September 24, 1991.

November 22, 1991

Date

Paul Calabresi, M.D.

Dr. Paul Calabresi, Chairman