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

Summary of Meeting
October 3-4, 1994

Building 31, Conference Room 10
National Institutes of Health
Bethesda, Maryland

Department of Health and Human Services
Public Health Service
National Institutes of Health
National Cancer Institute
National Cancer Advisory Board
Summary of Meeting[1]
October 3-4, 1994

The National Cancer Advisory Board (NCAB) convened for its 91st regular meeting at 8:00 a.m., October 3, 1994, in Building 31, C Wing, 6th Floor, Conference Room 10, National Institutes of Health (NIH).

NCAB Members

Dr. Barbara Rimer (Chairperson)
Dr. Frederick F. Becker
Dr. J. Michael Bishop (absent)
Mrs. Zora K. Brown
Dr. Paul Calabresi
Dr. Kenneth K. Chan
Dr. Pelayo Correa (absent)
Dr. Robert W. Day
Mrs. Barbara P. Gimbel
Dr. Alfred L. Goldson
Mrs. Marlene A. Malek (absent)
Ms. Deborah K. Mayer
Dr. Sydney Salmon
Dr. Philip S. Schein
Dr. Ellen V. Sigal
Dr. Vainutis K. Vaitkevicius
Dr. Charles B. Wilson (absent)

President's Cancer Panel

Dr. Harold P. Freeman (Chairperson)
Ms. Frances Visco (absent)
Dr. Henry C. Pitot

Alternate Ex Officio NCAB Members

Dr. Roy Fleming, NIOSH
Captain Bimal C. Ghosh, DOD
Dr. John Johnson, FDA
Dr. Hugh McKinnon, EPA
Dr. Lakshmi C. Mishra, CPSC
Dr. Sheila Newton, NIEHS
Dr. P. C. Srivastava, DOE
Dr. Ralph Yodaiken, DOL

Members, Executive Committee, National Cancer Institute, NIH

Dr. Samuel Broder, Director, National Cancer Institute
Dr. Edward Sondik, Acting Deputy Director, National Cancer Institute
Dr. Richard H. Adamson, Director, Division of Cancer Etiology
Mr. Philip D. Amoruso, Associate Director for Administrative Management
Dr. Marvin Kalt, 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. Alan S. Rabson, Director, Division of Cancer Biology, Diagnosis, and Centers
Mrs. Iris Schneider, Executive Secretary, Assistant Director for Program Operations and Planning

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

Liaison Representatives

Dr. Robert W. Frelick, Association of Community Cancer Centers
Dr. Elaine Locke, American College of Obstetricians and Gynecologists
Dr. Eve Barak, National Science Foundation
Ms. Michelle Cherry, American Cancer Society
Dr. Edward Gelmann, American Society of Clinical Oncology, Inc.
Dr. C. Michael Brooks, American Association for Cancer Education, Inc.
Mrs. Yvonne Soghomonian, Candlelighters Childhood Cancer Foundation
Dr. Edwin A. Mirand, Association of American Cancer Institutes
Ms. Sandra Lee Schafer, Oncology Nursing Society
Dr. Marston Linehan, Society of Urologic Oncology

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I. INTRODUCTION OF CHAIR—DR. SAMUEL BRODER

Before the call to order of the 91st National Cancer Advisory Board (NCAB) meeting, Dr. Broder acknowledged the many valuable contributions Dr. Paul Calabresi made as Chair of the NCAB and recognized the new responsibilities he has accepted in chairmanship of the review of the National Cancer Institute's (NCI) intramural program. Dr. Broder announced that the NCAB will continue to call upon Dr. Calabresi to act in different capacities.

Dr. Broder stated that Dr. Calabresi began his term as Chair of the NCAB in 1991, and never missed a meeting or an opportunity to be helpful. In addition to his intellect and expertise, Dr. Calabresi brought compassion and experience in practical accomplishments to the NCAB. Dr. Broder also mentioned Dr. Calabresi's independence and vision, as well as his ability to practice medicine with diplomacy. On behalf of the NCAB, Dr. Broder thanked Dr. Calabresi and presented him a memento of his achievement.

Dr. Calabresi thanked Dr. Broder and said that when he began working for the NCI, he never imagined he would chair the NCAB. He described his tenure as one of the highlights of his academic career and expressed his pleasure in working with all the Board members. Dr. Calabresi opined that the Board has charted an important course for the National Cancer Program (NCP) in its SENCAP committee report and that it is critical for the Board to take a strong leadership role to achieve future inroads in curing and preventing cancer. He closed by congratulating the new Chair, Dr. Barbara Rimer, and expressed their shared commitment to achieve a smooth transition.

Dr. Broder proceeded to introduce Dr. Rimer, a cancer control expert from Duke University Comprehensive Cancer Center, who is the first behavioral scientist and first woman to chair the NCAB. A graduate of the University of Michigan and Johns Hopkins University, Dr. Rimer has had a varied career, from community medicine to cancer communication, to various types of behavioral research. Dr. Rimer is a Professor of Community and Family Medicine at the Duke University Medical Center and a senior fellow at the Center for Health Policy, Research, and Education. She also served as a senior fellow of the Aging Center at Duke, which should prove helpful in understanding cancer in the context of current demographics.

Dr. Broder expressed his appreciation that President Clinton selected Dr. Rimer for this distinguished position. He referred to the present as a time of great challenge and redefinition for the NCI, in which Dr. Rimer, like each NCAB member, will make a mark on the present state and future of the Institution. He thanked her in advance for the long hours and effort she will contribute as Chair and turned the meeting over to her.

II. CALL TO ORDER AND OPENING REMARKS—DR. BARBARA RIMER

Dr. Rimer called the meeting to order and thanked Dr. Calabresi for his outstanding work as Chair of the NCAB. She cited the SENCAP report as just one example of the contributions made by Dr. Calabresi (as well as the Board and the President's Cancer Panel [PCP]).

By way of introduction, Dr. Rimer contrasted the discovery of the BRCA-1 gene exemplifying the recent accomplishments of cancer scientists with an article in the *JAMA*, co-authored by Dr. Pelayo Correa, showing that Black women are twice as likely as White women to die of breast cancer—the variance due to later stage at diagnosis. Dr. Rimer referred to this juxtaposition of progress in knowledge and disparity in racial mortality levels as exemplary of a constant reality in the field of cancer—steps forward are often concurrent with setbacks or new difficulties. This situation presents a challenge to continue to push the frontiers of basic and translational science while ensuring that new medical discoveries benefit everyone.

Dr. Rimer spoke of the diversity among the Board members and their common commitment to fight cancer, a formidable enemy that can only be beaten by building and disseminating knowledge. She expressed her pleasure to be working with the Board and NCI to advance the NCP and her hope that the future will bring many new victories over cancer. She requested the members' patience and thanked her well-wishers and Dr. Marvin Kalt for his help.

Dr. Rimer proceeded to introduce new Board members: Dr. Philip Schein, President and CEO of U.S. Biosciences of Pennsylvania, who previously worked at the NCI; Dr. Vainutis Vaitkevicius, President of the Michigan Cancer Foundation in Detroit; and Dr. Alfred Goldson, Professor and Chairman of Radiotherapy at Howard University Hospital. She also announced the appointment of Dr. J. Michael Bishop, Nobel Laureate Professor and Director of the George Williams Hooper Research Foundation at the University of California in San Francisco, who will begin his tenure on the Board at the December program review meeting.

Dr. Rimer also introduced guests representing a wide variety of medical, research, and professional organizations, as well as Federal agencies. Dr. Rimer welcomed members of the public in attendance and told them that they could express their views on issues discussed during the meeting by writing to Dr. Kalt, Executive Secretary of the Board, within 10 days of the meeting. She announced that copies of the May minutes were in the Board members' notebooks and noted that 3-day meetings are scheduled for dates in 1994, 1995, and 1996, but that the meeting dates and lengths could change. Ms. Mayer moved to accept the May minutes and the motion was unanimously approved.

Dr. Rimer emphasized the importance of all members being present to achieve the quorum necessary for a vote. She explained that the NCAB quorum requirement had been amended to require that a majority of the appointed members be present to vote. Due to the fullness of the agenda, Dr. Rimer requested that all speakers use only their allotted time.

Dr. Rimer stated that grant applications would be reviewed during the closed session of the day's meeting and that any Board member who wished to discuss an application should alert Dr. Kalt before the end of the coffee break. She reminded everyone of the full schedule of committee meetings (Cancer Centers, Clinical Investigations, Planning and Budget, and Special Priorities) following the lunch break and informed members that the closed session would begin at exactly 3:00 p.m. and that all members should arrive promptly to ensure a quorum. Dr. Rimer announced that because of limited seating, there would be closed circuit television coverage and additional seating in other rooms.

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

Dr. Freeman congratulated Dr. Rimer on her appointment as Chair and expressed his honor at being reappointed as Chairman of the PCP, stating it is a challenge he takes very seriously.

Dr. Freeman briefly reviewed the President's Cancer Panel meetings of the last 3 years beginning in July 1991: "Cancer and Poverty," highlighting the relationship between the circumstances of poverty and cancer outcome; "Training and Science," stressing the need to continue the pipeline for new and talented young scientists to enter the research arena; "Breast Cancer Research," held at the M.D. Anderson Cancer Center; "The Transfer of Technology," held in California; "Cancer in Minority Populations," held in New York City, hosted by the American Health Foundation; "The Role of Voluntary Organizations in the War Against Cancer," held at the NCI; "Prostate Cancer," looking at treatment options and the need for more learning in that area; "The SPORE Program and Breast Cancer," held in San Francisco; "Cancer in the Family," looking at cultural, ethnic, and socioeconomic influences as they relate to psychosocial factors; "Evaluating the National Cancer Program," assessing six 6-month studies to re-evaluate the NCP; "Chronic Disaster Areas," looking at areas in the United States with exceedingly high death rates from cancer; and "The Role of the Government in the Cancer Research Mission," bringing together representatives from many parts of Government to discuss the roles of their agencies in addressing cancer.

Dr. Freeman reminded the NCAB of the most recent PCP workshop on "Avoidable Causes of Cancer," held in April 1994 in Bethesda, Maryland, and informed them that Dr. Joseph Fraumeni, Dr. Devra Davis, and Dr. Shelia Hoar Zahm are coordinating the peer review of papers from that meeting for publication in the *Journal of Environmental Health Perspectives*.

Dr. Freeman announced two upcoming PCP meetings; the first, "Lung Cancer: Clinical, Societal, and Governmental Challenges," will cover the basic research and clinical aspects of lung cancer, segments of society having a more difficult time with outcome and smoking incidents, and the role of Government and conflicts within Government with respect to tobacco. The Food and Drug Administration (FDA), Environmental Protection Agency (EPA), and other Government and private sector representatives will be present to speak on the last issue.

The second upcoming meeting, "Culture and Cancer," is designed to look at the impact of culture on cancer incidence and outcome from the perspectives of anthropologists, ethnologists, linguists, sociologists, marketers, and scientists to form an approach to a complex and culturally diverse society.

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

Dr. Broder began by welcoming the new members of the NCAB and congratulating Dr. Harold Freeman on his reappointment as Chair of the President's Cancer Panel. He urged all NCAB members to attend the upcoming PCP meeting on "Lung Cancer—Clinical, Societal, and Governmental Challenges." Dr. Broder noted that although the NCI plays a leadership role in smoking cessation due to the causal relationship between smoking and lung cancer, smoking cessation should also be a concern of every categorical institute within NIH.

Turning to staff announcements, Dr. Broder reported the appointment of Dr. Jerry Rice as Acting Director of the Division of Cancer Etiology (DCE), replacing Dr. Richard Adamson, who retired in August; Dr. Rice was also recently appointed as Associate Director of the Frederick Cancer Center Research and Development Group. Dr. Broder asked for assistance from the Board in the search for a permanent DCE Director. Dr. Broder announced that Dr. Barton Weick recently joined the NCI as a Clinical Veterinarian and is assuming responsibility for the Animal Health and Quality Assurance Program for the DCE. Dr. Broder announced the retirement of Dr. William Blot as Chief of the DCE Biostatistics Branch, who will become Chief Executive Officer of the International Epidemiology Institute, and the resignation of Mr. Mark Kochevar, DCE Administrative Officer, to become Administrator of the University of Maryland Cancer Center in Baltimore. Ms. Virginia Kiesewetter, Dr. Broder added, will serve as Acting Administrative Officer.

In the Division of Cancer Treatment (DCT), Dr. Broder reported, Dr. Mike Grever recently resigned to become Director of Hematologic Malignancies at the Johns Hopkins Oncology Center.

In the Division of Extramural Activities (DEA), Dr. Broder continued, Dr. Paulette Gray, Chief of the Review Logistics Branch, has succeeded Dr. Bob Browning, Chief of the Grants Review Branch (GRB), as Acting DEA Deputy Director. Dr. Kirt Vener, head of the Prevention Epidemiology and Control Review Section, GRB, will be the Acting Chief of the Review Logistics Branch. Dr. Lester Gorelic, Health Science Administrator, has been reassigned to the Comprehensive Minority Biomedical Program to direct the Minority Supplement Program and Minority Health Professional Training Initiatives. Mr. Kevin Washington, Deputy Chief of Administrative Affairs in the DEA Planning Branch, has completed his detail at the Office of Technology Transfer.

Dr. Broder referred Board members to a handout containing further information on staff issues, including a number of awards and honors recently received by NCI staff. He added that the NCI's Award Ceremony would be held on October 11th, and invited Board members and the public to attend.

Dr. Broder reported that Dr. Harold Varmus, NIH Director, has asked for the assistance of the NCAB in evaluating the organizational structure, function, and resource allocations of the intramural research program. A new working group has been established, to be chaired by Dr. Calabresi and co-chaired by Dr. J. Michael Bishop in their capacity as NCAB members, to help the NCI seek innovative ways to participate in the "reinvention of government." The goal

of the group is to improve the focus, integration, and coordination of basic and clinical research and facilitate the redirection of resources towards the highest priorities. The working group will examine the scientific and medical priorities that are central to the mission of the NCI and discuss the priorities that are most appropriate for intramural research efforts versus those that can be accomplished through grants and contracts. In particular, Dr. Broder stated, the group will consider whether the NCI is making optimal use of "government owned, contractor operated (GOCO) facilities" and whether this concept can be extended. Dr. Broder suggested that the findings of this group may be coordinated and integrated with the findings recently submitted to Dr. Varmus by an advisory committee to the NIH Director's Advisory Group.

In addition to Drs. Calabresi and Bishop, Dr. Broder reported that the reorganization working group is composed of Drs. Judah Folkman, Harvard Medical School; David Livingston, Dana Farber Cancer Institute; John Minna, Simmons Cancer Center, University of Texas; Cecil Pickett, Schering Plough Research Institute; Louise Strong, M.D. Anderson Cancer Center; Bert Vogelstein, Johns Hopkins Oncology Center; and Samuel Wells, Washington University School of Medicine.

Dr. Broder turned his attention to recent scientific discoveries, observing that two breast cancer susceptibility genes have recently been in the news. The *BRCA-1* gene, he noted, has been identified and sequenced, and a second breast cancer-associated gene—*BRCA-2*—has been mapped to chromosome 13. Dr. Broder mentioned that approximately 5 percent of all breast cancer cases in the United States are related to *BRCA-1*, and this gene is also associated with increased risk for ovarian cancer. While less is known about *BRCA-2*, he said, it is associated with certain familial, early onset breast cancers.

Dr. Broder explained that many researchers have collaborated and competed constructively in the effort to locate *BRCA-1*, from the identification of its probable site on chromosome 17 four years ago in Berkeley to discoveries made recently at the University of Utah and the National Institute of Environmental Health Sciences (NIEHS). He noted that many of the scientists involved in this search received considerable support from NCI grants. The events associated with the discovery of *BRCA-1*, Dr. Broder reported, are presented in the latest issue of the *Journal of the National Cancer Institute*. Dr. Broder stressed the fact that these discoveries are only the first step in learning how to solve the problem of breast cancer.

Dr. Broder reported that on July 1st, he signed a memorandum of agreement between the NCI and the National Aeronautics and Space Administration (NASA), establishing a formal scientific collaboration between NCI and NASA's Office of Life and Microgravity Sciences and Applications for the exchange of technology applicable to common problems. The major goals of this effort are to enhance knowledge of the response of living systems to radiation exposure and apply this knowledge to problems such as radiation protection, risk assessment, and the diagnosis and treatment of cancer.

Acknowledging the fact that research often depends on special reserves of cells and tissues, Dr. Broder referred to a recent NCI-sponsored meeting on breast cancer resources, at which current resources and future needs were discussed. He welcomed input from the NCAB on approaches to the issue of tissue registries and banks. The NCI, Dr. Broder added, is examining the possibility of using the cooperative groups to access some tissues and to stratify

tissues in certain clinical trials, as well as the possibility of using specific tissue registries and resources as an additional framework for the Surveillance, Epidemiology, and End Results (SEER) program. Dr. Broder mentioned that one action item in a plan for breast cancer research being developed by an advisory group to the DHHS Secretary focuses on establishing comprehensive patient data and materials as a research tool; he suggested that this objective should be included as part of virtually all of the Institute's efforts.

Dr. Broder announced that President Clinton has made approximately $100 million available for earthquake disaster relief in southern California. He noted that NIH has received about $1 million from this fund for assistance to research groups to repair or replace buildings, equipment, and supplies. In addition, many institutions have requested an extension of time for submitting grant applications because of delays associated with the earthquake.

Turning to his overview of the NCI budget, Dr. Broder reminded the Board members that a separate presentation was planned relating to certain budget and full time equivalent (FTE) issues. Dr. Broder presented slides that summarized the following:

In fiscal year 1994, the NCI spent approximately $2.08 billion; the NIH total for FY 1994 was about $10.9 billion. For FY 1995, the President submitted a budget that proposed approximately $2.19 billion for the NCI and $11.5 billion for the NIH. This was reduced by the House Appropriations Committee to $2.14 billion and $11.3 billion respectively. The Senate figures were similar and were approved in the final conference report on the budget. While the President's budget proposed an increase of $112 million for the NCI and $534 million for NIH, representing respective increases of 5.4 percent and 5 percent, the NCI increase was reduced in conference to $60 million, or 2.9 percent (for a total of $2.14 billion), and the NIH increase was reduced to $389 million, or 3.6 percent. Dr. Broder stated that this is the first time in his memory that the Congress has appropriated less than the amount requested in the President's budget.

Dr. Broder pointed out that the Director of NIH has a new authority to move 1 percent of any Institute's budget to another Institute without having to invoke an emergency need (in prior appropriations, such transfers had to be associated with an emergency). He also pointed out that AIDS funds included in his budget presentation are no longer provided directly to the NCI, but are secondary distributions of the appropriation made to the NIH Office for AIDS Research.

Dr. Broder reviewed NCI's assessment of increases necessary to meet what he described as "bare bones" needs, based in part on the President's original budget, inferences and mandates from legislation, and the Institute's historic priority needs. These increases included about $2.6 million for high-performance computing; $50 million for breast cancer research ($10 million for the Secretary's Advisory Group action plan and $40 million for other breast cancer commitments); $6 million for AIDS; and $25 million for Cancer Prevention and Control (a statutory increase based on a mandate in the NIH Revitalization Act requiring the NCI to spend 9 percent of its budget on cancer control in FY 1995). These and other increased needs, Dr. Broder concluded, add up to at least $94 million, while the appropriation provides an increase of only $60 million.

Dr. Broder provided data on funding for the research project grant line, which is composed predominantly of R01s—traditional investigator-initiated grants. The amount for this line was approximately $916 million in FY 1994 and is just short of $920 million in FY 1995. Based on the way grants are cycling in FY 1994, there will be an increase of 12 percent for new and competing grants. Small business applications, which, Dr. Broder explained, result from a statutory requirement to set aside 1 or 2 percent from research and development funding, increased from about $22 million to nearly $29 million. Thus, the total for this line increased by approximately $9 million, from $938 million to $948 million, for an increase of 1 percent.

The Cancer Centers (P30s), Dr. Broder continued, increased from $131 million to $132 million, or about 1 percent. The SPORE (Special Programs of Research Excellence) line (P50s) fell from about $27 million to $25.8 million, a decrease of 4 percent. These two lines (which are linked by the Office of Management and Budget) increased from $157.5 million to $158 million, an increase of about one-half million dollars. Dr. Broder emphasized the NCI's commitment to stabilizing the traditional Cancer Center core grant. When the SPORE line was started, he noted, many people were concerned that funding for these programs would be taken from the P30 line. Dr. Broder stressed the fact that this did not happen, and that new monies were used to create the SPORE program.

Dr. Broder continued by stating that funding for research career programs, cancer education programs, and minority biomedical research was held essentially at the same level, and that the cooperative group line has received a slight increase. The totality of these grants programs, he stated, was funded at $1.2 billion in FY 1994 and has been increased by about $9 million, or 0.8 percent.

NRSA training increased by 2.8 percent, from $37 million to $38.5 million. The R&D contract line increased by approximately $7 million. Dr. Broder pointed out that this apparent increase in R&D will be offset by a Departmental tap that will remove funds for a program evaluation effort. Funding for the intramural program has increased by about 1 percent, to a level of $378 million. Cancer prevention and control, with by far the largest increase, has risen from $145 million to about $192 million, an increase of $47 million, or approximately 33 percent. Dr. Broder concluded his outline of the budget by noting that the construction line is falling, and that the $8 million currently available will be used primarily to cover the remaining obligations associated with the proton beam program and a few other commitments. The future of the construction program will be the focus of further discussions.

In comparing the NCI increase of 2.9 percent with the funding received by other Institutes, Dr. Broder noted that the National Heart, Lung, and Blood Institute, which is similar in size to NCI, received a similar increase. He added that all of the other Institutes received increases in the same range. Exceptions included the Human Genome Project, which was increased by about 20 percent, and the Office of the Director, NIH, which was increased by 7.3 percent. Overall, NIH received an increase of 3.6 percent. The Office of AIDS Research, from which all Institutes receive support, increased by 3.1 percent. In most cases, Dr. Broder observed, the categorical Institutes received less than the amount requested in the President's budget. He explained that this resulted at least in part from the Omnibus Budget Reconciliation Act, Public Law 101-508, also known as the Budget Enforcement Act, which sets substantial limits for several categories of spending. These restraints will continue to limit

domestic discretionary spending, Dr. Broder added, at least through FY 1998. He noted that these limits are unprecedented in the modern history of the NIH.

To illustrate the NCI's commitment to clinical research, Dr. Broder presented data on funding for the two major mechanisms—the clinical cooperative groups and the community clinical oncology program—by which the Institute supports interdisciplinary and interinstitutional clinical trials, particularly randomized clinical trials, which have the greatest potential for affecting medical perspectives and changing the way cancer is diagnosed and treated. These two mechanisms have increased by 54 percent since FY 1991, while the NIH budget as a whole has increased during the same period by about 25 percent. Dr. Broder added that the Institute's effort to maintain a commitment to clinical research has included the initiation of a number of new mechanisms, which could be discussed during future NCAB or subcommittee meetings.

Dr. Broder closed his remarks by pointing out that since FY 1992, the NIH budget has grown by about 15 percent, while the NCI budget has grown by 4 or 5 percentage points less.

Questions and Answers

Dr. Ellen Sigal expressed concern about the fact that NCAB representation on the new working group described by Dr. Broder is limited to two members and does not include any representatives from industry. Dr. Broder pointed out that Dr. Pickett is a representative of private industry.

Dr. Salmon added that he wrote to Dr. Varmus with his concerns about the composition of the group and the fact that the plans for its formation had not been brought before the NCAB prior to implementation, nominations, and selections. He stated that he has received no reply from the NIH Director's office; Dr. Rimer said she understands that an answer is forthcoming.

Dr. Calabresi noted that the selection of group members was made by Dr. Varmus, who placed an emphasis on selecting scientists. He added that as co-chair of the committee, he would like to have a special session with consultants from industry and business. In response to Dr. Salmon's comment, Dr. Calabresi pointed out that the committee is a working group whose responsibility will be to report back to the NCAB. Dr. Rimer added that a draft report is expected to be delivered at the May 1995 NCAB meeting.

Dr. Broder expressed his hope that the group will be able to address the legitimate concerns that have been expressed by the NIH Director. Many members of the Board, Dr. Broder suggested, could provide examples of the difficulties of dealing with managed care and other constraints in the private and academic sectors; he related, as an example of the difficulties faced by those in the Government sector, the fact that the NCI has recently lost one-eighth of its work force. While there has not been an official reduction in force, the effect has been the same. There are also profound limitations, Dr. Broder stated, on promotion of staff from the GS-13 to the GS-14 level and entry into the Senior Executive Service. Although the NCI is under the ceiling for FTEs, he said, there are still extreme limitations on hiring. In addition, the NCI is required to reduce the ratio of supervisors to employees from 1:8 to 1:13 by 1999.

Dr. Broder stressed that these restructuring efforts will have an impact on the NCI's ability to provide services such as grants management and processing of drug applications. He expressed hope that services can still be provided through increased efficiency and the use of innovative mechanisms such as the GOCO concept mentioned earlier. Dr. Broder noted that the NCI's mission must be carried out by highly trained professionals, and that the Institute cannot use other mechanisms sometimes available to other agencies. The NCI is heavily science-based, even at the administrative level.

As to the structural issues related to how the review of the intramural program should be conducted, Dr. Broder stated that the NCAB has virtually unlimited freedom in supplementing or paralleling this process. While Drs. Calabresi and Bishop will provide a mechanism for NCAB input, he said there could be a number of other formats for incorporating NCAB concerns, including the issue of business representation. Dr. Broder also noted that many issues contained in the recent report from the Subcommittee to Evaluate the National Cancer Program will overlap with the new working group's concerns.

Dr. Schein expressed concern that $210 million, representing 10 percent of the NCI budget, is placed at risk as a result of the new funding mechanism for AIDS research. He expressed hope that NCI's past efforts in this field will be fully recognized by the Office of AIDS Research and that appropriate distributions of AIDS-related research funds will be made in the future. Dr. Schein asked Dr. Broder to keep the Board informed on progress in this area and suggested that the Board could lend its support to the NCI's needs in terms of AIDS research funding.

Dr. Rimer remarked that the Planning and Budget Subcommittee might also address the risk of losing 1 percent through the transfer authority. Dr. Broder pointed out that the NCI could potentially lose or gain funds through the transfer authority.

V. LEGISLATIVE UPDATE—MS. DOROTHY TISEVICH

Ms. Dorothy Tisevich, the NCI's legislative liaison, presented a brief update of legislative activities related to NCI. NCI staff participated in several hearings and briefings since the last NCAB meeting. On June 15th, Dr. Broder testified before Congressman John Dingell (D-MI) in the second of two hearings that focused on the oversight and management of clinical research conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP). Other testimony was presented by officials from Zeneca Pharmaceuticals, the manufacturer of tamoxifen; and representatives from the University of Pittsburgh, which holds the NSABP Operations and Statistical Center Cooperative Agreements. After the hearing, Congressman Dingell commended both Dr. Broder for his testimony and leadership, and officials from the University of Pittsburgh for undertaking remedial actions. He indicated that his subcommittee will continue to monitor implementation of the promised reforms at the University of Pittsburgh.

On August 1st, Dr. Edward Sondik, Acting Deputy Director of NCI, and Dr. Iris Obrams, Director of the Long Island Breast Cancer Study Project, testified before Representative Sherrod Brown (D-OH) at a field hearing in Lorain, Ohio, regarding breast cancer rates in northeastern Ohio. Drs. Sondik and Obrams discussed national breast cancer rates, NCI research regarding the role of potential environmental causes of breast cancer, and other NCI breast cancer research programs.

A briefing was held on August 10th for Representative Charles Schumer (D-NY) on stem cells and cord blood transplants. Dr. Malcolm Smith from the Division of Cancer Treatment represented NCI, and representatives attended from the National Heart, Lung, and Blood Institute, the National Institute of Allergy and Infectious Diseases, and the National Institute of Diabetes, Digestive, and Kidney Diseases. These participants emphasized to Representative Schumer the need for more research before establishing a stem cell bank for transplantation purposes.

On August 11th, Dr. Bruce Cheson from the Division of Cancer Treatment testified before the Subcommittee on Compensation and Employee Benefits, chaired by Delegate Eleanor Holmes Norton (D-DC), regarding the role of autologous bone marrow transplantation (ABMT) in the treatment of breast cancer. The hearing focused on whether ABMT for breast cancer should be covered for Federal employees under the Federal Employee Health Benefits Program. Ms. Tisevich stated that late last month (September) the Director of the Office of Personnel Management announced that all Federal employee health plans would be required to cover high-dose chemotherapy and ABMT for breast cancer, ovarian cancer, and multiple myeloma, but the specifics of this coverage needed clarification.

Ms. Tisevich announced that during the previous week, Dr. Calabresi and other members of the NCAB's Subcommittee to Evaluate the National Cancer Program presented to Senator Claiborne Pell (D-RI) and other congressional staff a briefing on the report, "Cancer at a Crossroads," which is expected to be discussed at the FY 1996 appropriation hearings next spring. Many people called after the briefing to request copies of the report.

Ms. Tisevich added that the House and Senate report language regarding the Department of Defense (DoD) appropriation, mentioned by Dr. Broder, appears in the legislative update, and a table appears on page 17 of selected areas related to NCI research programs. She clarified that $237 million will be appropriated for cancer-related research activities for DoD, but it is not yet known how the funds will be spent. Ms. Tisevich predicted that the 103rd Congress will take no further action with respect to health care reform, but that instead, proposals will be reintroduced by the 104th Congress in January. She noted that attached to the legislative update was a report from the Congressional Research Service summarizing action on the major health care reform proposals that were introduced during the 103rd Congress.

Ms. Tisevich stated that House Joint Resolution 311 designating October 1994 as Breast Cancer Awareness Month is expected to be passed by both houses and forwarded to the President. Several new bills have been introduced in the House and Senate.

The Family Cancer Screening and Research Partnership Act of 1994, introduced by Senator Ted Stevens (R-AK), would authorize Federal partnerships with nonprofit organizations to facilitate breast, cervical, and prostate cancer screening activities and expedited development of effective treatments. The screening portion of the bill, Ms. Tisevich explained, would be established under the Centers for Disease Control and Prevention and would allow nonprofit organizations to acquire and equip mobile vehicles to conduct cancer screening procedures for low-income or geographically isolated men and women in areas like Alaska where access is a serious problem. The research component would be a responsibility of NCI through the award of cooperative agreements to qualified institutions or organizations. CAP CURE, the Association for the Cure of Cancer of the Prostate, has already expressed an interest in such a partnership with NCI and met to discuss options for cofunding research projects in prostate cancer, which can be done without the passage of legislation.

The Health Care Demonstration Screening Program (HR 4988), introduced by Representative Ralph Regula (R-OH), provides for a 4-year demonstration project under Medicare to test the cost-effectiveness of furnishing colon, prostate, and uterine cancer prevention screening examinations and evaluate their usefulness in decreasing the incidence of these cancers. The Prostate Cancer Diagnosis and Treatment Act of 1994 would provide Medicare coverage for prostate cancer screening and treatment, include screening and other services within the Department of Veterans' Affairs, expand prostate cancer research and education programs within the Public Health Service, authorize additional sums for prostate cancer research for FY 1994 through 1998, and require the Agency for Health Care Policy and Research to conduct research on the outcomes, effectiveness, and appropriateness of health services and procedures related to prostate cancer, as well as provide for the development, review, and updating of clinically relevant guidelines, standards of quality, performance measures, and medical review criteria.

New tobacco-related bills that have been introduced include: HR4658, the Truth in Tobacco Labeling Act, that would require any labeling, advertising, or promotion of tobacco products to disclose the additives to and constituents of the products in smoke; HR4698, Tobacco Programs Termination, that would end price supports and marketing quotas for tobacco, disallow the income tax deduction for certain advertising expenses for tobacco products, and establish a trust fund to support antidrug and antitobacco use activities; S2245, the Medicare and Medicaid Third Party Liability Act, that would allow the Federal Government to recover billions of dollars in Federal health care funds currently spent on tobacco-related illnesses and diseases by authorizing the U.S. Attorney General to seek third party payments from manufacturers of tobacco products. Ms. Tisevich offered to provide copies of the bills she had cited.

Ms. Tisevich briefly reviewed upcoming activities. She reported that Dr. Sondik and Dr. Barbara Edwards from the Division of Cancer Prevention and Control would testify on the following day before Representative Edolphus Towns (D-NY), Chairman of the Government Operations Subcommittee on Human Resources and Intergovernmental Relations, regarding breast cancer in minority women. Ms. Tisevich noted that this hearing is one of a series on NCI research activities.

Ms. Tisevich said that Dr. Susan Blumenthal would also testify on the following day about collaborative research projects between HHS and DoD before the House Armed Services Subcommittee on Research and Technology, chaired by Representative Pat Schroeder (D-CO). Ms. Tisevich announced that the NCI has been asked to testify at an October 5th hearing of the House Republican Task Force on Women's Issues to draw attention to Breast Cancer Awareness Month. Ms. Tisevich reported that both the House and Senate are scheduled to adjourn in early or mid-October. She concluded by remarking on the large number of congressional seats expected to change hands due to retirements and the election, and the consequences this will have in new committee memberships and chairmanships. Ms. Tisevich said she hopes to have an update on new committee assignments by January 1995.

VI. AWARDS/NEW BUSINESS: SESSION I—DRS. BARBARA RIMER AND SAMUEL BRODER

Award To Honor Dr. Howard Temin

Dr. Broder introduced Dr. Rayla Temin, a scientist of formidable stature in her own right, and thanked her for accepting the NCAB's invitation to be present in honoring her late husband, Dr. Howard Temin. Dr. Broder described Dr. Howard Temin as one of the most creative and determined scientists in the NCP, a leader in—and in a number of ways the founder of—the field of modern retrovirology. Dr. Temin's pioneering discoveries, despite great skepticism in the scientific community, paved the way for current scientific activity and biotechnology in the field.

Dr. Temin, Dr. Broder continued, was a Nobel Laureate whose contributions to basic and biomedical research have been central to the development of molecular biology over almost 35 years. Dr. Broder attested to the enduring usefulness of Dr. Temin's observations. The retroviruses Dr. Temin studied in his efforts to find the cause of cancer enabled development of important insights as to how cancer occurs and how to approach early diagnosis, prevention, and treatment. His research later provided the ability to respond to AIDS, and retroviruses are now at the heart of novel genetic therapies for cancer.

Dr. Broder described Dr. Temin as an exceptional public servant as well as a scientist, who served on several advisory committees and guided the NCI and the nation in shaping the early stages of both cancer and AIDS research. He also impacted the foundation of the NCI as a scholarly organization through his speeches to young scientists about their ethical responsibilities and the importance of standing up for the scientific truth, even when it is unpopular.

Dr. Temin was extremely dependable, with mature, balanced judgment and a sense of humor that enlivened debate and diffused anger. He always found time to talk to his colleagues about the NCI, according to Dr. Broder, and even when ill, made every effort to attend NCAB meetings, sometimes through conference calls.

To exemplify Dr. Temin's philosophy of science, Dr. Broder repeated his quote from a 20th anniversary presentation of issues related to the discovery of retroviruses, "Thus we see how apparently inefficient science is, how it is impossible to predict the consequence of

science, and how good science almost always has fruitful consequences. Specifically, good, untrammeled research, undirected except by the curiosity of the individual scientist, provides the knowledge necessary to understand and to treat human disease."

Following this introduction, Dr. Rimer read aloud the following NCAB resolution:

"Whereas, Howard Temin, born December 10th, 1934, in Philadelphia, began a life-long interest in science after attending a summer program for high school students at the Jackson Laboratory in Bal Harbor, Maine, and;

"Whereas, he published his first article at the age of 18 after graduating from Swarthmore College and completed his Ph.D. at California Institute of Technology in 1959 where he first began his research on cancer viruses in animals, and;

"Whereas, he joined the University of Wisconsin's McArdle Laboratory for Cancer Research in 1959 and spent the rest of his career investigating the links between viruses and cancer, and;

"Whereas, Howard Temin thrust aside criticism to speculate and then show that some viruses carry their genetic information in RNA, which is then copied into DNA. His theory was supported by his 1970 findings that reverse transcriptase helps in the development of the science of retrovirology, the study of retroviruses that cause cancer and AIDS, and;

"Whereas, Howard Temin was awarded the Nobel Prize for Physiology and Medicine in 1975, an award shared with his former professor, Renato Dulbecco, and David Baltimore, was awarded an Albert Lasker Award in 1975, and was presented with a National Medal of Science by President George Bush in 1992, and;

"Whereas, Howard Temin believed passionately in cancer prevention, as well as in basic cancer research, never smoked and was such an opponent of tobacco use that in his speech following acceptance of the Nobel Prize, he scolded the members of the audience who were smoking, and;

"Whereas, Howard Temin served 7 years as a member of the NCAB and became one of the most active members of the Board, continuing his participation until his untimely death from lung cancer February 9th, 1994, and;

"Whereas, with passion and brilliance he delineated the crucial role of investigator initiated basic research as a major force in advancing scientific knowledge, and the strength of his service was typified by the fact that he attended his final meetings of this Board by a speaker phone when unable to attend in person.

"Therefore, be it resolved that the National Cancer Advisory Board wishes to extend its deepest sympathy to his widow, Rayla Greenberg Temin, his wife, and to his daughters, Sarah Temin and Miriam Temin, and to express the appreciation of the Board for the life and work and courage of Howard Temin. He was an inspiration to all of us who continue the battle against cancer that Howard waged so well."

Dr. Rayla Temin thanked the Board on behalf of her daughters, Sarah Temin, who lives in Berkeley, California, and Miriam Temin, who lives in Cambridge, Massachusetts, both of whom were unable to attend. She corrected the fact that Dr. Temin' s Nobel Prize was for Physiology or Medicine. Dr. Rayla Temin told of how Dr. Howard Temin was diagnosed with cancer and had to curtail some activities and prioritize his time. She said that his family came first and that he tried to pursue all he could in teaching, research, and public service. Dr. Rayla Temin said that he carried on his laboratory work as much as possible, meeting with his students every Friday that his treatments allowed him to do so. Fifteen papers were published from his lab during the time he was ill, and a number of students continue to carry on his work.

While he was forced to resign from his other committee work, he stayed on the NCAB, which Dr. Rayla Temin considered testimony to his deep commitment to the work of the Board. She said that he was happy to participate in the decision making, even during the meetings for which he was ill and had to attend by speaker phone.

She reminded the Board of how far reaching cancer is and the tragedy of Dr. Temin losing his life to the disease he spent his life studying. She told of Sarah Temin's recent involvement with the Women's Cancer Resource Center and Miriam Temin's attendance at the Harvard School of Public Health, and reflected that Dr. Temin's legacy will be carried on through his daughters.

Dr. Rayla Temin stated that she had not been to Washington since Dr. Howard Temin became ill, and that she felt it appropriate to be in the room he had worked in, discussing issues important to cancer research. On her last trip to Washington, she accompanied Dr. Temin to the White House, where he received the National Medal of Science. He had spent weeks deciding what he would say to the President when he had that opportunity. He chose to emphasize the importance of maintaining support for basic research and bringing it into the clinical setting—an issue about which Dr. Temin felt very strongly.

In closing, Dr. Rayla Temin explained that in the Jewish religion, when someone passes away, you affix to the name the expression, "may his memory be a blessing, " and she hoped that Dr. Temin's memory would be a blessing to those who knew and loved him, and with whom he worked. Dr. Rimer thanked Dr. Rayla Temin for coming and thanked those who had contributed to the resolution in Dr. Howard Temin's honor.

New Business

Dr. Rimer opened the floor to new business by calling on Dr. Calabresi to discuss a resolution from the last Activities and Agenda Subcommittee about restructuring meeting dates. Dr. Calabresi explained that while Board meetings are typically held on Mondays and Tuesdays, there has been sentiment to change the days to Tuesdays and Wednesdays. He discussed the pros and cons that were examined by the Subcommittee and the ultimate recommendation that meetings be moved to Tuesday and Wednesday, allowing Monday to be used as a travel date for West Coast members and for early committee and subcommittee meetings. Dr. Calabresi made a motion to approve the change, and Dr. Salmon seconded it. The motion passed unanimously. The new meeting days will be scheduled beginning in January.

VII. FDA PERSPECTIVES ON TOBACCO PRODUCTS—DR. DAVID KESSLER

FDA Commissioner Dr. David Kessler presented a summary of developments regarding the regulation of cigarettes as a drug under the Federal Food, Drug and Cosmetic Act. Dr. Kessler explained that in December 1990, when he became Commissioner of the FDA, several petitions had already been filed that solicited FDA classification of low-tar cigarettes as a drug under this act. These requests were based on the assertion that there were implied health claims contained within the low-tar declarations these cigarettes displayed. Dr. Kessler reminded members that in the late 1970s the Shriker group sued the FDA in a class action on smoking and oral health to force the agency to begin regulating cigarettes. The agency declined at that time on the basis that requisite statutory criteria for such an action had not been fulfilled.

Dr. Kessler stated that the petitions, some of which had been pending action since 1988, were discussed soon after he arrived at the agency. The discussions focused on two primary points: 1) that it would be inappropriate as public health officials not to focus their efforts on all cigarettes; and 2) that the issue of regulation of all cigarettes would require a great deal of time and effort. Dr. Kessler explained that it was decided to address other issues first, such as food labeling and accelerated drug approval, as the enormous effort to regulate cigarettes would potentially exclude the agency from dealing with any other topic. He added that addressing the other issues first was not an indication of importance, as tobacco clearly poses the largest risks of all the substances the FDA regulates. It was more a result of the need to properly prepare the agency for this broad effort and to develop a plan of action.

Dr. Kessler informed members that during the following year and a half it became cle that the focus should not be on cigarettes themselves, but on nicotine regulation. He indicated that on February 25, 1994, the FDA issued a letter, which all NCAB members were provided with, that outlined their rationale and approach to cigarette regulation.

Dr. Kessler read a paragraph that stated that evidence was being compiled, which indicated that cigarette manufacturers intended to fulfill an addiction among their consumers by adding nicotine to their product. This was inferred through a growing body of evidence that pointed to the fact that nicotine was a highly addictive substance, as reported in the 1988 Surgeon General's report, and that the manufacturers were manipulating the amount of nicotine found in cigarettes to satisfy addictive cravings among consumers.

Dr. Kessler informed members that under the Food, Drug and Cosmetic Act, "an article except for food intended to affect structure and function of the body," may be regulated as a drug by the FDA. He stated that numerous studies have been published that document the effects of nicotine on the central nervous system, with the most significant effect being its ability to cause addiction to cigarettes, a harmful product. The definition provided by this Act also requires intent to act as a drug to be proved. Dr. Kessler indicated that by purposefully regulating the level of nicotine found in cigarettes, manufacturers are proving that they intend an effect from this substance. He reported that an additional indication of intent was provided through evidence that addiction research was being conducted by one of the large tobacco companies.

Dr. Kessler reported that research showed that tobacco companies had made statements in the 1960s and 1970s that nicotine was a beneficial drug and that cigarettes were the most ideal mechanism for administering it. Dr. Kessler asserted that the motivation for these statements was fear that they were losing marketshare to the tranquilizing business.

Dr. Kessler stated that the addictive properties of nicotine had been definitively concluded in the 1988 Surgeon General's report and reaffirmed by an advisory committee this past year. Regarding the issue of intent, Dr. Kessler informed members that one of the large tobacco companies secretly initiated a 10-year research project to develop a tobacco plant that contained twice the level of nicotine that occurred naturally. Dr. Kessler continued by stating that substantial other evidence exists of attempts by tobacco campanies to control nicotine levels through the use of ammonia technology and varying pH levels, as well as the discovery of internal documents mentioning threshold levels established by the companies. He indicated that the most impressive evidence of intent are statements by the companies themselves. One statement issued by the general counsel of one of the tobacco companies in the 1960s was extremely explicit, "We are then in the business of selling nicotine, an addictive drug."

Dr. Kessler pointed out that the main argument used against regulation is that smoking is a choice that adults make. He refuted this argument by stating that people do not begin smoking after age 21. Marketing research conducted by some Canadian tobacco companies indicated that initiation of smoking primarily occurs between 11 to 14 years of age. In addition, Dr. Kessler informed members that this research revealed that while these children are aware of the effects of smoking, they do not believe they will still be smoking in 5 years and, therefore, believe they will not be harmed by the habit. Data show that by 16 or 17 years of age, these children begin smoking on a daily basis, which is when they finally recognize that they are addicted. Dr. Kessler stated that at this point, however, it is often difficult for them to stop smoking.

Dr. Kessler expressed his belief that smoking is more appropriately characterized as a pediatric disease rather than an adult choice; nicotine is addictive and this addiction is occurring during childhood years.

Questions and Answers

Dr. Sigal commented that the Occupational Safety and Health Administration (OSHA) is in the process of creating indoor air legislation, which contains two components: 1) prohibition of cigarette smoking in any work environment, including restaurants, hotels, and office buildings; and 2) development of a systems approach to indoor air. He continued by stating that the second element is an extremely complicated and controversial piece of legislation and, therefore, will take a great deal of time to complete. Dr. Sigal asked Dr. Kessler whether he, as a result of the complexity of the second issue, has begun work with OSHA to get approval for the first segment, the smoking ban at work, which has wide support.

Dr. Mann responded by explaining that this is only proposed legislation at this point. OSHA is holding a series of hearings on these proposals to examine all the involved issues and to ensure they proceed in accordance with their statutory purview. Dr. Mann informed Board members that even if OSHA approved the legislation, the executive branch would still need to do so. He stated that while the various agencies work to keep each other informed, in terms of

advocating a specific position, the FDA's current undertaking, regulation of nicotine, deserves the most support. Dr. Mann expanded the importance of the FDA's efforts by saying that in addition to the regulation of cigarettes, the FDA would be able to control other nicotine products, such as snuff and chewing tobacco, which are being used more frequently among children, who are most susceptible to addiction.

Dr. Broder, Director of NCI, expressed the Institute's complete support for the FDA efforts to assume regulation of nicotine as a drug, as well as NCI support to conduct the standard safety and efficacy research regarding such drugs. He added that additional standards for the pediatric use of the drugs should be explored and applied, and offered NCI staff support for the research. Dr. Kessler responded by stating that the issue is more complicated than a unilateral prohibition of smoking. The FDA has to develop other mechanisms that would, for example, restrict children from acquiring cigarettes.

Dr. Freeman pointed out that tobacco is a very controversial issue even among the Government agencies, with some attempting to sell it, others to grow it and others to prohibit it. He asked whether the various agencies are working together on the issue of regulation of nicotine, and secondly, what the next step will be for the FDA. Dr. Kessler responded by saying that there is only one Government and that there is interagency communication; however, he asserted that the authority to classify nicotine as a drug under the Federal Food, Drug and Cosmetic Act is vested with the FDA. The next step will be to decide whether nicotine has fulfilled the criteria to be considered a drug under the Act.

Dr. Mann explained that the Government supports the growing of tobacco by the small farmer. The alternative would be to allow large corporate farms or imports from other countries to take over the market. Dr. Salmon supported the FDA focus on nicotine for regulation efforts, not only because of its addictive properties, but because it is known to behave as a carcinogen in the body.

Dr. Yodaiken clarified OSHA's position, in that it cannot regulate cigarettes or smokers; it can only regulate passive smoking as a result of the risks it confers on coworkers. Dr. Yodaiken added that OSHA has received approximately 100,000 letters, some of which have leveled serious complaints against the agency. He asserted that many of the letters are the result of letter-writing campaigns organized by the tobacco industry.

Dr. Rimer suggested that the NCAB discuss the possibility of passing a resolution in support of the FDA's regulation of nicotine during the next day's session.

VIII. FINAL REPORT: SUBCOMMITTEE TO EVALUATE THE NATIONAL CANCER PROGRAM—DR. PAUL CALABRESI

Dr. Calabresi reminded everyone that a copy of the final report is included in their handouts. He noted that although this is the final report, the implementation of the Committee's recommendations is just beginning. He indicated that he would review the essence of the report for the benefit of anyone unfamiliar with its contents.

Dr. Calabresi noted that the title of the report, "Cancer at a Crossroads," is indicative of the time of decision in which the Committee finds itself. The report was elicited by the Appropriations Committee of the House and Senate. The Congress questioned the progress of the National Cancer Program, citing the fact that in spite of a 23-year and $25 billion investment, cancer mortality is on the rise.

Dr. Calabresi complimented the success of the Subcommittee which was assembled to address Congress' request. He noted that approximately one-third of the team of experts from the fields of cancer, molecular biology, drugs and vaccines, clinical research, and patient care came from the National Cancer Advisory Board.

Dr. Calabresi described what the Subcommittee determined to be the six major issues in the fight against cancer: current health care reform, the absence of national coordination, inadequate cancer care, laws and public policy, the need to support translational research, and the unprecedented opportunities in basic research that exist today.

Although none of the members of the Subcommittee were opposed to health care reform, Dr. Calabresi said members felt that two issues had not received enough attention in the proposals they had reviewed. One was a lack of research money. The second was a concern that the current proposals would send patients to primary care physicians for cancer treatment. It is the Subcommittee's contention that giving the major responsibility for cancer care to primary care physicians will result in denying quality cancer care to the people.

Since there are many agencies involved nationwide, Dr. Calabresi stressed that placing the responsibility for winning the war against cancer on the NCI alone is unfair and that some type of national coordination among these agencies is necessary. He noted that many people are receiving inadequate cancer care, and that the battle against cancer cannot be won until the knowledge that is currently available is delivered to all the population. Currently, Dr. Calabresi continued, about 50 percent of cancer cases can be cured. If all of the current knowledge were available to and utilized by the American population, he added, half of the remaining 50 percent of cases could probably be prevented or cured. He maintained that this dilemma clearly illustrates the need to support translational research to ensure the transference of research from the laboratory to the general public.

Dr. Calabresi observed that seeming contradictions in current laws, public policy, and Government regulations undermine cancer prevention, treatment, and control efforts. He cited the policy of spending millions of dollars trying to prevent lung and other cancers, while at the same time providing subsidies to tobacco farmers. He then summarized the three major barriers to the NCP as: ineffective coordination and inconsistent legislation, policy, and regulation; lack of access to effective cancer care and education among the poor, elderly, and special populations; and funding constraints and resource shifting that affect training, outreach, treatment, and research of all types.

Dr. Calabresi reiterated that although there are many other Federal agencies, it is often the NCI that receives the blame for not having cured cancer. In addition to Government and Federal agencies, there are also many private organizations and health care providers which should be involved in part of a coordinated network of cancer organizations.

Finally, perhaps the most difficult barrier to overcome is resistance of individuals to changing their habits. No matter how many recommendations are made and how much knowledge is amassed, unless the public is willing to take on its share of the responsibility, the war against cancer cannot be won.

Dr. Calabresi described the structure of the report, which is divided into three chapters: Application of Research: Bringing the Benefits to All of the People; Translational Research: Bridging the Gap Between the Laboratory and the People; and Basic Cancer Research: Maintaining Excellence, Accelerating Progress. He stressed that the sequence of the chapters was intentional, to emphasize up front the amount of progress which has already been made. The Subcommittee believed that Congress would be most interested in knowing the information that is already available and the means to disseminate it among their constituents.

Next, Dr. Calabresi addressed fiscal issues. He explained that it was beyond the time constraints and the scope of the Subcommittee to report how much it would cost to fund the cancer program nationally. He observed that a large portion of the money needed would have to be spent in the delivery of health care, which alone would produce staggering figures.

However, there were some research areas for which the Subcommittee was able to estimate costs. One of the areas for which funding was recommended was investigator-initiated cancer research grants. Until around 1989, funding for investigator-initiated cancer research was keeping up with a 3 percent cost of living increase. After 1989, funding reached a plateau. The Subcommittee recommended $180 million in additional funds to raise total funding from $710 to $890 million in order to bring the funding back up to a reasonable level. The Subcommittee further requested a 3 percent increase over and above the cost of living to ensure that opportunities for basic science research will be available.

The Subcommittee's second recommendation is to allocate $60 million for translational research. This figure was reached based on the assumption that an additional $1 million for translational research to each of the 55 to 60 Cancer Centers nationwide would substantially aid in bridging the gap between the research and the general public.

Dr. Calabresi observed that the allocation of $60 million to translational research and $180 million for investigator-initiated research is not excessive with an annual budget of $2 billion.

The four final recommendations of the Subcommittee were next reviewed by Dr. Calabresi. The first is that a Presidentially led plan be established for overall coordination of the National Cancer Program that includes appropriate Cabinet-level representation. Secondly, a detailed evaluation on cancer research programs and priorities should be performed by a committee to be chaired by Drs. Calabresi and Michael Bishop. Thirdly, sufficient funding to maintain a balanced portfolio of basic translational and applied research should be provided. And, finally, the number of NCI Cancer Centers and community-based oncology programs should be expanded and their scopes broadened to enhance research, expand outreach, and improve distribution.

Dr. Calabresi addressed the implementation of these recommendations, noting that both Dr. Barbara Rimer and Dr. Sam Broder have expressed a strong interest in seeing that the

NCAB aid in the implementation of these recommendations. He also stated that Dr. Harold Freeman from the President's Cancer Panel will be a great asset in accomplishing the Subcommittee's goals.

Dr. Calabresi restated the recommendations for basic research to increase the pool of funds for investigator-initiated grants; preserve the infrastructure that supports the academic research; and improve as well as simplify the grant application, review, and award process. These tasks will, in part, be the responsibility of Congress and the executive branch. However, Dr. Calabresi maintained that the participating agencies—NCI, NIH, and other Federal agencies, as well as private organizations—will also be responsible for implementation of the recommendations.

Dr. Calabresi presented a slide on recommendations for translational research, which encourage the establishment of Cooperative Research and Development Agreements (CRADAs) and the expedited review and approval of drug devices. Dr. Calabresi stressed that NCI will be involved in the implementation of these recommendations. He also noted the need to reduce tobacco products and improve cancer care delivery under the Cancer Centers Program.

Dr. Calabresi acknowledged that the recommendation to provide universal access to state-of-the-art cancer care and extend the knowledge about cancer prevention and care is outside of the jurisdiction of the Subcommittee and will require Federal action.

The final recommendation discussed was the coordination of the National Cancer Program. The Cancer Program is an executive and congressional decision to reestablish the 1971 legislative authority and evaluate the cancer research programs and priorities. Dr. Calabresi stated that Dr. Sam Broder, the NCAB, and other Federal research agencies will be involved in the coordination effort.

Ms. Cherie Nichols was recognized for her work as Executive Secretary of the Subcommittee. Ms. Nichols acknowledged everyone on her staff for their efforts.

Additional Comments—Dr. Harold Freeman and Ms. Ellen Stovall

Dr. Calabresi requested that Dr. Freeman and Ms. Ellen Stovall give their interpretation of the congressional session. Dr. Freeman observed that the greatest single obstacle in the war against cancer is the misconception on the part of the American public that any one person or agency can solve the problem. He stressed the importance of universal access to health care and the need for the Government to take a stand on the issue of tobacco. He reiterated that the President's Cancer Panel would like to be involved in monitoring the progress of the Subcommittee's plan.

Dr. Calabresi then introduced Executive Director of the National Coalition for Cancer Survivorship and cancer survivor Ms. Ellen Stovall.

Ms. Stovall thanked the other members of the Subcommittee for their acceptance and for sharing with her their knowledge. She urged everyone to understand the importance of the Subcommittee's recommendation to establish a nationally coordinated cancer program, and

stressed the need to recognize the level of importance that cancer should have in the United States as the leading cause of death in people under the age of 65.

Dr. Rimer thanked Ms. Stovall and all of the members of the Subcommittee for their work. She stated that she and Dr. Calabresi would make further suggestions at the next day's session as to how to ensure that the report functions as a guiding plan for the Board and other agencies. Questions were also postponed until the next day's session.

IX. UPDATE ON UNIVERSITY OF PITTSBURGH—DRS. BRUCE CHABNER AND LESLIE FORD

Therapy Trials and Status of Appointment Search—Dr. Bruce Chabner

Dr. Chabner noted that his presentation would be an update of the presentation he made at the previous NCAB meeting. Since that time, he said, the clinical trials have resumed for the National Surgical Adjuvant Breast and Bowel Project; however, accrual to the studies has been slow. He noted that fewer than 50 patients have been accrued over the last 3 months, probably because there were only two protocols open. He attributed this to the dilemma of choosing new leadership.

Dr. Chabner said that most of the recent efforts by the NSABP have been related to addressing administrative and monitoring problems. Disease-specific committees have recently been organized, and Dr. Chabner said he believes they should improve the scientific efforts and accrual rates.

Dr. Chabner reported that site visits have been resumed by the NSABP. This has been accomplished by using their own staff as well as through contracted workers. A site visit schedule has been submitted, and Dr. Chabner expressed his belief that NSABP is back in a position to monitor its own trials.

Dr. Chabner then discussed the B06 data reanalysis. The B06 trial, he explained, was one of the studies that established the efficacy of lumpectomy as an alternative to radical mastectomy. Approximately 85 percent of the charts from the study have been reanalyzed, and a summary will be presented November 15th at NCI. At that time, some of the leading clinical trial practitioners will also present updates of their own trials.

Returning to the NSABP leadership question, Dr. Chabner stated that the group is in the process of searching for a new chairperson. They are reviewing nine applications, and the executive committee of the NSABP is expected to reach a consensus as to the new chairperson by the end of October. The candidate will be proposed to NCI as the next chairperson and principal investigator. Dr. Chabner added that the chairperson and principal investigator positions are separate and the acceptance of the candidate as chairperson will not guarantee acceptance as the principal investigator.

Turning to the subject of NSABP oversight, Dr. Chabner said that the NCI has increased its activities in this area. In June, he said, NCI staff began weekly visits to Pittsburgh to review the monitoring activities and the resumption of the clinical trials. This

additional oversight, he commented, has put a strain on NCI staff in light of the Government hiring freeze. It has particularly affected the Clinical Trials Monitoring Branch, which was recently created to oversee the auditing activities of the cooperative groups. Dr. Chabner commended Dr. Michele Christian for the exceptional job she has done running the new Branch. He stated that staffing the Branch has proved difficult because of the hiring freeze and that other mechanisms will be pursued to remedy that problem. Dr. Chabner expressed concern over the staffing problem, because the auditing function will be an important aspect of NCI's future responsibility.

Dr. Chabner said that new contracts are being competed for developing information systems to monitor site visit activities. These systems will enable NCI to know exactly when investigators are site visited and will help resolve some of the problems that occurred with the NSABP.

A new concept plan has been developed for recompeting the NSABP, and it was approved by the DCT Board of Scientific Counselors in June. The concept, Dr. Chabner said, is being fleshed out into a Request for Applications, which will be competed later in 1995 and awarded in early 1996. This new competition will move up the planned recompetition of the project by a few months, since the original grant was to be awarded toward the end of 1996.

Questions and Answers

Dr. Salmon asked the reason for the low accrual rates. Dr. Chabner responded that NCI staff are not sure about the exact reasons, but suggested that it is in part due to a hesitancy on the part of the investigators (who are unsure of where the group is going), the lack of scientific leadership in the wake of Dr. Fisher's departure, and the demoralizing effect that the negative publicity has had on the members of the group. Dr. Chabner expressed his hope that accrual will increase when the new chairperson is selected. He added that the investigators are very enthusiastic about a new neoadjuvant trial that is being prepared.

Ms. Mayer asked about the selection of the principal investigator. Dr. Chabner noted that NCI usually is consulted in the principal investigator selection process.

Dr. Broder commented that functions that have been separated in some trials have been combined in the NSABP study. He mentioned the biostatistical function as an example of a component that is independent from headquarters in some groups; these functions are part of the same mechanism in NSABP. He added that the CALGB study, which has its headquarters at Dartmouth and its biostatistical center at Duke, is a good model for other groups.
Dr. Broder stated that moving the biostatistical function of the NSABP to a new oversight status or principal investigator is an option, but this will not be done without peer review.

Dr. Broder then reminded the Board that there is a scheduled Type 2 recompetition for the chemoprevention (tamoxifen) study, which will proceed as scheduled in August.

Tamoxifen Trial Update—Dr. Leslie Ford

Dr. Ford briefly reviewed the tamoxifen trial, reminding the audience that it involves 16,000 women at increased risk for developing breast cancer. The women are selected on the

basis of the Gale model and are randomized to receive either placebo or tamoxifen for 5 years. The study is double-blind and placebo controlled with three major endpoints: invasive breast cancer incidence and mortality, cardiovascular disease and mortality, and bone fractures. Quality of life data are also collected on all participants and will be factored in the analysis of the utility of tamoxifen for preventing breast cancer.

Companion studies, Dr. Ford pointed out, include endometrial changes, other cancers, bone mineral metabolism, bone density in peri- and postmenopausal women, and a genetic component still in the planning stages.

Randomization to the trial began in June of 1992 and, as of the end of June 1994, there were 11,100 women in the trial. The trial was implemented across 299 sites in the United States and Canada, with 5.4 being the average relative risk of the women entering the trial—about twice the relative risk required for entering the study. Dr. Ford emphasized that accrual to the study stopped due to the administrative problems that racked the NSABP, not due to the soundness of the science.

Dr. Ford then explained that the study has had a formal oversight structure in place since the inception of the study. The oversight structure includes an Endpoint Review Safety Monitoring and Advisory Committee (ERSMAC), a steering committee, and a number of subcommittees, including those for gynecology, cardiology, recruitment and compliance, quality of life, and bone.

Dr. Ford noted that the FDA has taken a keen interest in the study, so much so that they presented an Investigational New Drug Application to their Oncologic Drug Advisory Committee in 1991 with an update in 1994. The trial has also been reviewed by the NCAB and the Boards of Scientific Counselors (BSCs) of both the DCT and DCPC.

Discussing the risk-benefit of tamoxifen and endometrial cancer, Dr. Ford stated that a number of reviews have been performed. The first was in April before the Congressional Caucus on Women's Issues, specifically directed at new information about tamoxifen issued in a "Dear Doctor" letter received by physicians across the country from the manufacturer of tamoxifen, Zeneca Pharmaceuticals. In May of 1994, she continued, the ERSMAC met to review the latest information. That was followed by meetings of an Ad-Hoc Breast Cancer Prevention Trial (BCPT) working group, a DCPC BSC meeting, Senate Cancer Coalition hearings, the May NCAB meeting, an FDA Oncologic Drug Advisory Committee, and then a BCPT steering committee meeting. The major recommendation of all the committees, also endorsed by the FDA, was to inform participants of their age-specific individualized risk for developing breast cancer as well as potential benefits related to cardiovascular disease and their age-specific risk of endometrial cancer (which is zero for women who have had a hysterectomy). Given this information, each woman would be able to make an informed choice about her own participation in the trial. Another recommendation was to require endometrial sampling for new participants which was incorporated into the study. Other recommendations included that no changes be made to the eligibility criteria and that the study be reopened as soon as possible.

Dr. Ford explained that in June 1994, the trial was reopened for risk assessments at all sites that had acceptable audits by the Clinical Trials Monitoring Branch and an updated

consent form reflecting the full disclosure of information. Forms for all 299 sites were reviewed by the NSABP and NCI staff.

In August 1994, a presentation was made to Dr. Phillip Lee, the Assistant Secretary for Health. In September, another ERSMAC meeting was held to review the most recent data, an the committee recommended that the study go on as planned. A Recruitment and Compliance Committee meeting was also held in preparation for restarting accrual to the trial. Revised protocols incorporating changes made by these committees were mailed to all sites. The sites will begin accrual after their revised protocol and consent forms are reviewed by their Institutional Review Boards (IRBs). Dr. Ford mentioned that the steering committee will meet in October, and a major workshop for all program coordinators and investigators is planned in October to explain the protocol changes and initiate the accrual. There may also be another briefing of the Congressional Caucus on Women's Issues.

In summary, Dr. Ford stated that the trial is now trying to recruit 5,000 additional women, to join the 11,000 already entered for a total of 16,000. Maintaining the participation of the women already in the trial is critical. She noted that there is a Program Coordinator Committee, and described the Program Coordinators as being essential to the BCPT because they are the first line of contact with the women. A Participant Advisory Board has also been formed that includes women on the study, including some who have reached endpoints and some who chose to leave the study. A participant newsletter was implemented as a communication tool, as well as regional workshops for coordinators and participants. Dr. Ford said that an NCI review of the consent forms passed by each individual IRB will be conducted in conjunction with the OPRR to ensure that women are being adequately informed of the risks and benefits. Lastly, Dr. Ford noted that the scheduled Type 2 recompetition of the CCOP research base award (under which the prevention trial is conducted) will go on as planned, since the original 5-year award is ending.

Questions and Answers

Dr. Day asked if the women currently on the trial will have to sign another consent form. Dr. Ford answered that they will need to sign either an addendum or a completely new consent form.

Dr. Rimer asked how many women have dropped out of the trial during the period of controversy. Dr. Ford responded that a 10 percent per year noncompliance was built into the original study design; before the controversy, she said, they were below that number, and after the controversy they are clearly above the 10 percent figure. She added that by ERSMAC's calculations, they still have the statistical power to detect their endpoints with the planned sample size. Dr. Rimer asked to receive the data on the dropouts and Dr. Ford agreed to make them available.

Dr. Salmon asked how many risk assessments have been done since the trial was reinstated. Dr. Ford said that 8,000 risk assessments came in as a result of an article in *Good Housekeeping* and an additional 1,500 have been received since July when the trial was reopened.

Dr. Salmon asked about the schedule for sites to restart accrual. Dr. Ford said that sites can start as soon as their consent forms are approved by their IRBs and by NCI. NCI, she added, has promised sites a 1-day turnaround for reviewing of consent forms.

Dr. Mayer asked if there are any new data on minority recruitment. Dr. Ford said that there are no new data, since they have not been recruiting; however, 19 percent of the risk assessments in the past 2 months have been from minority women, although Dr. Ford said she does not know how many of these women are eligible for the study.

Dr. Broder asked the Board for advice on how to handle the Canadian studies that will have difficulty enrolling minorities and how to compensate for that by recruiting additional minorities in the United States. It is a serious problem, he stated, that they will be asking the cooperative groups to review with care and develop some recommendations.

Dr. Rimer suggested that the clinical investigations subcommittee might want to discuss this matter.

Dr. Freeman asked if low-income Canadian women are recruited into Canadian studies in an attempt to correlate information across people of similar ethnicity but different economic class. Dr. Broder stated that he is unaware of any program to stratify Canadian patients by economic status.

Dr. Ford mentioned that Canada has a national health service. Dr. Freeman stated that in a recent trip to Canada he was surprised to learn that even given the Canadian national health service there is a difference in level of care according to economic status. Dr. Broder added that he feels sure that poverty causes the same problems in Canada as it does in the United States. He also said that the Institute is required to achieve results that are applicable to American populations.

Dr. Salmon asked about funding research to foreign investigators. Dr. Broder responded that the Cancer Institute also has an international mission and that some studies will fall within the international public health arena. He emphasized that the focus on applicability to American populations does not mean that the NCI cannot fund activities in other countries, only that special care must be exercised when reviewing such grants.

Dr. Salmon noted that if the prevention studies were carried out in the United States and Canada, it would be reasonable to expect the results to be applicable to Canadians as well as U.S. citizens; if not, it would be a mistake to involve the Canadians.

Dr. Broder responded by saying that NCI is obligated to reach findings that are applicable to all U.S. populations, minority and otherwise. Therefore, if a major part of the accrual draws on nonminorities, that issue needs to be addressed before the study begins. Dr. Broder noted that statutory requirements exist now to ensure that investigators address those minority applicability issues in grant applications.

Dr. Rimer asked Dr. Ford to consider providing an update on the BCPT at the January meeting.

X. 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 1,086 applications were received, requesting support in the amount of $226,931,574. Of those, 1,086 were recommended as being eligible for funding at a total cost of $203,976,694.

XI. DAY TWO: OPENING REMARKS—DR. BARBARA RIMER

After welcoming everyone to the second day of the meeting, Dr. Rimer noted that *JCNI* monographs on breast cancer in younger women were available, as well as copies of *Cancer Facts* and a display from the Information Associates with Sue Hubbard. She described the morning's agenda to include an overview of NCI review committee activities by Dr. Bob Browning, new business, an overview by Dr. Bob Day of the Fred Hutchinson Cancer Research Center, committee reports, a summary of a meeting on colon cancer and a discussion of advances in colon cancer, an update on the Long Island Breast Cancer studies, and an opportunity for the Board to recommend new agenda items.

XII. NCI REVIEW COMMITTEE UPDATE—DR. ROBERT BROWNING

Dr. Robert Browning, Acting Deputy Director for the Division of Extramural Activities, discussed progress on chartering NCI's review committees and the results thus far for program project applications that were included in the en bloc action. He announced that at the September 1993 meeting, the NCAB's P01 task force presented its final report, including a recommendation that NCI reinstate chartered committee review of program project applications, ending a 5-year experiment with ad hoc review of each P01 by a special review committee. Dr. Browning noted that Dr. Samuel Wells, task force chairman, believed chartered committees would "facilitate a more equitable review of P01s".

Dr. Browning explained that in order to comply with Executive Order 12838, which called for a reduction in the number of Federal advisory committees, the Division of Extramural Activities adopted a flexible committee strategy that allows the use of large committees comprised of multiple subcommittees. As a result, even with the addition of chartered committee review of program projects, the number of chartered review committees will be reduced from seven to four.

Dr. Browning reviewed progress in reorganizing review committee structures. The Contracts Review Branch plans to incorporate the functions of three committees into one committee with a total of seven subcommittees, reducing the number of contract reviewers needed by more than 20 percent. The Grants Review Branch had four chartered review committees and reduced them to three committees with three new subcommittees. The Cancer Education Review Committee that reviews academic teacher awards and cancer education projects and the Cancer Research Manpower Review Committee that reviews institutional training grants and clinical investigator and physician/scientist awards were combined into one committee with two subcommittees. The charter of the Cancer Center Support Review Committee was expanded to include five subcommittees retaining Cancer Center Support as one, adding three to accommodate P01 reviews (in the areas of basic translational; clinical

studies; and prevention, epidemiology, and control) respectively, and one to review for cancer center comprehensiveness. No changes were made, Dr. Browning added, to the Clinical Cancer Investigation Review Committee, a long-standing committee that reviews clinical cooperative group applications.

Dr. Browning listed some advantages of flexible committees: members can be interchanged, as needed, to accommodate variations in subject matter and work load; more flexibility exists to review applications within a committee context if there is a conflict of interest on the part of a committee member (i.e., by having another appropriate subcommittee with expertise conduct the review); and additional reviewers to cover specific topics can be recruited from the NIH Reviewers Reserve, who retain voting privileges in chartered committees.

Dr. Browning referred Board members to a chart in their books showing the FY 1994 DEA review load, by mechanism. There were 1,311 applications from 13 different mechanisms—R01s, clinical cooperative groups, core grants, program projects, training grants, conference grants, etc. There were an additional 430 contract proposals to review.

Dr. Browning briefly reviewed progress in implementing the recommendations of the P01 task force. The goal of the task force was to create one chartered committee with three subcommittees to review applications for FY 1995 funding. Dr. Browning reported that, in accordance with the task force's recommendations, a two-stage review of applications was conducted, consisting of an initial, in-depth review by a team of carefully chosen experts that assigned scores to each project of each application, followed by a meeting of each subcommittee for final overall scoring of each application. The same review process will be applied to the next set of program applications.

The committees have now been chartered and an official roster for each subcommittee is being developed. Knowledgeable and committed individuals are currently being recruited to serve from 1 to 4 years on the P01 subcommittees. Once the rosters are finalized and approved by the Director, Dr. Browning promised to distribute them to Board members.

Dr. Browning showed a slide depicting the greater range of priority scores and mean and median scores given by a chartered review committee as compared with those given by ad hoc review committees. He announced plans to monitor scores in the future to determine whether the beneficial spreading of scores continues and to assess consistency in scoring behavior over time.

Also, Dr. Browning mentioned the task force's recommendation that NCI retain its current site visit policy of visiting first-time P01 applications and renewals, but typically not visiting amended applications. Current policy is to review amended applications by teleconference in order to retain previous reviewers, who can best judge the quality of the amended material. Dr. Browning informed the Board that the NCI is one of the few Institutes and Centers at the NIH with a policy to site visit P01s, and that this policy may have to be changed if staff resources become too limited or NIH invokes a general policy of not visiting sites in its efforts to streamline Government.

Finally, Dr. Browning acknowledged Dr. David Irwin for his work with the P01 Task Force and efforts to implement its recommendations in his capacity as the overall Scientific Review Administrator for the Cancer Center Support and Research Programs Review Committee.

Questions and Answers

Dr. Broder elaborated on the background to Dr. Browning's presentation, explaining that under the ad hoc review system of P01s, there was a priority score drift towards increasingly higher scores. Dr. Broder explained that this phenomenon was probably due to the narrow perspective in which ad hoc reviewers saw their applications—by only reviewing one application without others for comparison, reviewers were effectively trying to decide whether or not to fund the application rather than provide a priority ranking. Peer review is most effective, Dr. Broder said, when reviewers are forced to prioritize, and not make absolute decisions. He expressed gratitude to the Board for its recommendation of the new, more effective system and the high degree of excellence it affords to the P01 program.

Dr. Broder mentioned the need for continued contact with the NCI Review Committee about the review process and the possibility that site visits will be discouraged, either explicitly or through circumstances that limit the resources available to conduct them.

Dr. Salmon complimented Dr. Browning and his staff and noted the importance of the program project in that it allows the NCI to excel in translational research through the P01s. He voiced his support for retention of site visits for initial P01s, because these visits allow reviewers to observe the differences between what they read in an application and the explanations they receive in person.

Dr. Broder suggested to the Board that they consider adopting a more efficient triage system for P01s, similar to the experimental triage being used in the R01 system. He proposed that the Board consider whether triaging could be done that would, in effect, look at the probability of a project's success and, based on this, prioritize the need for a site visit. This would conserve resources and allow site visits for the top 40 to 50 percent of P01s.

Dr. Salmon agreed that grants deserving further consideration after initial review should be identified to avoid making unwarranted site visits. Dr. Rimer noted a show of hands in favor of support for continued site visits to at least some proportion of eligible PO1s, and triaging to be consistent with other efforts to streamline the review process. Dr. Salmon suggested that the triage only be applied to new applications.

XIII. NEW BUSINESS: SESSION II—DRS. BARBARA RIMER AND MARVIN KALT

Motion—Delegations A, B, and C

Dr. Rimer stated that there were three delegations that required a Board vote and were necessary to allow the NCI to continue to conduct its business in a timely manner. She referred the Board members to "New Business: Section II" in their notebooks and stated that,

for the benefit of new members, she would read these delegations aloud. The first, labeled Delegation A, continues to permit the Director of the NCI to appoint special experts or consultants with scientific or professional qualifications to assist in accomplishing the mission of the NCI. Delegation B continues permission for the Director of the NCI to appoint one or more advisory committees, including the Boards of Scientific Counselors. Delegation C authorizes NCI staff to take limited interim administrative actions to make minor changes in the timing and budgets of awards. Dr. Rimer explained that this is essential in enabling NCI staff to take prompt action on grant negotiations between regularly scheduled Board meetings. Dr. Rimer requested a motion for continuation of these delegations and a motion was so made, seconded, and unanimously approved by the Board.

Tobacco Resolution

Dr. Kenneth Chan expressed his concern that the tobacco industry has been increasing its efforts to advertise and promote cigarette smoking in developing countries, especially in Asia and Africa. He attributed this to the reduction of cigarette sales in the United States. Dr. Chan went on to state that, because the United States has had a policy of assisting developing countries through the Peace Corps, UNICEF, and other programs, exporting lethal substances and poisons, such as cigarettes, is unacceptable. He urged the Board to issue a resolution to curtail or condemn this activity by the tobacco industry.

Dr. Freeman supported Dr. Chan's resolution, recalling that a recent CNN news report estimated that 300 million people in China are smoking and that Marlboro advertising is prolific. He stated that while the Board has not addressed this issue before, it would make sense to publicly announce that it abhors this kind of activity.

Dr. Rimer asked Dr. Chan if he would state a formal resolution. The resolution was tabled until later in the session so that Dr. Chan could develop its wording. At this time, Dr. Chan presented the following resolution:

"Whereas, cigarette smoking contributes to over 400,000 cancer deaths annually in the United States, and higher worldwide,

"Whereas, the Unites States health community at large found that cigarette smoking is harmful to human health, and

"Whereas, the U.S. scientific community found that cigarettes contain addictive and cancer-causing substances,

"Be it resolved that the NCAB condemns the tobacco industry's aggressive advertisement campaign in developing countries. The NCAB demands that the tobacco industry immediately cease these irresponsible advertisement efforts."

Dr. Sigal expressed concern that this resolution may be illegal, since it attempts to regulate the free press. Ms. Brown disagreed and stated that she believes the NCAB can propose that the tobacco industry be prohibited from advertising, since they are currently prohibited from advertising on electronic media in this country. Dr. Salmon concurred that this is not an illegal resolution simply because it condemns something—there is still a free

press, but the practice of advertising cigarettes can be condemned. He commented further that condemning this practice should apply to all countries, not just developing ones.

Dr. Freeman suggested stating some facts in the resolution, including data from the Peto study indicating that one person dies in the world every 10 seconds and that there are 3 million deaths per year internationally from tobacco.

A vote was taken on the resolution, and it was approved by a majority of the Board. Dr. Rimer expressed her approval of the Board's stand on tobacco.

Grant Review

Dr. Rimer asked Dr. Kalt to update the Board on grant review issues. Dr. Kalt stated that he wanted to bring to the attention of the Board two NIH decisions that will be implemented by the Division of Research Grants (DRG) with respect to triaging and streamlining summary statement formats for R01 application reviews.

Beginning October 1st, all DRG standing study sections will be required to triage investigator-initiated research grant applications (R01s and R29s). Reviewers, by unanimous agreement of the study section, shall designate applications as "noncompetitive," which will appear on summary statements as "NC." This is to be distinguished from the previous practice of using the designation "NRFC"—"not recommended for further consideration." The percentage of applications receiving an NRFC was approximately 10 to 15 percent, while it is expected that 30 to 40 percent of applications will be designated noncompetitive. The implication for the Board is that noncompetitive summary statements will not be included in Board books, since they cannot be funded.

Dr. Kalt also explained that applicants receiving a designation of NC would receive summary statements consisting primarily of verbatim reviewer critiques with a short summary paragraph. Ms. Mayer asked if applicants would be informed of what process to follow in seeking further clarification. Dr. Kalt responded that it is the same process, and that applicants also have the privilege of submitting amended applications.

The second change Dr. Kalt reviewed involved differentiation of coding on the summary statement relevant to the inclusion of women and minorities in clinical research, defined broadly as all clinical trials, including intervention and controlled trials. Dr. Kalt presented a slide depicting the 31 codes that will be appearing on summary statements. The former numeric 60 and 70 series codes relating to gender and minorities will be replaced by a three-character code for each. For example, the first character may be "G," which means it relates to gender; the second character could be a number from 1 to 4, 1 being both genders; 2, only women; 3, only men; and 4, gender unknown (i.e., tissue blocks or samples). The third character will be either "A," scientifically acceptable, or "U," scientifically unacceptable. The third character is most important to the Board, since a "U" represents a bar to an award—no application may be funded until that designation is changed to an "A." There is a similar coding system for minorities, with "M" being a minority code; 1, all-inclusive; 2, only minority; 3, only non-minority; and 4, minority representation unknown. The third character is the same—scientifically acceptable or unacceptable.

Dr. Kalt went on to explain that if the third character designation is "scientifically unacceptable," it can only be changed if the applicant proposes a remedial plan that is negotiated with program staff and approved by Dr. Kalt through the NCI. He stated that it is important to understand that in using this coding scheme, study sections take into account whether or not the scientific merit of the application is affected by the population design. Therefore, it is possible that priority scores could be affected.

Dr. Becker expressed concern over the designation of an application as "scientifically" unacceptable because of its failure to include gender or minorities, and that the application may be triaged out for failing to meet this requirement, which could be met retrospectively. Dr. Kalt responded that this is an administrative code separate from the scientific merit code and priority score. He also emphasized that this a requirement put forth by NIH and supported by Congress to avoid conducting studies that do not answer questions for the entire population, unless there is an extremely cogent reason to do so. Dr. Salmon concurred with Dr. Becker's point that use of the word "scientifically" in the designation of gender or minority acceptability is cause for concern. He asked whether NCI committees could use the terms "acceptable" and "unacceptable." Dr. Kalt stated that this may not be possible, since there is one NIH policy and statements are generated electronically. He suggested that NIH staff responsible for extramural policy might be able to clarify the use of the term "scientifically unacceptable."

Dr. Rimer suggested a motion be made to change the wording to "acceptable" or "unacceptable," removing the word "scientifically." The motion was approved by the Board.

FDA Tobacco Resolution

A revised resolution was distributed to Board members and read aloud, as follows:

"Given the fact that more than 400,000 Americans die each year from diseases related to their use of tobacco—more than the combined annual toll from AIDS, car accidents, alcohol, suicides, homicides, fires, and illegal drugs,

"Given the fact that, on average, smokers who die from these diseases would have lived at least 15 more years,

"Given the fact that smoking is the main cause of deaths from lung cancer and 30 percent of all cancer deaths,

"Given the fact that smokeless tobacco is a cause of oral cancer,

"Given the fact that an estimated 3,000 young people become regular smokers every day,

"Given the fact that the medical and scientific communities have concluded that the nicotine in nicotine-containing products, such as cigarettes and smokeless tobacco, create and sustain an addiction,

"Be it resolved that nicotine-containing tobacco products should be regulated as a drug and subject to a health based, disease preventing regulatory regime by the Food and Drug Administration, according to the applicable standards of safety and efficacy."

Dr. Schein expressed his feeling that while the Board can and should support Dr. Kessler's efforts in declaring cigarettes and tobacco products as drugs and, therefore, subject to FDA regulation, the Board should go beyond this and broaden its statement to include other concerns about tobacco products, particularly health concerns.

Ms. Mayer referred Board members to page 21 of the SENCAP report, where nine separate recommendations of the Board are presented regarding tobacco activities. She observed that while the resolution may appear narrow when viewed in isolation, in toto, the Board has broadly addressed tobacco activities. Dr. Rimer concurred that the Board would be addressing tobacco issues in a very consistent and unremitting manner by following the SENCAP recommendations.

Dr. Salmon suggested a wording change after the word "addiction" in the next to last paragraph so that it would read, "sustain an addiction, and because it is known that nicotine is a potent pro-carcinogen." Dr. Schein suggested that reference be made to other statements the Board has made on this issue. Dr. Broder suggested referencing the SENCAP report. Dr. Schein said this would be acceptable and proposed the language, "in keeping with the Board's previous statements with regard to this, as referenced in. . . ." Dr. Chabner pointed out that the words "create and sustain" should be singular, not plural.

Dr. Chabner commented that referring to nicotine-containing products as "drugs" may be glorifying them, since drugs are beneficial to people when they are used properly. Dr. Rimer stated that there are negative drugs, such as cocaine and heroin. Dr. Chabner responded that these could be used for pain control and, therefore, be beneficial. Dr. Greenwald stated that you would not want these drugs on the market. Dr. Broder concurred, explaining that while angel dust is a drug, and would be regulated on that basis, the FDA would prevent its manufacture and shipment across State lines. Dr. Chabner proposed using the term "addictive drug."

Dr. Kalt reviewed the amendments to the resolution: in the next to the last paragraph, changing to "creates and sustains"; adding Dr. Salmon's statement, "because it is known that nicotine is a known pro-carcinogen"; and adding a reference to the SENCAP report. The Board unanimously approved the resolution, as amended.

SENCAP Report

Dr. Rimer surmised that the NCAB is already taking action on the SENCAP report, suggesting that Dr. Kessler's participation and the adoption of tobacco resolutions at this meeting are continuations of the SENCAP recommendations. A video clip from a press conference held on the SENCAP report was shown which, Dr. Rimer stated, is important because it shows that the work of the Board and the President's Cancer Panel is taken very seriously.

Dr. Calabresi briefly reviewed suggestions that he and Dr. Rimer had discussed for implementing the SENCAP recommendations. First, he suggested that the recommendations be implemented through the NCAB committee structure, since many of the recommendations already fit within existing committee charters. For example, the Subcommittee on Cancer Centers will examine the issue of expansion of the cancer centers; the Subcommittee on Clinical Investigations already has as part of its mission evaluating translational research; the new Committee on Basic Environmental Cancer Research can address basic research issues; the Subcommittee on Information and Cancer Control can participate in cancer control activities; and the Subcommittee on Special Priorities can play an important role in addressing issues relating to the elderly, minorities, and other special populations.

Dr. Calabresi noted that not all of the recommendations can be implemented through subcommittees; some will apply to the NCI and will be implemented by Dr. Broder and his staff. He recommended that Dr. Freeman and the President's Cancer Panel be involved in terms of the broader application of current knowledge to the general population. Finally, he stated that he and Dr. Rimer agree that an oversight committee is needed to ensure that progress is monitored on a regular basis.

Dr. Freeman agreed with these suggestions and, in particular, emphasized the need for an integrated, organized monitoring mechanism that evaluates, on a quarterly or semiannual basis, progress in implementing the SENCAP recommendations. Dr. Rimer informed the Board that she has already begun assigning recommendations to appropriate committees and that she would like the chairs of the subcommittees to convene at the December NCAB meeting to develop a plan for implementing the recommendations through the various subcommittees. She also suggested that an overarching group, chaired by Dr. Calabresi and including Dr. Freeman, Dr. Sigal, Ms. Mayer, and Ms. Stovall, be established to monitor progress.

Dr. Day asked if there will be any discussion with congressional committee members about their receptivity to the SENCAP recommendations, and noted the importance of congressional input in terms of funding considerations. Dr. Calabresi responded that several meetings have already been requested by congressional staff and that Dr. Freeman would be very helpful in giving the recommendations broader visibility.

Dr. Salmon asked what input major organizations, such as ACI, American Society of Clinical Oncologists (ASCO), American Association for Cancer Research (AACR), and ONS, have had to the report, in light of their ability to further interact with Congress.
Dr. Calabresi pointed out that, as a report to Congress, the SENCAP report was distributed to Congress first. However, the document was distributed in draft form to many outside organizations for review and comment. In addition, both ASCO President Karen Antman and AACR President Margaret Kripke served on the Subcommittee to Evaluate the National Cancer Program, and kept their executive committees and administrations well informed.
Dr. Freeman, a past president of the American Cancer Society, will be discussing the report with them at their next meeting in November. Dr. Salmon reiterated his point that the Board should request the assistance of these organizations in communicating information in the report.

Dr. Broder suggested that Dr. Freeman include the SENCAP report as part of his annual President's Cancer Panel report to the President and request a personal briefing. He also suggested that the Board facilitate a meeting between the co-chairs of the SENCAP report and the chair of the House Appropriations Committee or the chair of the Senate Appropriations Committee, and offered to facilitate these meetings for the first part of next year. Dr. Sigal agreed with Dr. Broder's comments, stating that how the program is implemented with the NCI is very important.

Dr. Freeman expressed his opinion that a small group should meet with the congressional staff who supported the report as soon as appropriate, and that since he has just been reappointed by President Clinton, it may be feasible to arrange a meeting with the President, at which the report would be the major topic. Finally, Dr. Rimer suggested that the NCI provide Board members with additional copies of the SENCAP report to distribute, as appropriate.

NCI Reorganization Ad Hoc Committee

Dr. Salmon recommended that additional NCAB members be added to the ad hoc committee, appointed by Dr. Varmus, for the purpose of reporting to the Board on an NCI reorganization. He specifically recommended members with expertise in radiotherapy, drug discovery and development, and business and administration, and suggested that Dr. Goldson, Dr. Schein or Dr. Chan, and Dr. Sigal be added to the committee. Dr. Sigal recommended that a representative be added from the pharmaceutical or biotech industry, as well as a management consulting firm specializing in structural reorganizations. Drs. Calabresi and Broder pointed out that the Committee has access to two individuals who can represent the pharmaceutical community—Drs. Schein and Pickett.

Dr. Salmon proposed as a formal resolution that the Board members he identified be added to the ad hoc committee and that this be communicated by a letter to Dr. Varmus. Dr. Sigal amended the resolution by proposing that an additional person with reorganizational expertise be added to the committee. Dr. Salmon accepted the amendment. A majority of the Board approved the resolution with one abstention.

XIV. ACTIVITIES IN CENTERS/FRED HUTCHINSON CANCER RESEARCH CENTER—DRS. ROBERT DAY AND LEE HARTWELL

Dr. Robert Day, Director the Fred Hutchinson Cancer Research Center (Hutchinson Center) began his discussion by providing information on the background of the Center. The Hutchinson Center, not quite 20 years old, was founded in 1975 by a surgeon, Bill Hutchinson, in honor of his brother, Fred Hutchinson, a famous baseball player from Seattle. Dr. Day pointed out that Senator Magnuson (D-WA) was a major advocate of the cancer center program. The Hutchinson Center today is an independent, nonprofit corporation, governed by a board of trustees in the State of Washington. The Center is composed of three science Divisions: Basic, Clinical, and Public Health. An interdisciplinary program in molecular medicine is currently housed within the Division of Basic Sciences but is represented in all three Divisions. The primary structure of the Center is derived from corporate guidelines, while the divisional structure has evolved over the years based on the disciplinary similarities

of the scientific staff. The program structure, Dr. Day explained, can and does change from time to time depending upon the Center's research emphasis. Although the Hutchinson Center is not part of an academic institution, Dr. Day stressed that its affiliation with the University of Washington is highly valued.

Dr. Day emphasized the importance of the Hutchinson Center's *research* orientation; this enables it to rapidly change the direction of research to fit institutional needs as well as the needs of the scientific field. Also, as an independent institution, the Center has considerable flexibility in setting research priorities and organizing its Divisions. The Division of Public Health Sciences is the largest Division of the Center, which may be unique. The Clinical Research Division has since its inception emphasized bone marrow transplantation in the treatment of hematologic and other malignancies—at one time probably half of the transplants in the world were performed by this group. Dr. Day noted that while the clinical program has broadened its focus, it continues to place a heavy emphasis on transplantation research.

Since he became the Director of the Hutchinson Center in 1981, Dr. Day related, growth in personnel, presently about 2,000, and in the budget has been rapid. He acknowledged the difficulty in managing such rapid growth, concluding that it has only been possible by maintaining the primacy of the Center's scientific programs. He pointed out that this year, the Board of Trustees for the Center engaged in a strategic planning process to review various approaches to resolving the problems of cancer. Based on this review, the Board concluded that scientific research is still foremost in priority.

Along with it's successes, Dr. Day raised several issues and concerns involving the Hutchinson Center. Patient reimbursement for clinical trials has been a major issue. Because of the Center's unique patient base—only 20 to 30 percent of patients originate from the region the Center serves (Oregon, Idaho, Alaska, and Montana) with the remaining patients originating from throughout the United States and abroad—it routinely seeks reimbursement from 40 to 50 different jurisdictions. In approximately 58 percent of clinical trial cases, insurance companies refuse to pay all or part of the bill.

Another issue is the high cost of clinical trials. The Center's ability to provide transplantations and complex therapies results in a high number of patient referrals. However, the Center oversees only 60 to 80 beds at any given time. Because of the nature of transplantation, individual patient costs tend to be high and the Center does not have the patient base to shift such costs. Due to these circumstances, the Hutchinson Center is one of only 10 centers in the country that is exempt from Diagnostic Related Groups under Medicare. Because of the high costs of clinical trials and patient reimbursement difficulties, Dr. Day explained that the Hutchinson Center has been actively involved in the health care reform movement in the State of Washington (similar to that proposed by President Clinton), in hopes that such reform will provide coverage for all patients and reimbursement for clinical trials approved by a third party.

Dr. Day continued by discussing the activities of the Public Health Science Division. Referring to the Doll and Peto study, "Preventable Causes of Cancer in the United States," Dr. Day emphasized the preventability of cancer, noting that the Public Health Sciences Division has dedicated itself to understanding the specific causes of cancer and conducting intervention trials to prevent cancer. Specifically, researchers at the Hutchinson Center have been studying

the two leading causes of cancer deaths in the United States—diet and tobacco. Additionally, the Basic Sciences group has provided major contributions in cell and molecular biology, ranking the Hutchinson Center among the top centers in the world in molecular biology and genetics, as listed in the *Citation Index.*

Dr. Day then described the Hutchinson Center's infrastructure. Because of increasing growth, the Center is moving to a new location. The first two buildings at the new site have been completed and a third is under development. The primary site is still being maintained for clinical program development until laboratory development on the new site is completed. Dr. Day explained how utilizing an indirect cost reimbursement method enables the Center to pay for many of its activities, noting that the operating costs and facility leasing costs of the Center are approximately equal at 33 percent. The Center leases space for the outpatient clinic, the research component of the outpatient clinic, and the Public Health Sciences Division. Dr. Day concluded that indirect cost reimbursement issues will be important for the National Cancer Advisory Board to consider, since it has been a significant means of supporting the research infrastructure.

Dr. Day continued by summarizing his observations about the separate and distinct cultures that exist in cancer research today. He stated that the intensity of technological developments have made communication between research investigators more difficult and that there is little time for investigators to pursue other avenues of learning or broaden their interests in areas which may not lead them to direct grant or contract support. Dr. Day suggested that this phenomenon may be more characteristic of a research center than a university, where there are teaching opportunities available to diversify individual experience.

In regard to other cultural issues, Dr. Day suggested, first, that science has developed three distinct cultures: Population Science, Clinical Science, and Basic Science. Because there is a great deal to learn in any one of these areas, it becomes difficult for communication to take place cross-culturally. Secondly, while the Hutchinson Center, like many other centers, has developed a program designed to apply molecular insights to prevention, diagnosis, and treatment of human disease, it has been a difficult program to institute because of its cross-disciplinary nature. Dr. Day summarized these observations by noting that learning better ways of communicating, performing interdisciplinary work, and fostering translational research must be addressed.

Dr. Day concluded by introducing Dr. Lee Hartwell, professor of genetics at the University of Washington, who has been serving as a special advisor to the Hutchinson Center. Dr. Day explained that Dr. Hartwell is working to improve the Hutchinson Center's effectiveness in interdisciplinary and translational research.

Dr. Hartwell began his discussion with a brief personal background. As a postdoctoral fellow approximately 30 years ago, he became interested in issues of cancer biology and growth control. After leaving that position to begin a career in academia, he felt a strong need to incorporate genetics into cancer biology and, since then, has been involved in the basic genetics of cell biology using yeast cells. With the development of important new theoretical insights in this field, Dr. Hartwell explained that he has renewed his interest in applying basic information regarding cell biology to understanding, diagnosing, and treating cancer. He is

spending time at the Hutchinson Center evaluating different research efforts in the context of the Center's divisional structure.

Dr. Hartwell shared some of his observations about the Hutchinson Center, developed over a period of 3 months. He noted a tremendous opportunity to synthesize the Center's three disciplinary efforts—basic science, clincial research, and public health—as a means of understanding human biology and disease. He also observed a strong desire among the scientists for greater interdisciplinary activity; it is his impression that the Center would rank high in terms of national comparisons of institutions where interdisciplinary activities are ongoing. Dr. Hartwell stressed that the focus of the scientific community should not be short-term accomplishments but, rather, assessing the problem—what is responsible for the distinct cultures among these three scientific discipines, i.e., different approaches to collecting information, different research questions, basic value systems. For a basic scientist, the highest goal is to determine the mechanisms by which biological processes occur; for an epidemiologist, identifying risk factors takes precedence; and for the clinical scientist, the highest goal is to design and implement therapies that cure people of their diseases.

The intense linear focus that has developed in science, Dr. Hartwell continued, has made it increasingly difficult to engage in interdisciplinary activities. He emphasized the need to bridge gaps between disciplines, concluding that in order for greater interdisciplinary action to take place, a systematic change must occur, in which both the institute as a whole, as well as its individual staff, are committed to the necessary cross-cultural education. Dr. Hartwell explained that accomplishing this will require forums, procedures, and processes that make cross-cultural education an ongoing process. These forums must be developed with individual needs in mind and can be organized in a variety of ways, such as disease basis or site of action (i.e., breast cancer, prostate cancer) or by horizontal dimension (i.e., by basic cellular processes/mechanisms which are involved in all diseases, such as signal transduction, cell division, control, apoptosis, angiogenesis, metastasis).

Dr. Hartwell concluded his presentation by expressing his interest in the Hutchinson Center's future efforts to engage individuals in a way that can begin a long-term, ongoing systemic process that will have an effect in bridging the cultural gaps that exist in the scientific community.

Questions and Answers

Dr. Freeman agreed there is a cultural dichotomy within the scientific community and suggested anthropological interventions to bridge the gaps. Dr. Freeman referred to articles in the *Wall Street Journal* and the *Times* which discussed the intervention of anthropologists in these types of divisional dilemmas within the corporate setting.

Dr. Salmon asked to what extent an effort has been made to bridge gaps through selective recruitment procedures that focus on dual disciplinary training (i.e., physician/molecular biologist, genetic epidemiologist). Dr. Day responded that there are some researchers with dual degrees, i.e., approximately 20 to 30 M.D./Ph.D.'s are serving as post-doctorates; however, broader basic training does not negate the reality that for scientific staff to be successful, they must first be self-supporting, which usually entails specialization versus interactive research.

Dr. Broder suggested that the members of the NCAB explore funding instruments within the NCI that might be available for "administrative experiments" on interdisciplinary and cross-cultural activities, and give thought to what types of experiments should be funded. One means of advancing cross-cultural activity might be to implement more Specialized Programs of Research Excellence. SPOREs focus on human disease and emphasize research that explores novel ideas with the potential to reduce cancer incidence and mortality and improve survival and quality of life, with the express purpose of rapidly translating basic insights into practical clinical application. Dr. Broder explained that it is an implicit requirement that investigators from multiple disciplines interact and work collaboratively in planning, designing, and implementing research programs. Although the first SPORES had a disease orientation, another program focus could be recommended. Dr. Broder concluded by noting that this approach would be more likely to receive institutional support because of the funding attached to it.

Dr. Day noted that there are also many ways to use institutional resources to promote the interaction of different scientific disciplines, such as the Center's molecular medicine program, and cautioned that any effort must ensure successful scientific outcomes.

Dr. Goldson suggested offering fellowships in interdisciplinary interaction. He stated that fellowships usually involve only one specialized area and suggested a cross-breeding of fellowships, in which individuals involved are exposed to interdisciplinary theories and approaches, versus small categorized areas of science. Dr. Hartwell mentioned mentorships involving projects pertaining to two disciplines.

As a final point, Dr. Freeman encouraged NCI to foster interdisciplinary efforts by providing funding that encourages creative thinking in this area.

XV. SUBCOMMITTEE REPORTS

Cancer Centers

Dr. Day reported that the Cancer Centers Subcommittee primarily addressed budgetary issues. He informed Board members that the subcommittee report provides a complete analysis of the number of existing planning grants, the anticipated number of applications that will be received, and the resulting budget deficit. Dr. Day stated that the budget shortfall incited the resurgence of the issue of whether there should be a standard ratio of core grants to support. He reported that the Subcommittee decided to devote sufficient time at the next meeting to a discussion of various models that have been developed to address this issue. Dr. Broder commented that it might be worthwhile to invite prior committee members to provide relevant historical information, particularly Dr. Durant. Dr. Broder asked Dr. Day to provide Dr. Kalt with a list of members he would like to invite to the next meeting.

Activities and Agenda

Dr. Calabresi reported that this Subcommittee met last August. He reminded members that future NCAB meeting dates had been changed during yesterday's meeting. Dr. Calabresi added that the committee/subcommittee structure was altered as well. In light of this change, he requested that a motion be made to activate a new committee on the interaction of

environment, AIDS, and basic science called the Basic and Environmental Cancer Research Subcommittee. Dr. Calabresi pointed out that one of the purposes of restructuring was to condense the number of subcommittees. As a result, there are now six major subcommittees, with an additional Special Action Subcommittee in which all members participate. Since the Activities and Agenda Subcommittee includes the chairpersons of all the other subcommittees, Dr. Calabresi recommended that it become a coordinating committee.

Dr. Calabresi reminded members that there is a fund for gifts, remembrances, and memorials and requested that each member contribute what he or she can. The recommended amount is $50. He added that a letter stating this information has been mailed to members.

Dr. Rimer moved to form the Subcommittee on Basic and Environmental Cancer Research with Dr. Fred Becker as the chairperson and the motioned was seconded. Dr. Calabresi pointed out that it is not appropriate to move that Dr. Becker be the chairperson, he should be appointed by Dr. Rimer. Dr. Rimer agreed and the motion was passed.

Planning and Budget

Dr. Sigal provided members with a brief overview of the complicated issues discussed by the Subcommittee. Members addressed the phasing out of the Outstanding Investigator Grants (OIG) by the year 2000. A significant amount of time was spent discussing methods for more effectively presenting the Bypass Budget to Congress. Dr. Sigal emphasized that the budget reflects scientific needs, not wishes. In order to clearly present these needs and recommendations to Congress, the Subcommittee recommended that the NCAB create an executive summary of the budget. Dr. Sigal suggested that a group of the document's supporters should then present it to Congress and other interested parties. She moved that the Board accept the Subcommittee's recommendation to develop a stand-alone executive summary of the Bypass Budget.

Dr. Broder expressed his approval of this idea, and noted that it could be designed under a variety of formats. He cautioned only that a unified set of budgetary principles be presented by the Board, consistent with those of NCI, in order to avoid confusion. Dr. Broder recommended starting on the 1997 Bypass Budget at the next meeting by outlining the primary issues. He concluded that the document could be ready by next September and that it should be created in conjunction with the Office of Cancer Communications. Dr. Sigal suggested that a summary document be created for the 1996 Bypass Budget document that was recently presented to Congress. Dr. Broder stated that this is acceptable, especially as the 1997 Bypass Budget is primarily based upon the 1996 budget. The motion received unanimous support.

Dr. Sigal continued her summary of the issues addressed by the Planning and Budget Subcommittee. Other topics discussed included the SENCAP recommendations, Government-owned/contractor-operated facilities, and concerns regarding full time equivalents. Dr. Sigal explained that there has been pressure to reduce the number of FTEs by 15 percent, or 227 employees. This is an extremely difficult task. The Subcommittee decided that more time will be required to adequately address this issue and, therefore, will revisit the topic more thoroughly at the next meeting.

Special Priorities

Ms. Mayer began by stating that the Special Priorities Subcommittee meeting consisted of two presentations. Dr. Edward Sondik informed subcommittee members of two proposals recently approved by the DCPC Board of Scientific Counselors. One proposal involved the funding of a meta-analysis of data from clinical trials of mammography in women in their 40s. The other proposed NCI financial support of an English clinical trial of mammography in women in their 40s and possible support for coordination of a Euro-trial of mammography screening in this same age group. Ms. Mayer reported that Dr. Sondik also presented two semi-final booklets, one for lay and one for scientific audiences, explaining current knowledge about the benefit of screening mammography. Board members may send comments on the booklets to Dr. Sondik.

Ms. Mayer reported that Dr. Musallam from the Department of the Army delivered the second presentation, updating Subcommittee members on the DoD funding actions for breast cancer research. Dr. Musallam stated that DoD received some 2,700 proposals, of which 15 to 20 percent will be funded through this fiscal year. He added that DoD will probably be appropriated $150 million in fiscal year 1995, and will solicit another round of proposals, still based on the Institute of Medicine recommendations.

Questions and Answers

Ms. Brown raised two concerns regarding the budget and special priorities: the reduction in full time equivalent staff and the special populations staff. Ms. Brown asserted that there is currently less focus on hiring minorities, particularly women and ethnic minorities, than there was in previous years. She noted there was not time to address this issue during the Special Priorities Subcommittee meeting yesterday, and asked Dr. Broder whether NCI is concerned about the staff reductions and what he believes the impact will be on minority staffing.

Dr. Broder responded that there is extreme concern about the 15 percent reduction in work force that had already occurred and expected future cuts. Dr. Broder continued by describing additional concerns. A significant concern is the new barrier that prevents NCI from promoting staff from level GS-13 to GS-14. Severe restrictions have been placed on promotions to the Senior Executive Service (SES), which will limit outreach activities and career development opportunities. All of these restrictions affect NCI's ability to provide certain services in a timely and effective manner. Dr. Broder pointed out that these reductions also limit the infrastructure that supports NCI's research agenda, such as the filing of INDs as part of new drug development. Furthermore, the number of authorized supervisors has been reduced. Dr. Broder asserted that these reductions will affect an individual's decision to remain a Government worker, as well as to become one. He indicated that NCI will examine methods for using other funding instruments to accomplish former in-house tasks externally through contracts and cooperative agreements. Dr. Broder concluded by stating that the reductions will severely limit career opportunities and that minorities will definitely be affected by these new challenges.

Ms. Brown explained that she brought up this issue because she believes it is appropriate to integrate their concerns into the executive summary of the budget, which can be used to argue for more funding for staffing. She added that she believes that the low level of minority hiring and staffing at NCI needs to be addressed by Congress. Dr. Broder commented that two primary challenges will be faced by such an action. Congress has agreed to an overall domestic spending budget cap, which has led to almost every NIH Institute being appropriated less than President's budget level. He added that this is a very rare occurrence. Dr. Broder indicated that the second issue is that the Government has a specific plan and set of goals for reducing the scope of all Government work. Dr. Broder recommended that arguments for increased funding and staffing be based on the assertion that the needs of a science-based agency are different than those of other Government agencies. He asserted that it is not possible to recruit and provide career opportunities for surgeons and other highly qualified professionals at GS ranks that other agencies might able to work with. Dr. Broder reminded members that despite its effects, there is a great deal of political and popular support for Congress' Government spending cap.

Dr. Rimer indicated that the Board has a responsibility to make people aware of the ramifications of the politically popular idea of unilateral staffing and work scope reductions. Dr. Freeman asked how the reductions will affect the Special Populations program. Dr. Greenwald responded by stating that discussions of program consolidation are under way and will be presented to the DCPC Board of Scientific Counselors. He indicated that they will probably propose to the Board that the number of program areas be reduced from four to three to allow more depth of staff without reducing the scope of the programs. It will be recommended that cancer control science be combined with surveillance, since there is a logical connection between the two program areas in that surveillance entails a great deal of population-based work and services research. Dr. Greenwald emphasized that there is no intention to reduce minority hiring; conversely, he believes that NCI does all it can to recruit minority scientists and leaders into its programs.

Dr. Freeman asked whether there is a special program for special populations and whether it will be maintained. Dr. Greenwald indicated that there is a branch for special populations and that efforts are being made to maintain it. Dr. Freeman asked why the cancer control program area is being downsized when it appears to be receiving an increased budget over other areas. Dr. Greenwald responded by saying that this area is not being reduced, and added that all Divisions are on a 1-to-1 hiring ratio. Dr. Broder commented that while 50 NIH positions have been reserved for recruitment, not one person has been hired as a result of the need to monitor and conserve resources. Dr. Broder added that NIH is currently 500 FTEs below its cap and, yet, there are still severe hiring freezes, which indicates that the FTEs have been transferred to other components. He reasserted that the staff reductions will have ramifications for the services NCI can provide.

Dr. Freeman asked where the increased money for cancer control will be directed, as it usually is targeted to personnel. Dr. Broder indicated that it will be used for project grants, contracts, and cooperative agreements, but not additional personnel. Dr. Freeman commented that increased grants and contracts will require additional personnel to administer them. Drs. Broder, Rimer, and Greenwald agreed that this is a central paradox and challenge for cancer control.

Dr. Greenwald reviewed discussions regarding effective methods for ensuring minority recruitment, focusing on whether it is better for an existing office to examine every program regarding minority inclusion or whether a branch should be created for this purpose. Dr. Greenwald reported that no decision has yet been reached. Dr. Rimer emphasized the importance of programs that support minority recruitment, and noted that many of these issues are highlighted in the SENCAP report. Dr. Rimer requested that either Ms. Brown or Dr. Freeman attend the Board of Scientific Counselors meeting to ensure NCAB representation.

Several comments were made about reorganization and streamlining of goals. Dr. Freeman commented that it is important to let the public know that consolidation does not mean reduction, particularly among minority staff. Dr. Greenwald indicated that support contracts and other mechanisms are being employed to the fullest extent possible without compromising the effectiveness of programs. In-house staff are required to administer external programs effectively. Dr. Greenwald acknowledged that at the same time, it is important to adhere to the streamlining goals for the Federal Government. He emphasized that efficiency will become very important and that special populations will remain a focus.

Dr. Rimer requested a copy of the proposed reorganization of the DCPC. Dr. Greenwald indicated that until it is presented to the Board of Scientific Counselors, he does not feel comfortable providing a copy to NCAB. He suggested that after the meeting is held, a summary of the discussion and results can be reported to the NCAB and that the BSC chair could attend that meeting. Ms. Brown agreed to accommodate Dr. Rimer's request that she attend the BSC meeting.

XVI. ADVANCES IN THE MANAGEMENT AND DETECTION OF COLON CANCER—DR. BRUCE CHABNER

Clinical and Preclinical Investigations in Gastrointestinal Malignancies—Dr. Carmen Allegra

Dr. Bruce Chabner introduced Dr. Carmen Allegra, Chief of the NCI-Navy Medical Oncology Branch (NCI-NMOB). Dr. John Minna was one of the founders of the Clinical Oncology Program Unit (now NCI-NMOB) established at the Washington Veterans' Administration Hospital approximately 20 years ago. In 1992, Dr. Allegra replaced Dr. Minna, who pioneered the etiology and molecular aspects of lung cancer. Under the direction of Dr. Allegra, the scope of research at the NCI-NMOB has refocused toward the area of colon cancer.

Dr. Allegra said he would present an overview of the various preclinical and clinical investigations currently ongoing at NCI-NMOB, rather than describing in detail only one or two areas of research within the Branch. He stated that colorectal carcinoma is a major public health issue, since it ranks second in overall incidence and death due to cancer. Approximately 150,000 new cases of colorectal carcinoma are reported each year and about 60,000 of those patients die annually.

The NCI-NMOB's objective is to develop novel approaches for the treatment of colorectal carcinoma. Extensive research within the Branch has been directed toward the biochemical modulation of fluoropyrimidines. Fluorouracil (5-FU), which has been available

for a long time, is the only drug that exhibits a reproducible antineoplastic activity against most gastrointestinal (GI) cancers, including colorectal carcinoma. An attempt to enhance 5-FU's activity through biochemical modulation is being actively pursued by NCI-NMOB investigators. In addition, reduction of 5-FU-associated toxicity is being evaluated through the use of colony-stimulating factors and transforming growth factor-beta. Identification of new agents, particularly chemotherapeutic agents such as topoisomerase-1 inhibitors is also being pursued. A Phase I clinical trial with 9-amino[20S]-camptothecin, a topoisomerase-1 inhibitor, has recently been completed. The use of monoclonal antibodies and vaccines, mainly those developed in the laboratory of Dr. Jeffrey Schlom, including carcinoembryonic antigen (CEA) vaccinia and mutated Ras, have been under evaluation at the NCI-NMOB. A recent effort has been initiated within the Branch to develop a Genetics Program primarily aimed at prognosis, but also at genotype-directed therapy.

Dr. Allegra indicated that the principal target of the biomodulatory efforts at NCI-NMOB is thymidylate synthase. This enzyme is solely responsible for the *de novo* synthesis of thymidylate, an essential substrate for the synthesis and repair of DNA. The chemical reaction catalyzed by thymidylate synthase is potently inhibited by fluorodeoxyuridine monophosphate (F-dUMP), an anabolite of 5-FU. Thymidylate synthase has been a choice target enzyme exploited in cancer chemotherapy mainly because: 1) there appears to be a close inverse relationship between its cellular expression and fluoropyrimidine sensitivity; that is, those cells that contain high levels of thymidylate synthase tend to be less sensitive to fluoropyrimidine therapy, and vice-versa; 2) there is a close association between the degree to which this enzyme is inhibited and the clinical outcome; and 3) there have been a number of clinical trials using leucovorin as an adjuvant to modulate the activity of 5-FU. A twofold increase in response rates has been reported in studies using 5-FU and leucovorin. This combination therapy has been particularly effective in prolonging the survival of patients with Dukes' B and C colorectal carcinoma.

Dr. Allegra referred to the synergistic interaction between 5-FU and interferon. He noted that the interaction—particularly identified using human colon carcinoma cell lines—between these two compounds has been investigated by a number of researchers around the world, including Dr. Edward Chu at NCI-NMOB. A 20-fold increase in the sensitivity of human colon carcinoma cells to 5-FU has been reported in studies where this compound has been administered in combination with interferon—at concentrations of interferon that do not produce growth inhibition. Studies to determine the mechanism by which interferon and 5-FU interact synergistically have revealed that 5-FU produces an acute enzyme induction of thymidylate synthase. Colon carcinoma cells exhibit a three-o fourfold increase in thymidylate synthase levels 24 hours after exposure to 5-FU. This acute increase in enzyme levels is repressed when the cells are exposed to both interferon and 5-FU. Thus, interferon increases the sensitivity of colon carcinoma cells to 5-FU. A similar acute enzyme induction of thymidylate synthase has been observed in patients with advanced breast cancer 24 hours after administration of 5-FU.

Dr. Allegra explained that one early objective of the NCI-NMOB in the development of new colorectal carcinoma therapies was to combine two biochemical modulators that converged on the enhancement of 5-FU-associated thymidylate synthase inhibition; namely, the use of leucovorin and interferon in combination with 5-FU. Dr. Jean Grem served as Principal Investigator in a Phase II multi-institutional clinical trial using this combination

therapy which was conducted in 46 patients with colorectal carcinoma. Interferon was subcutaneously administered, during 5-FU and leucovorin intravenous bolus infusions, on a daily regimen for 7 days. Leucovorin and 5-FU were administered from day 2 through 6, and the cycles were repeated every 21 days. Results from this clinical study indicate no dose-limiting hematologic toxicity. However, the dose-limiting toxicity was GI toxicity (mucositis and diarrhea) expressed in approximately 40 percent of the patient population at a Grade III or IV level. Overall, four patients exhibited complete remission of their tumors, while 20 patients showed a partial response; thus, a 54 percent response rate was achieved with this combination therapy. Subsequently, the National Surgical Adjuvant Breast and Bowel Project conducted a Phase III multi-institutional clinical trial with the same combination of drugs as an adjuvant therapy for patients with Dukes' B and C colorectal carcinoma. The 5-FU/leucovorin/alpha-interferon regimen is being compared with a 5-FU/leucovorin regimen to determine the role of interferon in leucovorin's modulation of 5-FU. The trial completed its accrual of about 2,000 patients in February 1994; data analysis is under way.

Dr. Allegra summarized the cellular regulation of 5-FU-induced acute increase in thymidylate synthase levels. He indicated that the level of mRNA encoding thymidylate synthase protein does not increase during exposure to 5-FU, suggesting that the cellular contro of the enzyme is not at a transcriptional or pretranscriptional level but, rather, is at a translational level. Subsequent experiments have demonstrated that the intracellular levels of thymidylate synthase are controlled by an autoregulatory system through translational efficiency. Thymidylate synthase mRNA contains two binding sites, one of which includes the translational start signal. Thymidylate synthase can bind to its own mRNA and, thus, regulate the translational efficiency of its message. When the enzyme is bound to physiologic ligands (e.g., dUMP and folate) or to fluoropyrimidines, it can no longer bind to its mRNA; therefore, translation is enhanced and the intracellular level of thymidylate synthase is increased. Dr. Allegra indicated that there are various approaches in which this new information on the regulatory mechanism of thymidylate synthase can be therapeutically applied. Examples of such therapeutic applications may include: design of thymidylate synthase inhibitors that would not only block the catalytic function of the enzyme, but also strengthen the enzyme's interaction with its mRNA—as opposed to 5-FU, which decreases this protein-mRNA interaction; development of other small molecules, in addition to interferon, that will inhibit the acute induction of thymidylate synthase; identification of the enzyme's binding site to the mRNA and its subsequent use as a target for inhibition of translation; and development of antisense molecules that would directly target the binding sites on thymidylate synthase mRNA.

Recent studies have demonstrated that thymidylate synthase also binds to the c-myc mRNA—c-myc is an important protein involved in malignant cell proliferation. The potential therapeutic application of this recently discovered interaction is currently being investigated.

To determine the prognostic significance of thymidylate synthase, Dr. Patrick Johnston at NCI-NMOB developed a series of monoclonal antibodies to detect and quantitate the level of thymidylate synthase. These antibodies were first applied in a retrospective study to a series of 300 patients with rectal carcinoma that were enrolled in an NSABP R01 clinical trial during the 1970s and 1980s. Results of this study indicate that patients who expressed low levels of thymidylate synthase had a much better survival rate over 5 years—irrespective of the stage of

Dukes' disease—than those with high enzyme levels. The monoclonal antibodies, therefore, constitute a unique marker for patients with rectal carcinoma.

Monoclonal antibodies against thymidylate synthase have also been applied to patients with advanced disease to determine the role of thymidylate synthase expression in response to chemotherapy. Results of these studies indicate that patients who respond to 5-FU-based therapy tend to have lower (pretreatment) levels of thymidylate synthase compared with those who do not respond to 5-FU therapy.

Current research has focused on both retrospective and prospective studies in the adjuvant setting evaluating patients with colorectal carcinoma and breast cancer, as well as other types of cancer, in an attempt to define more carefully the potential of thymidylate synthase as a prognostic tool. The ultimate goal is to apply the monoclonal antibody test to define populations of patients who may most benefit from therapy with thymidylate synthase inhibitors.

Dr. Allegra reviewed the vaccine development efforts currently ongoing at NCI-NMOB. He indicated that research in this area has focused on the use of tumor-associated antigens such as carcinoembryonic antigen and prostate specific antigen (PSA), and ras and p53 mutated peptides, as vaccine targets. In addition, the use of viral proteins such as those associated with human papillomavirus as potential targets for vaccine development is being investigated. These studies have been performed in collaboration with Drs. Berzofsky and Schlom, both of the Division of Cancer Biology, Diagnosis, and Centers. Dr. Allegra explained that the rationale for using recombinant vaccinia vaccines—both with CEA and PSA in patients with tumors that express these antigens—is to elicit a stronger immunogenic response with release of cytokines and T-cell activation than that produced by the tumor-associated antigen alone. In addition, vaccinia virus exhibits a very stable genome and there is ample experience regarding the safety, storage, and preparation of vaccinia vaccines.

A Phase I clinical trial using recombinant vaccinia virus expressing human CEA was performed by Dr. Hamilton in 26 patients with GI, breast, and lung carcinomas. Patients were treated every 4 weeks with three consecutive immunizations. The starting dose was $2x10^5$ plaque-forming units (pfu), and the dose was escalated up to 10 million pfu. All patients exhibited a local skin reaction during the first treatment cycle; however, the incidence of local reaction diminished with subsequent immunizations. Two of four patients who presented stable disease remained stable for up to 6 months. In addition, CD8-positive T-cell lines were established from six patients after their cells were incubated with peptide fragments of CEA. These T cells are cytotoxic to autologous cells expressing CEA. These results successfully demonstrate the development of an immune response, albeit not sufficient to induce tumor regression. Specifically, this clinical trial proved the ability to select and expand antigen-specific cytotoxic T cells (CTLs) using peptide-activated lymphocytes. The potential for expanding this population of CTLs *ex vivo* and reinfusing the cells into patients as an adoptive immunotherapy can be anticipated. Furthermore, the coadministration of interleukin-2 and/or CD8 peptide to enhance the immune responsiveness of CTLs is also warranted.

Dr. Allegra listed other vaccine clinical trials that have been completed, are currently ongoing, or are in the process of being initiated. Among the clinical studies, there is one study with PSA vaccinia vaccine that has been approved by the NCI Review Board, but is awaiting

final approval by the Food and Drug Administration for its initiation. There are two clinical trials currently accruing patients, one study is using the ras peptide and the other the p53 peptide. Two studies using papillomavirus peptides are currently ongoing to determine the potential of these peptides as vaccine targets in patients with cervical carcinoma. Finally, there is a planned Phase I clinical trial to reevaluate CEA vaccinia with the generation of peptide-activated lymphocytes for reinfusion into cancer patients. A ras vaccinia trial is also being designed.

Dr. Allegra concluded his presentation with a review of current efforts on the development of a Genetics Clinic at the NCI-NMOB. He explained that recent findings have demonstrated that human genes are associated with the development of colorectal carcinoma in approximately 20 percent of patients. A correlation between alterations in these human genes and the development of the malignancy has been detected in more than 90 percent of patients with hereditary nonpolyposis colorectal carcinoma. In addition, an association between the development of the disease and mutations in mismatch repair genes (e.g., MSH2, MLH1, PMS1, and PMS2) has been reported in 5 percent of patients with sporadic colorectal carcinoma. These genes are responsible for maintaining genetic accuracy; mutations in the repair genes leads to generalized genomic instability. The genomic instability can be assessed phenotypically in microsatellite regions on a particular chromosome using specific probes. Patients exhibit either expanded or deleted microsatellite regions in cancer tissue compared with normal tissue. Since this test can be easily applied to clinical samples, it is used as an index of overall genomic instability.

Dr. Allegra noted that the Genetics Clinic is a collaborative effort between investigators of the NCI-NMOB, Human Genome Center, Division of Cancer Prevention and Control, Division of Cancer Treatment, and Johns Hopkins University. He explained that patients who enter the Clinic, either because they are accrued for active colorectal trials or because they constitute the intramural population of patients attended at the NCI-NMOB, are screened to determine whether they carry the mutant phenotype. In the near future, genotypic evaluation of these patients to specifically determine the mutant gene will be possible. If these patients exhibit a germinal mutation, they could be entered into family-based prevention and surveillance clinical studies at the Human Genome Center.

Dr. Allegra added that the response to standard therapy can be retrospectively analyzed in cancer patients by evaluating the phenotype of the mismatch repair genes. In addition, since the mutant phenotype is specifically expressed in cancer cells, it represents a potential target for therapy. The sensitivity to various chemotherapeutic agents is substantially different for cells that exhibit a mutant phenotype than for cells containing intact mismatch repair genes. This difference will be used to select patients who may benefit from therapy specifically directed at their mutant mismatch repair genes.

Dr. Allegra acknowledged both basic science and clinical investigators as well as research nurses that have collaborated in the various preclinical studies and clinical trials.

Questions and Answers

Dr. Schein congratulated Dr. Allegra for his outstanding work. He commented that the type of research that Dr. Allegra is conducting, in which the research hypothesis is validated

clinically and then evaluated through a large cooperative group to determine whether the findings have any effect on the overall practice of medicine, should be preserved within the NIH intramural program.

Summary of International Meeting—Dr. Bernard Levin

Dr. Barbara Rimer introduced Dr. Bernard Levin, Vice President for Cancer Prevention at the M.D. Anderson Cancer Research Center in Houston, Texas. Dr. Levin indicated that his presentation would only include the highlights of the workshop held at the International Meeting on Colorectal Cancer Screening held in Bethesda, Maryland, in June 1994.

Dr. Levin recalled from Dr. Allegra's presentation the epidemiologic data on colorectal carcinoma and indicated that while recent data demonstrate a decrease in mortality among White males and females, the mortality rate has remained unchanged for African American women and has increased in African American men. Thus, colon carcinoma still represents an important leading cause of cancer mortality in the United States.

Dr. Levin indicated that the workshop was cosponsored by NCI, through Drs. Peter Greenwald and Barry Kramer, and the National Digestive Diseases Advisory Board; and it was cochaired by Dr. Donald Henson and himself. Dr. Levin stated that the objectives of the workshop were to: 1) assemble a critical number of active investigators to provide a forum for evidence-based discussions; 2) evaluate the cause of discrepancies between published and a number of unpublished studies; 3) identify the limitations of the current knowledge in the field of colorectal carcinoma; 4) consider new directions; and 5) publish a summary for use by NCI investigators and the scientific community in general. Dr. Levin stressed that the formulation of guidelines was not within the context of the meeting, unlike the United States Preventive Task Force that is about to issue its report in which colorectal cancer has been upgraded from Class C evidence to Class B.

Dr. Levin listed the topics discussed at the workshop: theory of screening, fecal occult blood testing, the role of flexible sigmoidoscopy, access of minorities to screening, patient compliance and adherence, radiographic studies, colonoscopy and the importance of post-polypectomy surveillance, inherited syndromes, genetic testing and screening, future technologies including endoscopy and imaging, and cost-effectiveness.

Dr. Levin discussed the topic of fecal occult blood testing. He indicated that the University of Minnesota clinical trial evaluating the benefits of this screening test has been criticized on the basis that the test is not sufficiently sensitive and cost-effective, and that the observed reduction in mortality is due to random colonoscopy rather than the fecal occult blood screening process itself. Dr. Levin explained that the analysis of the data based on 47,000 participants in the study, as reported in the *New England Journal of Medicine*, indicates a significant reduction in 13-year mortality in individuals screened annually compared with those screened biannually or with controls. In addition, investigators at the workshop concluded that the sensitivity of the screening test is a program sensitivity calculated over 7 or more years rather than a one-time sensitivity calculation.

Several issues regarding the fecal occult blood screening clinical trial remain unresolved, including: the cause of mortality reduction (colonoscopy versus fecal occult blood

screening), the apparent lack of benefit of the screening test in individuals screened biannually, effectiveness of the screening test among all age groups and sexes, and the effect of polypectomy on the incidence of colorectal cancer. Dr. Levin indicated that the available data on the clinical trial require further reanalysis, since the answer to many of the unresolved issues is buried within the already collected information. For instance, a more recent evaluation of the data appears to indicate that the reduction in mortality preceded the increase in the use of colonoscopy, suggesting that the mortality reduction was due to the screening process rather than colonoscopy. Dr. Levin noted that a remarkable difference (eightfold) in colorectal cancer incidence is also apparent between patients who were screened by fecal occult blood testing and controls who were not screened.

Dr. Levin indicated that conclusive data from the English, Danish, and Swedish clinical studies will be available in 1995. So far, all preliminary data from randomized studies support a favorable outcome for the fecal occult blood testing.

Dr. Levin stated that flexible sigmoidoscopy has received considerable attention in view of the data reported from the Kaiser Permanente and Marshfield Clinic studies. At the workshop, investigators expressed interest in a proposed study to be conducted in the United Kingdom. In addition, investigators reviewed and discussed data on the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial currently in progress in the United States. The possibility of providing flexible sigmoidoscopy through the training of nurse endoscopists was also discussed at the workshop, thereby expanding the number of individuals able to perform such procedures.

Dr. Levin referred to the case-control study of Dr. Joe Selby. He indicated that this study demonstrates a significant reduction in odds ratio of having a colorectal cancer within reach of the sigmoidoscope for those who had undergone a rigid sigmoidoscopy during a 10-year period before the diagnosis was made. The comparisons were made with those whose cancers were above the reach of the rigid sigmoidoscope and those who were not screened.

Dr. Levin indicated that Dr. Atkin and colleagues from the Imperial Cancer Research Foundation and St. Mark's Hospital proposed a study in the United Kingdom that includes a once-only sigmoidoscopy at age 55 to 60, and subsequent surveillance only for those individuals found to hold large or villous adenomas or cancers. Follow-up is not recommended for individuals who present no polyps or only small polyps. In addition, no fecal occult blood testing is included in the study. This model estimates a distal colorectal cancer prevention of approximately 70 percent by age 75. Data, obtained from a previous study, at St. Mark's Hospital, showed that individuals at high risk of developing subsequent colon cancer, who underwent surveillance after finding a rectosigmoid adenoma, were those who exhibited lesions greater than 1 centimeter in diameter. The risk was low or standard for individuals whose adenomas were small or tubular, even though they were multiple.

Dr. Levin referred to the National Polyp Study, indicating that this study has provided critical information regarding the chronological sequence of the development of adenomas and cancers in the sporadic population—individuals with no genetic predisposition. The study compared the observed incidence of colorectal cancer with that expected in individuals who had had their adenomas removed in two retrospective studies (as well as the SEER cross-

sectional database). Results show a 76 to 90 percent reduction in subsequent colorectal cancer due to removal of the adenomas.

While a number of limitations of the double contrast barium enema technique were identified during radiographic evaluations performed within the confines of the National Polyp Study, the final data concerning sensitivity of this technique is being analyzed. Colonic ultrasound and sophisticated CT scans with three-dimensional representation remain investigational.

Dr. Levin stated that the importance of familial clustering in the development of colon cancer is well recognized. Mutations in the adenomatous polyposis coli (APC) gene have been shown to be involved in the development of familial and sporadic colorectal cancers. The identification of genetic contributions of the autosomally inherited dominant syndromes as well as family history are both important factors for the understanding of colon cancer etiology. Dr. Levin recognized that although genetic screening has recently received substantial attention, important issues about this technology remain unchallenged or unresolved. These issues include: sensitivity, specificity, reliability, and feasibility of the technique, as well as financial, ethical, and legal implications of the use of such technique. Gene-based tests have also been in demand as tools for colorectal cancer diagnosis. For instance, polymerase chain reaction-based techniques have been used for the identification of the *ras* mutated gene in the stool—in colorectal cancer, *ras* mutations are primarily localized in codons 12 and 13. Such tests require extensive further validation and comparison with existing technology.

Dr. Levin indicated that patient behavior and compliance are two important factors related to the success of colorectal cancer screening procedures. Population studies of fecal occult blood testing indicate that in the United States patient compliance ranges from 18 to 82 percent. Community programs, however, have been able to increase the population compliance through appropriate advertising. Similarly, preliminary data on flexible sigmoidoscopy suggest that patient compliance is rather low.

Dr. Levin ended his presentation by summarizing the conclusions of the workshop. He stated that the mortality of colorectal cancer can be reduced with the use of fecal occult blood testing. However, future challenges include improvement of the technique by designing a more sensitive, specific, and efficient test for human blood, improvement of patient compliance, and reduction of costs. Dr. Levin added that polyp removal reduces subsequent colorectal cancer mortality. Additional useful information can be extracted from the National Polyp Study, and the United States PLCO Trial requires critical and careful evaluation. The British study of flexible sigmoidoscopy might be a unique opportunity to study the contribution of this screening procedure with a control group. Strategies for enhancing patient compliance and availability of screening procedures to minorities have to be identified and implemented. Finally, exploration of novel genetic- and imaging-based technologies has to continue.

Questions and Answers

Dr. Rimer asked Dr. Levin about the projected date for availability of the workshop summary report. Dr. Levin indicated that single reports from the various Writing Committee

members are being revised and their final formats are being prepared. The final summary report will be available for submission to the NCI by the end of 1994. Thereafter, it is expected that a summary report tailored to the general public will be issued.

Dr. Freeman asked Dr. Levin whether there is a specific age at which total colonoscopy is of critical value as a screening method, and whether the technique is cost-effective. Dr. Levin replied that age 60 to 65 appears to be reasonable for colon cancer screening. A study currently performed at the Veterans' Administration by the University of Oregon will provide important information regarding the usefulness of total colonoscopy. Dr. Levin indicated that it would be worth exploring the potential widespread availability of total colonoscopy, by training the appropriate number of personnel, as an alternative to developing technologies in the event that the latter do not become available on a widespread basis.

Diagnostic Imaging of the Colon—Dr. David Vining

Dr. Levin introduced Dr. David Vining, assistant professor of radiology at Bowman Gray School of Medicine, indicating that his presentation would include the description of new technologies such as helical computerized tomography (CT) and real-time three-dimensional (3D) rendering, or virtual reality.

Dr. Vining stated that the field of radiology has had a tremendous advancement from the discovery of x-rays 100 years ago, to the development of 3-D imaging in the 1990s. He explained that the field of virtual reality is setting the future for radiology. Dr. Vining added that his research field includes the application of virtual reality for scanning the airways and the colon. A videotape was then displayed showing the application of virtual reality in the scanning of the airways.

Dr. Vining indicated that in order for virtual reality to succeed in medicine it has to meet several criteria: 1) it must be accurate to display the expected anatomy; 2) it must be fast to encourage patient compliance; 3) it must be simple, since most physicians are computer-illiterate; and 4) it must be inexpensive, especially in a managed care environment.

Four steps are involved in the generation of virtual reality. First, a patient is scanned; second, a volume of data is obtained; third, the anatomy is segmented; and fourth, virtual reality simulated images are generated. Dr. Vining described the technical differences between conventional CT scanning and virtual reality using a helical CT (also called spiral CT), which is the device used in his research. In conventional CT scanning, an x-ray beam is turned on and moves around 360 degrees until an image is obtained. Subsequently, the patient breathes and is moved 1 centimeter; the beam moves again while a second image is obtained, and so forth until a tumor is scanned. If different degrees of inspiration are taken by the patient, the images can fall out of sequence and the tumor is missed. By contrast, in helical CT scanning, the x-ray beam is turned on and maintained throughout the entire procedure. In addition, the patient moves at a constant speed through the beam. The helical CT images form a volume of data. The latter technique presents various advantages: small lesions can be depicted when respiratory missregistration artifacts are eliminated; and recreation of overlapping slices is possible; thus, a small tumor can be centered in the slice so that its characteristics can be highlighted. In addition, the overlapping slices produce high quality 3D reconstructions.

Dr. Vining presented a number of slides (images of the airways and colon), stressing the difference in image quality between conventional scanning and virtual reality in which the technology has been pushed to its limits.

Dr. Vining explained that after a volume of data is obtained (e.g., a patient's chest), a subvolume of data is created which is processed by the virtual reality software to generate a model of the anatomy (e.g., trachea/bronchial tree). Subsequently, the desired anatomy is segmented. While this step can be accomplished by drawing regions of interest around the organs on each image, this strategy is not efficient. Instead, automatic means to isolate the anatomy of concern are being developed. Finally, virtual reality images are generated using a Silicon Graphics Crimson computer. Dr. Vining noted that virtual reality is an extension of 3-D, the major difference is that virtual reality is faster.

The clinical usefulness of virtual reality must be explored further; however, its use as an image-guided technique for biopsy of tumors shows promise.

Regarding colon cancer, Dr. Vining indicated that colonoscopy and barium enema are the only two available techniques to examine the complete bowel, and neither is outstanding from a patient's perspective. Thus, he stated that he has designed a new technique called virtual colonoscopy. This procedure consists of a 30-second helical CT exam which minimizes patient discomfort and, hopefully, will increase compliance. This technique provides the investigator with the ability to evaluate 400 to 500 CT slices, whereas in conventional practice, only 40 or 50 slices would be evaluated. Virtual reality processes hundreds of CT images and generates essentially a simulated colonoscopy. Dr. Vining presented another videotape on the application of virtual reality to colon examination.

To conclude his presentation, Dr. Vining maintained that while the cost of a diagnostic colonoscopy ranges between $1,000 and $2,000, including sedation and recovery room time, the cost of a basic CT scan and virtual reality processing is only $500.

Questions and Answers

Dr. Greenwald commented that the Cancer Control Program is planning to hold two workshops, one on virtual colonoscopy and the other on molecular diagnosis of colon cancer. The objective of these workshops will be to generate research thrusts that aim toward a practical endpoint that can be evaluated in clinical trials of early detection. The ultimate goal would then be to reduce colorectal deaths by 80 percent within some cost limit, arbitrarily $800. The translational research must advance rapidly to either incorporate this end point into the PLCO Trial or to conduct another clinical trial that might compare the diagnostic technologies side by side.

Dr. Broder asked Dr. Vining about the number of patients on whom both virtual and conventional colonoscopies have been conducted. Dr. Vining indicated that 12 patients have been tested with virtual colonoscopy performed in the morning, followed by conventional colonoscopy in the afternoon. All 12 patients have shown good correlation between the two diagnostic technologies. Three of the 12 patients have been diagnosed with cancer.

Dr. Vining indicated that retained feces in scanned patients can mask or simulate polyps. Therefore, his laboratory is currently working on the development of a stool contrast agent. In the meantime, a combination of barium and Metamucil to opacify any retained feces is being evaluated.

Dr. Broder asked Dr. Vining to comment on the potential for adapting virtual reality to mammography. Dr. Vining replied that breast cancer constitutes a complicated issue for the application of virtual reality—as an adaptation to mammography—since the lesions targeted with mammography are microscopic and are already malignant when they are detected. In contrast, colonoscopy detects 1-centimeter polyps before colon cancer is imminent.

Dr. Rimer ended the discussion on advances in the management and detection of colon cancer by stating that the NCAB will need to follow-up on the report issued by the U.S. Preventive Services Task Force, review the summary report on the workshop held at the International Meeting on Diagnostic Imaging of the Colon, and continue discussions on state-of-the-art screening technologies.

XVII. PROGRESS IN THE LONG ISLAND BREAST CANCER STUDY—DR. IRIS OBRAMS

Dr. Susan Sieber provided members with a brief history of the Long Island Breast Cancer Study (LIBCS), which was enacted in June 1993 as a result of the high mortality rates associated with breast cancer Long Island was experiencing. Dr. Sieber explained that the study was enacted under Public Law 103-43, which directed that NCI and NIEHS conduct a collaborative case-control study of potential risk factors attributing to the high rate of breast cancer on Long Island and two other northeastern counties. She added that Congress directed NCI to assess biological markers of environmental exposures, including contaminated drinking water, indoor and outdoor air pollution, electromagnetic fields, pesticides and other toxic materials, and hazardous and municipal waste. Dr. Sieber informed members that the study has encountered numerous challenges and NCI has allocated a large amount of financial and staff resources to the Project. Dr. Sieber then introduced Dr. Iris Obrams, Director of the Long Island Breast Cancer Study Project, to report on progress of the Project.

Dr. Obrams stated that the principal objective of the LIBCSP is to evaluate the potential contribution of environmental factors to the etiology of breast cancer. She added that since there has been a growing demand for research regarding breast cancer, NCI has responded by initiating the LIBCSP and making it a high priority. Dr. Obrams explained that like other areas in the Northeast, Long Island has high incidence and mortality rates of breast cancer, especially among White women. She informed members that one of the first steps within the LIBCSP will be to confirm these rates through a project coordinated by NCI's SEER Program to ensure they are not due to abstracting effects.

Dr. Obrams emphasized that the LIBCSP is part of a broader NIH research program on breast cancer, which examines the role of genes, diet, and hormones and other risk factors in the development of breast cancer in addition to environmental exposures. She pointed out that these other risk factors will be explored among LIBCSP participants as well. She stated that the Project is planned to examine exposures to organochlorines, pesticides, polychlorinated

biphenyls, polycyclic aromatic hydrocarbons, and radical-induced DNA damage. Traditional approaches for assessing individual exposures have not yet been developed to a level where they can detect associations between risk factors and development of cancer. She explained that biological markers are necessary to determine whether inappropriate cell division, cell cycle disruption, or gene expression are factors contributing to the development of environmentally induced breast cancer. Dr. Obrams stated that findings from the LIBCSP will address breast cancer issues for women across the United States.

Dr. Obrams informed members that in order to involve the communities, the study has worked closely with advocacy groups, particularly those representing special populations, of which there are large communities on Long Island. To increase the interaction, an update is issued regularly to Congress and the community. Dr. Obrams added that open meetings are held and a list of community members and advocates is being developed to form committees and a network of contacts for the study. An ad hoc advisory group consisting of community members and scientists is also being formed.

Dr. Obrams reported that various mechanisms are being utilized to conduct the study, including peer-reviewed cooperative agreements and grants, as well as interagency agreements. Quality control procedures have been established to ensure that every stage of the research is well conducted. She explained that the core component of the LIBCSP, a grant for the case-control study, will be peer reviewed next month. It proposes a multidisciplinary, population-based study developed by the cancer centers in the New York area. The Columbia Cancer Center has developed a protocol for all centers to follow for obtaining and storing biologic and environmental specimens and for interviewing participants. In addition, Columbia University has been awarded a grant that will partially support the development of biologic markers required for the LIBCSP.

Dr. Obrams informed members that an agreement has been forged with Brookhaven National Laboratories to aid in the development of a geographic information system (GIS) for Long Island. GIS, an application of virtual reality to environmental research, has the ability to integrate data regarding water, air, soil contaminants, waste sites, toxic releases, Superfund sites, and a host of other potential exposures in layers over one specific area. Dr. Obrams explained that the strength of this system is its specificity, which allows detailed examination of the environmental exposures of participants according to their residential and occupational histories. This information will provide a fairly thorough description of the participants' past and present environmental exposures.

Dr. Obrams stated that the EPA and other county regional offices will share their data on environmental exposures in the area, as well as their expertise regarding GIS. She reported that study designers are consulting with other environmental groups that have experience using GIS, such as Boston University and the New York State Health Department.

Dr. Obrams also provided a brief outline of additional research included within the overall project. A study conducted by the American Health Foundation will examine pesticide levels in fat tissue of both breast cancer and study control participants. Dr. Obrams explained that another study is under way at the State University of New York at Stony Brook to explore the reduction of barriers to participation in screening for breast cancer, primarily among underserved and special populations. NCI is conducting a telephone survey to compare risk

factors and explore environmental exposures among residents of Long Island, the Northeast, and known low-risk areas. She mentioned that other projects include a Columbia University research program to identify biomarkers of dose for pesticides, organochlorine compounds, polycyclic aromatic hydrocarbons, and DNA adducts, and a Cold Spring Harbor Laboratory study on point mutations in breast tumor tissue that will utilize a new technique termed "representational difference analysis." She concluded the summary with a description of a study by Memorial Sloan-Kettering and Strang Clinic-Cornell that will measure urinary levels of two estrogens to determine whether an individual's metabolism affects the impact of environmental estrogens on breast tumor tissue.

Dr. Obrams recognized that in the future additional research needs will surface and some avenues of research will prove ineffective. She emphasized that flexibility within the project will be necessary. In terms of cost, Dr. Obrams estimated that about $2 million has been utilized for research already and that an additional $4 million will be needed for the second year of research.

Questions and Answers

Dr. Day commented that data exist from international studies regarding areas with even higher incidence and mortality rates than are present at Long Island that may be utilized by the LIBCSP. Dr. Obrams agreed with Dr. Day and reiterated that the Project is not isolated in its focus. Dr. Day suggested that the increased incidence in breast cancer on Long Island may be attributable to dietary differences. Once again, Dr. Obrams agreed, and assured members that the case-control study will examine dietary factors.

Dr. Becker commented that while the LIBCSP is an impressive study in its comprehensive examination of various exposures and risk factors, it is disappointing in that other geographic areas have significantly higher incidence and mortality rates and, therefore, should have been targeted instead.

Dr. Goldson suggested that the smaller and more efficient hospitals are more likely to abstract cancer incidences and mortalities in their areas which supports the idea that differences in abstracting may influence the varying rates of incidence and mortality for breast cancer. In addition, there is a strong breeze that comes across the Long Island Sound in certain areas of New York that will remove most of the atmospheric contamination. Dr. Rimer concluded by stating that the LIBCSP will clearly present a statistical challenge.

XVIII. DISCUSSION AND FUTURE AGENDA ITEMS—DR. BARBARA RIMER

At this time, Dr. Rimer responded to the tobacco resolution revised by Dr. Chan and solicited new items for the NCAB meetings agenda. She stated that her goal is to reflect the Board's priorities as much as possible in the next several meetings.

Dr. Rimer first referred to Dr. Chan's resolution, which was distributed to Board members. Dr. Chan began by reading a modification suggested by Dr. Salmon to strike the last sentence of the resolution and substitute it with, "We further condemn the promotion of icons for tobacco that interest the young, who are most susceptible to addiction." By this, Dr.

Salmon clarified, he is referring to Joe Camel and the marketing of images. Dr. Chan accepted Dr. Salmon's modification.

Dr. Yodaiken suggested as a clarification that references to "tobacco industry" be changed to references to the "U.S. tobacco industry." He also cautioned using the phrase "developing countries," and asked what that meant. Dr. Rimer suggested referring to "countries abroad" instead. Dr. Chan said his reference to "developing countries" was meant to reflect the CNN reports he had referred to earlier, but that he would accept this modification. A motion was made and approved to adopt Dr. Chan's resolution.

Dr. Rimer then opened the floor for discussion of new items for the January NCAB meeting agenda. She stated that the December meeting will be for program review and will include a meeting of subcommittee chairpersons in order to move the SENCAP report forward. Dr. Rimer suggested that an update on the Secretary's Breast Cancer Action Plan be presented by Dr. Susan Blumenthal and Ms. Fran Visco. She also requested that Dr. Salmon deliver a cancer center presentation, and he agreed to do so.

Dr. Calabresi noted that a number of agenda items were suggested at the Activities and Agenda Subcommittee meeting. Dr. Day, Ms. Mayer, and Dr. Becker offered to plan a presentation on the impact of health care reform in changing patterns of care and reimbursement under research. Other suggested topics included developing strategies to proceed forward with the SENCAP report; hosting a strategic session on the intramural programs based on the NIH's Marks report and other documents (Dr. Calabresi noted that one aspect of this is already being implemented, which involves field trips to major intramural sites, such as the NIH clinical center, the Bethesda Naval Hospital, and the Frederick Cancer Research and Development Center.); biotechnology and industry relationships with the NCI, and the changing policies with respect to technology transfer data, fair pricing clauses, conflict of interest among awardees, etc.; a coordinated presentation by voluntary and philanthropic agencies that support cancer research regarding their priorities and interests and how they might complement or interact with the NCP; and the focus of research programs on treatment in elderly, underserved, and culturally unique populations, and how this relates to clinical trials.

Dr. Rimer queried the Board as to whether any of these topics would be of interest for the January meeting. Dr. Day stated that while health care reform has stalled in Congress, there are many changes occurring at the State level that can have a major impact on the performance of cancer research. Therefore, he emphasized that this issue is an urgent one. Dr. Rimer noted that this topic will be placed on the agenda list.

Ms. Brown noted that she would like to follow up on the discussion of clinical trials and lack of accrual. Dr. Rimer said that she will talk with Ms. Brown to determine how to formulate that as part of a future agenda. A final suggestion was made by Dr. Salmon to schedule a business session at the end of the first day of the December meeting, which can be canceled if no business items arise. Dr. Rimer agreed. She then referred the Board to a copy of a draft letter to Dr. Varmus and asked Board members to fax or leave any changes with her by the end of the day.

XIX. ADJOURNMENT—DR. BARBARA RIMER

In closing, Dr. Rimer thanked the Board members and NCI staff for their participation and stated that she is available to them between meetings. She emphasized that what occurs between meetings is as important as what occurs during meetings in moving the business of the NCAB forward. There being no further business, Dr. Rimer adjourned the 91st National Cancer Advisory Board meeting at 12:36 p.m.

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Date Dr. Barbara Rimer, Chairperson