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

# Summary of Meeting
May 4 and 5, 1993

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

Department of Health and Human Services
Public Health Service
National Institutes of Health
National Cancer Institute
National Cancer Advisory Board
**Summary of Meeting**[1]
**May 4 and 5, 1993**

The National Cancer Advisory Board (NCAB) convened for its 86th regular meeting at 8:00 a.m., May 4, 1993, in Building 31, C Wing, 6th Floor, Conference Room 10, National Institutes of Health (NIH).

**NCAB Members**

Dr. Paul Calabresi (Chairman)
Dr. Frederick F. Becker (absent)
Dr. Erwin P. Bettinghaus
Dr. David G. Bragg
Mrs. Zora Brown
Dr. Kenneth Chan
Dr. Pelayo Correa
Dr. Robert W. Day
Mrs. Barbara P. Gimbel
Mrs. Brenda Johnson (absent)
Dr. Walter Lawrence, Jr.
Mrs. Marlene A. Malek
Ms. Deborah K. Mayer
Dr. Sidney Salmon
Dr. Ellen V. Sigal
Dr. Howard M. Temin (absent)
Dr. Samuel A. Wells, Jr.
Dr. Charles B. Wilson

**President's Cancer Panel**

Dr. Harold P. Freeman (Chairman) (absent)
Mrs. Nancy G. Brinker (absent)
Dr. Henry C. Pitot (absent)

**Alternate Ex-Officio NCAB Members**

Captain Bimal C. Ghosh, DOD
Dr. Robert McGaughy, EPA
(for Dr. Hugh McKinnon)
Dr. Lakshmi C. Mishra, CPSC
Dr. Ralph Yodaiken, DOL
Dr. John Johnson, FDA
Dr. Theodore Lorei, DVA
Dr. Kenneth Olden, NIEHS
Dr. P. C. Srivastava, DOE
(for Dr. David J. Galas)
Dr. Clifford J. Gabriel, OSTP

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

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

---

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

**Liaison Representatives**

Dr. Robert W. Frelick, Association of Community Cancer Centers
Dr. Eve Barak, National Science Foundation
Dr. Edward Gelmann, American Society of Clinical Oncology, Inc.
Ms. R. Davilene Carter, American Association for Cancer Education, Inc.
Mrs. Yvonne Soghomonian, Candlelighters Childhood Cancer Foundation
Dr. Edwin A. Mirand, Association of American Cancer Institutes
Ms. Carol Curtiss, Oncology Nursing Society
Mr. Alan Davis, American Cancer Society
Dr. Nancy Colburn, American Association for Cancer Research (for Dr. Thomas King)

In addition to NCI staff members, meeting participants, and guests, a total of 25 registered members of the public attended.

# TABLE OF CONTENTS

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

Dr. Calabresi called the 86th meeting of the National Cancer Advisory Board (NCAB) to order and introduced several guests representing medical, research, and professional organizations. He welcomed members of the public and informed them that they could express their views on issues discussed during the meeting by writing to the NCAB Executive Secretary, Mrs. Barbara Bynum, within 10 days of the meeting. Dr. Calabresi asked for the Board's approval of proposed NCAB meeting dates for 1995. Dr. Sidney Salmon related that a meeting of the American Society of Hematology could interfere with the proposed meeting dates in December. Dr. Calabresi stated that the 1995 dates stand as confirmed, except the December dates, which Mrs. Bynum will check for any conflict. He then called for approval of the minutes of the previous meeting, which were unanimously approved without change.

Dr. Calabresi reported that, due to the absence of Dr. Harold Freeman and Dr. Henry Pitot, the report of the President's Cancer Panel would be postponed until the September NCAB meeting.

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

Dr. Broder announced several honors awarded to National Cancer Institute (NCI) staff and close associates of the National Cancer Program: Dr. Stuart Yuspa of the Division of Cancer Etiology (DCE) won the 33rd Clowes Memorial Award; Dr. Joseph Fraumeni won the American Society of Preventive Oncology's Distinguished Achievement Award and the American Cancer Society Award for Research Excellence in Epidemiology and Prevention; Dr. Steven Rosenberg of the Division of Cancer Treatment (DCT) won the Claude Jacquillet Award; and Dr. Michael Blaese became a member of the Association of American Physicians. Dr. Broder announced that Dr. Peter Howley, Chief of the Laboratory of Tumor Biology, DCE, and Dr. George Vande Woude, Director of the Basic Research Program and the Advanced Bioscience Laboratory Center Program at the Frederick Cancer Research and Development Center, were elected to the National Academy of Sciences. On April 22, 1993, Drs. John Bonadonna of the NCI in Milano and Bernard Fisher of the University of Pittsburgh received the Bristol-Meyers-Squibb Award for Distinguished Achievement in Cancer Research.

### Workshop on Breast Cancer Screening

Summarizing some recent NCI activities, Dr. Broder noted that the Institute hosted an international workshop on breast cancer screening on February 24 and 25, 1993. After reviewing international clinical trial data, workshop participants assessed the current state of knowledge on breast cancer screening. They discussed breast self-examination, clinical breast imaging and examination, and results of various randomized trials of mammography (including Canadian and Swedish studies) in detail. A report from this workshop indicates that there is a high level of confidence that screening technologies, including mammography, can reduce mortality related to breast cancer by approximately 30 percent in women over the age of 50, up to the age of 69. Dr. Broder noted that the optimal screening interval has not been established. The NCI, he added, advocates annual clinical examinations and mammography for this age group.

Dr. Broder reported that there are no data to support a statistically significant reduction in mortality related to breast cancer in the first 5 to 7 years of disease for women aged 40 to 49 years as a result of screening. There is, however, a possibility that a decrease in mortality could occur at 10 to 12 years. Dr. Broder stated that there is disagreement concerning public health screening recommendations for women in this age group. Resolution of this issue may arise from clinical trials, additional research in this area, or individualized recommendations

based on patient risk factors. He added that the report from this workshop is only one step in the process of establishing or revising NCI screening guidelines and emphasized that the NCI will consider all relevant scientific information in a public health context before it recommends changes in its guidelines.

Dr. Broder requested that NCAB members, as special Government employees and representatives of the NCI, collaborate with the Institute to ensure a steady transfer of accurate information on this issue.

Dr. Broder emphasized that mammography has a proven, life-saving value in a major population group. He added that it is necessary to ensure that this message is not misconstrued by postmenopausal women as a result of any uncertainty or disagreement in the scholarly community. Data are insufficient, he continued, for randomized clinical trials to judge the effectiveness of screening in women aged 70 and older. Dr. Broder stressed that the NCI is collaborating with the American Cancer Society (ACS) and other interested groups on breast cancer screening and will continue its interaction with the NCAB and other components of the NCI on this subject.

**Special Commission on Breast Cancer**

Dr. Broder reported that the Special Commission on Breast Cancer, a component of the President's Cancer Panel, met in Miami on March 18 and 19, 1993, to consider screening, early detection, and the development of new technologies for detection and diagnosis, as well as potential new therapies. Conclusions from the workshop on international studies were presented, in addition to data on radiation risk, newer breast imaging technologies, and screening strategies in special populations of women.

The Commission met again on April 29, 1993, in New York to discuss possible environmental influences on breast cancer, health care delivery issues, and the role of third-party payers. Dr. Edward Trimble summarized the findings of a recent NCI conference on breast cancer in younger women; Dr. Susan Sieber presented an overview of NCI-supported research on environmental and other causes of cancer; Dr. Mary Wolff discussed recent data on possible associations of organochlorides, such as ddT and ddE, with breast cancer risk; and Dr. John McLachlan, Scientific Director of the National Institute for Environmental Health Sciences (NIEHS), discussed estrogenic chemicals in the environment that may influence the risk of breast cancer. Other speakers included Dr. Deborah Davis, who discussed environmental influences on breast cancer susceptibility; Dr. Scott Davis, who discussed his research on the influence of electric power sources on breast cancer risk; and Dr. John Kovach, who discussed his studies on specific alterations of the *p53* gene due to potential environmental influences. Several other representatives from the NCI and the NIEHS also attended the meeting.

Dr. Broder reported that the remainder of the meeting concerned the delivery of breast cancer care and the issue of payment policies. Clinical providers (including those at NCI-designated cancer centers) and representatives of the Health Insurance Association of America, Blue Cross/Blue Shield, the Health Care Financing Administration, and Cancer Care made presentations. Dr. Howard Greenwald discussed the influence of income on services received and survival. Dr. Broder noted that the next meeting of the Special Commission on Breast Cancer will be held in Los Angeles and will focus on information dissemination to the public, patients, scientists, and clinicians.

**President's Cancer Panel**

Dr. Broder informed the Board that the President's Cancer Panel met on April 1, 1993, in San Francisco to discuss the newly formed Specialized Programs of Research Excellence (SPOREs), with a focus on the University of California at San Francisco, a new SPORE

grantee. Discussion concentrated on the definition of a SPORE, a SPORE's advantage in utilizing local resources, scientific and advocacy resources of the community, and methods to speed the development of novel approaches to basic research, prevention, diagnosis, and treatment. The panel also assessed models for interaction with breast cancer patient advocates at the grassroots level. Dr. Broder mentioned that many of the SPORE program's novel approaches could serve as a potential template for other programs.

**General Accounting Office Briefing**

Dr. Broder announced that the NCI participated in a General Accounting Office briefing on March 23, 1993. The briefing focused on the Institute's collaborative relationships with other Public Health Service agencies, particularly the Centers for Disease Control and Prevention (CDC). Dr. Broder noted that, at this time, no report from the meeting has been issued. He commented that the NCI established clear priorities for prevention and control efforts that provide an important foundation without overlapping or impinging on the activities of the CDC.

**Bypass Budget**

Dr. Broder reported that the NCAB Planning and Budget Subcommittee met in Chicago on March 24, 1993, to discuss the Bypass Budget process. He reminded the Board that the Bypass Budget presents a forum for the presentation of the needs of the National Cancer Program according to the Institute's best professional judgment, emphasizing that the Bypass Budget is a scholarly, not a political, document. He stated that there is debate about how the Bypass Budget should be written, partially because it is allegedly incomprehensible to members of Congress. Dr. Broder expressed his belief that the Bypass Budget is understandable and commented that problems sometimes arise when sections are extracted and the document is not considered an "organic whole."

**Workshop on Epigenic Factors of Inheritance**

Dr. Broder stated that the NCI cosponsored a workshop on epigenic factors of inheritance with the National Institute of General Medical Sciences and the National Institute of Child Health and Human Development on April 26 and 27, 1993. This workshop, he maintained, included excellent presentations, most notably a discussion of some novel ideas on genomic imprinting and the principle that the relaxation of physiologically imprinted genes can lead to, or be highly associated with, some cancers (particularly Wilm's tumor) under certain conditions. Dr. Broder expressed his belief that this phenomenon is more prevalent than commonly assumed and that this scientific discovery will have substantial implications.

**Update on Gene Therapy**

Dr. Broder explained that gene therapy for adenosine deaminase (ADA) deficiency, the Institute's first gene therapy research project, has been underway since September of 1990. This research involves the use of lymphocytes that have been transduced to express ADA. Two young girls have received this therapy successfully for approximately 1 year, with treatments every 6 to 8 weeks. One of these patients may receive stem cell therapy in the near future at the NIH clinical center, and a third patient is being evaluated for therapy. Dr. Broder noted that the physicians involved consider the most important effect of this therapy to be an increased normalization of the children's lives. Although limited in application, he added, this strategy marks an important scientific development.

Dr. Broder announced that seven patients with brain tumors have been treated with gene therapy in a protocol involving Drs. Michael Blaese, Kenneth Culver, and Edward Oldfield, in a collaboration between the NCI and the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS). In this therapy, brain cancer cells become potentially susceptible to the administration of ganciclovir by mechanisms that are not fully

understood at this time. The therapy involves the insertion of cells that have been transduced to carry the herpes virus' thymidine kinase gene, followed by treatment of the patient with ganciclovir. Four patients with glioblastoma, one with metastatic glial cell cancer, and two with metastatic melanoma are under evaluation. Although the protocol is too new for a realistic assessment, Dr. Broder indicated that there are signs of antitumor effect. The NCI is expecting other groups to join in this effort; the University of California at San Francisco will probably become a major participant in the project.

Dr. Broder reported that 10 patients have been treated in a clinical trial of gene therapy using tumor-infiltrated lymphocytes transduced with the gene for tumor necrosis factor. Thus far, he explained, there have been no unwarranted toxic side effects of the treatment. A 46-year-old woman with disseminated melanoma, who had failed conventional therapy, had a substantial response to this therapy. Dr. Broder also announced that a gene therapy vaccine for advanced melanoma, composed of tumor cells transduced with the gene for either tumor necrosis factor or interleukin-2 (IL-2), is underway. Three patients have received autologous tumor cells transduced with the gene for tumor necrosis factor, and two patients have received transduced autologous tumor cells that express the gene for IL-2. Dr. Broder added that permission was recently granted to treat patients with advanced breast cancer using this approach.

Dr. Broder suggested reexamining conventional models for conducting experimental therapy in the realm of prevention and diagnosis. Perhaps, he said, some clinics should be reformulated to take advantage of new and available opportunities. The NCI will probably assess its own intramural program, he added, expressing the hope that other institutions will incorporate multidisciplinary approaches in their organizational structures.

Dr. Broder reported that a vaccine involving recombinant vaccinia virus with carcinoembryonic antigen (CEA) has been administered to one patient with colon cancer and will probably be administered to other patients with colon cancer, breast cancer, and other diseases. He explained that several tumor types express CEA on their cell surfaces, especially cancers of the pancreas, colon, and breast (about 50 percent). A modified version of the recombinant vaccinia virus vector has been used in smallpox vaccines for many years and can be combined genetically with CEA. Dr. Broder clarified that when the entire recombinant vaccinia CEA gene is expressed, CEA is coexpressed with the immunogenic, but noninfectious virus that elicits an immune response directed against the vaccinia CEA construct. Therefore, this approach, in theory, provides a type of tumor cell immune response in a context where one might not otherwise occur.

Dr. Broder noted the 40th anniversary of a major breakthrough in genetics—the 1953 discovery of the structure of DNA by Watson and Crick. Although there was great fear of the misuse of genetic discoveries in 1953, he observed, gene therapy research conducted today promises to answer many important questions, frame new ideas, and, hopefully, inspire more hope than fear.

**Budget**

Dr. Broder told the Board that he would attempt to discuss the extremely complicated 1994 budget. He informed those members who would like to discuss the budget in more detail that they could attend a special meeting of the Planning and Budget Subcommittee, at which Mr. John Hartinger would be making a presentation. Dr. Broder explained that this year's NIH budget, especially the NCI allocation, is historically unique. He reported that the President's budget for 1994 for the NCI is approximately $2.15 million, which consists of an approximate 8.3 percent increase over the 1993 budget. There is, however, a component of multiyear funding involved, which complicates the budget and distorts the actual level of funding. In

other words, Dr. Broder explained, some of the figures represent money appropriated *en bloc*, apparently for 1 fiscal year, but intended to cover 4 years of activities.

Dr. Broder announced that the NCI would testify before Representative Natcher's (D-KY) subcommittee on May 11, 1993, along with the National Heart, Lung, and Blood Institute (NHLBI), the National Institute on Allergy and Infectious Diseases (NIAID), and the National Center for Human Genome Research (NCHGR). Dr. Bernadine Healy, he continued, is scheduled to provide an overview to the subcommittee on May 13, 1993. On May 26, 1993, a Senate hearing is scheduled with a panel presentation of all NIH Institute directors.

Dr. Broder outlined some deficit reduction strategies being implemented by the new administration that have been incorporated into the 1994 Bypass Budget: reducing full-time employee levels; freezing pay increases; reducing administrative expenses by 3 percent; and maintaining the average cost of a research grant at the 1993 level. Some NIH Institutes experienced actual dollar losses in the 1994 President's budget, compared with 1993: the NHLBI was reduced by 1.3 percent; the NINCDS by 1.6 percent; the National Eye Institute by 1.3 percent; the National Institute on Aging (NIA) by 1.3 percent; and the National Institute of Arthritis and Musculoskeletal and Skin Diseases by nearly 1 percent. The total NIH budget was reduced by 3.2 percent. Appropriations for the NCI and the NIAID increased more than other Institutes; other increases were conferred to the Office of the Director of the NIH, the NCHGR (26 percent), and the National Library of Medicine (18 percent). Substantial growth for the Office of the Director was justified on the basis of women's health studies and minority-related activities.

Dr. Wells asked if the multiyear funding component extends throughout the NIH. Dr. Broder explained that the NIH received a $210 million package for breast cancer with a 4-year commitment. There was a concerted effort to identify trans-NIH initiatives that could be supported in Institutes that conduct important activities in breast cancer, such as General Medical Sciences. The NCI received $167 million of the original $210 million, with the remainder allocated to several other Institutes under the 4-year commitment, which Dr. Broder referred to as "forward funding." He added that the forward-funding mechanism applies only to breast cancer-related projects.

Dr. Broder presented information on the distribution of the Institute's budget. Research project grants increased nearly 4 percent, the Cancer Centers program about 9.2 percent, and total research grants about 5.7 percent. He noted that a substantial amount was appropriated to construction, primarily related to breast cancer research ($12.5 million). Dr. Broder then described the distribution of monies earmarked for breast cancer. Slightly less than $197 million was committed for breast cancer in 1993. The 1994 budget included a 4-year increase of $167 million, or approximately $43 million a year.

Dr. Broder noted that the NCI has tried to develop a priority for traditional components of the NCI, including a substantial proportion in research project grants. He pointed out that the Division of Cancer Prevention and Control will receive a substantial increase.

Dr. Broder reported that approximately 40 breast cancer-related research project grants were funded in 1991; 111 applications were received, for a success rate of about 36 percent. Regarding all research project grants, 840 of 3,040 were funded, for a 28 percent success rate. Many programs from the investigator community, stimulated by program announcements, Requests for Applications (RFAs), and anticipation of additional money, were initiated in 1992. Therefore, the NCI funded a large increase (nearly 93 grants) in breast cancer in 1992. However, because 370 applications were received, the success rate fell. While the number of grants funded increased by 2.3 percent, the number of applications received increased by 3.3 percent. Dr. Broder emphasized that although the success rate in breast cancer fell, it is

inappropriate to argue that this decrease was the result of a withdrawal of the commitment of the NCI.

**Questions and Answers**

Dr. Bettinghaus asked if the NCI is required to obligate the $167 million appropriation during the first year, or if it may examine its needs and allocate the funds over the course of 4 years. Dr. Broder explained that Institutes within the NIH, except for the Office of the Director, must commit all money in the year that it is appropriated while adhering to the Anti-Deficiency Act. Some Government agencies, he continued, have multiyear authority and can, thus, delay obligation of funds. The Department of Defense (DOD), for example, has a 2-year authority. Regarding forward funding, Dr. Broder explained that an institution obligates its money within the fiscal year to which it is committed. The money is not, however, transferred directly to the institution, nor will the institution be given the 4-year appropriation for deposit in a bank. Dr. Broder noted that funding can be terminated for failure to perform. In the case of termination, the money reverts to the Treasury. Dr. Bettinghaus commented that this regulation restricts the flexibility to plan for distribution. Dr. Broder added that because of this regulation, it would not be possible to reprogram if a change in scientific priority or some other problem occurred.

Dr. Greenwald commented that chemopreventive agents for breast cancer prevention are developed through master contracts, which are "pay as you go." Therefore, he speculated, the forward-funding appropriations may not be available for this purpose.

Dr. Broder emphasized that the NCI is pleased with any funding that is appropriated, and is able to wisely utilize the resources in whatever form they are given.

Dr. Salmon inquired about the proposed split between intramural and extramural construction supported by the breast cancer funding. Dr. Hartinger replied that most of the funding will be allocated to the extramural program.

Dr. Bettinghaus recommended that the NCI and the American Cancer Society cooperate further to standardize screening guidelines for public debate, since there is potential for significant public confusion and disapproval on this issue. Dr. Broder agreed with Dr. Bettinghaus and stated that there is significant merit in the current guidelines for both premenopausal and postmenopausal women. Dr. Broder stated that the NCI should make proposals based on the best information available, but added that it is also appropriate to alter those proposals based on new information. Regardless, Dr. Broder acknowledged that there is substantial controversy in the scholarly community about the role of mammography for women between the ages of 40 and 49.

Dr. Lawrence noted that he chaired the American Cancer Society meeting on February 1 and 2 but did not attend the NCI meeting held on February 24 and 25 concerning the issue of breast cancer screening. Although the newspapers conveyed that the two meetings each had a different outcome, both organizations, Dr. Lawrence said, concluded that this is an uncertain area in which data must be continually reexamined. Dr. Lawrence explained that he perceived Dr. Broder's comments to mean that the NCI would not make any dramatic changes to the guidelines agreed upon with 11 other organizations in May 1991.

Dr. Broder clarified that the message being conveyed supports the belief that mammography is a valid, life-saving approach for the average American postmenopausal woman and that the combination of clinical examination and mammography has definite value. This approach, he stressed, should not be considered prevention, but early detection. Dr. Broder estimated that approximately 80 percent of women who have breast cancer are over the age of 50, and the median age for women with breast cancer is 63. Therefore,

mammography has unquestionable benefit in this population and some value for women aged 40 to 49 years. Dr. Broder emphasized the importance of the doctor-patient relationship and individualized approaches to care and prevention. He pointed out that breast cancer is a fundamentally different disease in different age groups, suggesting that the age for which the guidelines should be targeted is open for discussion.

Dr. Bragg recalled the debate on mammography in the 1970s, which suggested that the procedure could be harmful and affected the public's confidence in mammography. He contended that current debate in the scientific community is also undermining the public's perceived value of mammography.

Dr. Day suggested that current statistical information—sample size and length of time of follow-up for mammography—is not adequate for judgment on this issue at this time. He expressed concern about risk factors and suggested that mammography could be valuable for even younger age groups. Dr. Day agreed with Dr. Bragg's concerns and asserted that the provision of information to the patient should not be considered interference in a physician-patient relationship. Dr. Broder agreed that a patient and his or her doctor should decide on the best course of prevention and treatment, regardless of a governmental authority's guidelines. Dr. Day also mentioned that modified guidelines could affect issues of reimbursement. He requested that the Board conduct a full discussion on the broad issue of breast cancer screening.

Dr. Lawrence conveyed his reservation in having a meeting devoted to this topic, since more data are needed. He suggested that the Board wait until after the meeting in Europe in September, at which new data from additional trials will be presented. Dr. Lawrence cautioned against causing further public confusion. Dr. Calabresi suggested that the Board conduct a forum on the pros and cons of this issue. Dr. Lawrence remarked that reports from the NCI and ACS meetings will be published, the ACS meeting appearing in a supplemental issue of *Cancer*.

Dr. Sigal emphasized that reimbursement will be a major aspect of the breast cancer screening debate. She noted that insurance carriers are not addressing this issue in the context of health care reform.

Dr. Salmon urged that it is the Board's responsibility to be informed about the debate on mammography and differences in studies, regardless of whether or not reports of the two meetings will be published, or whether it is too early to reach a conclusion.

Dr. Calabresi emphasized that it is extremely important to separate the public health and economic aspects of these studies with an individual patient concept.

Although mammography is important, Dr. Broder argued, the scientific community should not forget that better diagnostic tools are needed. He emphasized that it is the Institute's duty to ensure that basic science programs are heavily involved in checking for easily quantifiable markers, such as genotypic markers, that can be adapted for mass screening. Perhaps by working with the Human Genome Project, it may be possible, he continued, to develop more effective and individualized screening tools. Dr. Broder proposed that the scientific community should not overstate mammography's efficacy. He stressed that mammography's ability to attain a 30 percent reduction in mortality is unacceptable—a 100 percent reduction should be the goal.

**Department of Defense (DOD) Appropriation for Breast Cancer Research**

Dr. Broder stated that approximately $200 million has been appropriated to the Department of Defense for fiscal year 1993, to be used primarily for breast cancer research. This allocation has a forward-funding component and a 2-year authority. Dr. Broder related

that the Institute of Medicine has reviewed this appropriation and will probably recommend that a portion of these funds be distributed through a peer review process, perhaps involving the NIH Division of Research Grants. He explained that the NCI has core grants that have passed the peer review process and are ready to be funded upon approval. However, these grants cannot be funded with the money currently under discussion. These investigators will be required to submit new applications to receive funding via the DOD appropriation.

## III. LEGISLATIVE UPDATE—MS. DOROTHY TISEVICH

Ms. Tisevich reported that the Senate and House versions of the reauthorization bill are in conference committee. Since the last NCAB meeting, the House added a new provision to the bill requiring the NCI, in collaboration with the NIEHS, to conduct a case-control study to assess biological markers of environmental and other risk factors contributing to the incidence of breast cancer in four counties in the Northeast. This study must be completed within 30 months of enactment of the bill. Ms. Tisevich indicated that the Senate is likely to agree to this provision in the House bill. A second change in the House's markup of this bill was an increase in the overall NCI authorization of appropriations, from $2.2 billion to $3.2 billion. An additional $325 million is provided for breast cancer and other women's cancers, and an additional $72 million for prostate cancer.

There was also a change in the reauthorization bill related to the "prevention and control line." Ms. Tisevich explained that the bill provides for one overall authorization for both cancer research and cancer prevention and control, rather than two separate authorizations, but specifies that prevention and control be funded as a percent of the total appropriation. The bill originally allowed for a 2-year phase-in of this change, with funding at 75 percent of the bypass request in 1994 and 10 percent of the appropriation in 1995 and 1996. It now allows for a 3-year phase-in period without a tie to the bypass request. The first year of funding for prevention and control would be at 7 percent of the appropriation, the second year at 9 percent, and the third year at 10 percent. Ms. Tisevich clarified that the "prevention and control line" is about $138 million (6.4 percent of the total NCI budget of $2.142 billion) in the 1994 President's budget, or approximately $12 million short of the 7 percent earmark.

Ms. Tisevich reported that issues regarding coordination of AIDS research activities at the NIH and the Senate provision on immigration policies relating to HIV-infected individuals have not been resolved. The Board passed a resolution regarding the proposed changes in authority for the Office of AIDS Research.

Ms. Tisevich said that many new members of Congress and their staffs have been visiting the NIH campus. On April 26, 1993, approximately 40 Congressional staff members came to the campus for a day-long program sponsored by the Ad Hoc Group for Medical Research Funding. Several presentations concerning AIDS, gene therapy, cystic fibrosis, cancer research, women's health, and minority health were given at this meeting. Ms. Tisevich reported that three members of the House Appropriations Subcommittee would be touring the clinical center on the day of the NCAB meeting.

Ms. Tisevich apprised the Board that technology transfer, drug pricing, and high-performance computing initiatives continue to be of great interest to Congressional members. She reported that Representative Ron Wyden (D-OR) introduced the Federal Research Production Commercialization Act to establish a process to ensure the reasonable pricing of drugs, devices, and other products made available to the public as a consequence of NIH funding. As a result of Representative Wyden's continuing interest in the impact of NIH funding on the development and commercialization of these products, he has proposed that taxpayers' interests be protected through competitive bidding for nonexclusive licenses to

further develop products that have had some NIH support. The bill, Ms. Tisevich explained, would require that royalties be negotiated during the competitive bidding process and paid to the NIH.

Ms. Tisevich stated that Representative Henry Waxman (D-CA) and Senator David Pryor (D-AR) are also interested in the amount of support that the NIH has been providing for the development of agents such as AZT, ddI, and ddC, as well as several other agents that cross other Institutes. She indicated that there may be a hearing on this issue sometime during the next several weeks or months.

## IV. CANCER SURVIVORSHIP—MS. ELLEN STOVALL

Dr. Ihde introduced Ms. Ellen Stovall, who is the Executive Director of the National Coalition for Cancer Survivorship (NCCS), a board member of the National Coalition for Cancer Research (NCCR), and a cancer survivor. He highlighted Ms. Stovall's involvement in patient advocacy. She has presented the NCCR's position on breast cancer research, prepared recommendations to the Department of Defense for use of the Army's appropriation for breast cancer research and presented them to the Institute of Medicine, and requested that the National Cancer Program work with the National Coalition for Cancer Survivorship to address concerns of cancer survivors. Ms. Stovall has also testified on the need for health insurance for Americans under the age of 65 years, discussed quality-of-life issues, represented her organization in tobacco cessation campaigns, and advocated for special counseling for young cancer survivors.

Ms. Stovall expressed her pleasure in presenting to the Board on behalf of cancer survivors, having been diagnosed with cancer twice in the last 21 years. She explained that she received state-of-the-art cancer treatment on both occasions, in 1971 and 1984. Ms. Stovall reminded the Board that the CAT scan was not an available diagnostic tool in 1971. She was treated then for Hodgkin's disease with cobalt radiation and total nodal irradiation and given a poor prognosis. MOPP, standard chemotherapy for Hodgkin's disease, was in clinical trial during Ms. Stovall's first diagnosis in 1971. Ms. Stovall noted the progress of the National Cancer Program by explaining that when her cancer recurred in 1984, she was treated with MOPP.

Ms. Stovall presented the history of the National Coalition for Cancer Survivorship. In 1986, three cancer survivors living in Albuquerque, New Mexico, assembled 21 representatives from a cross-section of cancer survivor organizations around the country to discuss the growing survivorship movement. At the end of a 3-day meeting, this group composed of survivors, support group leaders, physicians, and professionals had established the NCCS. The NCCS was chartered in 1986 as a nonprofit corporation dedicated to the development of a network of people and organizations concerned with cancer care. The original NCCS mission included a commitment to provide a voice for cancer survivors, undertake advocacy, and stimulate research in the area of survivorship.

Ms. Stovall noted that many of the major cancer research and treatment centers in the United States are members of the NCCS. To establish itself as a more visible leader in the survivorship movement, the NCCS moved its headquarters to the Washington, DC, metropolitan area in January of 1992.

Ms. Stovall asked the Board to examine the meaning of the term "survivor." Webster's dictionary, she said, defines a survivor as "one who remains or continues alive or in existence or use" and "one who continues to live or exist after the occurrence of." Ms. Stovall pointed

out that those who survive with the survivors are also survivors. She added that it is preferable to call someone newly diagnosed with cancer a survivor, rather than a "cancer victim" or "cancer patient."

Ms. Stovall related an anecdote involving Dr. Fitzhugh Mullan, one of the founders of the National Coalition for Cancer Survivorship. She then clarified that she herself was not a cofounder of the original NCCS but, rather, of a local chapter of the organization. In 1982, Dr. Mullan had written a book called *Vital Signs*, which chronicled his struggle with cancer in 1975, and was invited to speak at a Baltimore meeting called "The Cured Cancer Congress." After Dr. Mullan delivered his speech, Ms. Stovall recounted that a woman approached him and explained that she should not be at the meeting because she was not cured. This admission prompted Dr. Mullan to realize that he had never celebrated a cure day and told the woman that he also did not belong at the meeting because no one had ever told him that he was cured.

Ms. Stovall explained that although Dr. Mullan was given a poor prognosis, he serves today as Chair of NCCS and Director of the Bureau of Health Professions in the Public Health Service with the rank of Assistant Surgeon General. In 1985, Dr. Mullan defined the concept of cancer survivorship in an article entitled "Seasons of Survival: Reflections of a Physician With Cancer" in the *New England Journal of Medicine*. Ms. Stovall noted that she had brought copies of this article for distribution to Board members and then read an excerpt from the article.

Ms. Stovall described the three stages of cancer defined by Dr. Mullan—acute, extended, and permanent. The acute phase is the diagnostic and treatment phase, in which support systems are available and mortality is usually addressed for the first time. The extended stage is the recovery/reentry stage following treatment, which, Ms. Stovall explained, is a period of great uncertainty characterized by diminished physical strength, the emergence of psychosocial/inter-family issues, and the disappearance of support systems. The permanent stage, Ms. Stovall noted, is the "good news/bad news" stage; although it corresponds to cure, it often does not acknowledge the many changes that result from surviving cancer.

Ms. Stovall emphasized that "survivorship is a dynamic concept that avoids erecting unnecessary and inaccurate boundaries in the lives of people with cancer," adding that everyone lives in defiance of this disease and in an affirmation of life. She related the NCCS' belief that a person becomes a survivor at the time of diagnosis and remains one for the rest of his or her life, regardless of the timeframe.

Ms. Stovall described several publications through which the NCCS reaches out to individual survivors. The NCCS publishes a quarterly newsletter called *The Networker*, which sometimes devotes entire issues to specific topics of concern to members. It has also published booklets called *Teamwork* (NCCS is working with the M.D. Anderson Cancer Center to produce a Hispanic version of this publication) and *A Cancer Patient's Guide to Talking With Your Doctor*. In 1990, the NCCS wrote and edited *Charting the Journey*, an almanac of practical resources for cancer survivors. This guide is published by Consumer Reports Books and, in addition to other resources, forms the foundation of the NCCS library. Ms. Stovall added that the NCCS collaborated with the NCI to produce *Facing Forward* in 1990, which provides a concise overview of and practical ideas for life after cancer treatment.

Since its founding, the NCCS has brought the survivor community together twice each year. Each fall, survivors and their caregivers and supporters meet, network, and participate in panel discussions with national leaders in the cancer community. The Fred Hutchinson Cancer Research Center, Ms. Stovall pointed out, is helping to support this year's meeting, which will address such topics as health care reform, sexuality, and cancer-related pain. On the first Sunday of each June, the NCCS cosponsors National Cancer Survivors' Day, which is celebrated throughout the United States. Ms. Stovall explained that the NCCS also helps

individuals identify information and support services in their local communities or from an agency or organization that specializes in addressing their particular concerns.

Last year, the NCCS received a grant from the Robert Wood Johnson Foundation to study the feasibility of establishing a nationwide toll-free information support and referral service to respond to the insurance, employment, and legal problems faced by cancer survivors, known as Confronting Employment, Insurance, and Legal Barriers (CEILB). As part of the grant, 400 NCCS members were surveyed to assess the scope and prevalence of these problems. Based on a 55 percent response rate, 58 percent of respondents reported at least one insurance problem. Thirty-nine percent related that they had taken at least one action to resolve a problem with their insurance carrier. Almost one-third of respondents had experienced some form of job discrimination; 12 percent had taken specific action to resolve employment difficulties. Ninety percent of survey participants said they would call on this service for information. In a separate survey of NCCS member organizations and institutions, 84 percent responded that such a service would benefit their members and clients, and 76 percent responded that it would help their staffs. Plans are now underway to implement CEILB.

Ms. Stovall told the Board that the NCCS has worked with many consumer groups to address the many challenges that face cancer survivors. Barbara Hoffman, a cancer survivor and NCCS general counsel, worked with a consortium of disabled citizens and contributed to the language drafted for the Americans With Disabilities Act. With coordination by the Women's Defense Fund and the Older Women's League, the NCCS supports the Family and Medical Leave Act.

The NCCS, Ms. Stovall said, strives to more effectively reach survivors in underserved populations. It has established a task force to address the challenge of involving socially and medically disadvantaged groups in the survivorship movement.

Last summer, the NCCS hosted a meeting of many leading cancer and advocacy organizations, which resulted in a general consensus that collaboration among these organizations on issues of common interest would be more effective than working alone. A majority of these groups collectively supported passage of the Medicare Cancer Coverage Improvement Act. Ms. Stovall reported that this cooperative effort to effect a piece of legislation has stimulated the group to continue collaboration in the future. The NCCS public policy committee also addressed two regulatory issues during the last year—accelerated approval of promising anticancer drugs and the voluntary moratorium and subsequent restriction on the sale of silicone gel breast implants. Although the NCCS generally supported a streamlined approval process for new anticancer drugs, it questioned whether the proposed abbreviated withdrawal procedures protected those who might benefit from treatment with drugs approved under these new standards.

On the State and national levels, the NCCS testifies for the need for more cancer research dollars and passage of legislation requiring insurance policies to cover all physician-prescribed chemotherapy. Although it has become more involved in issues of national policy, Ms. Stovall stressed that the NCCS is fundamentally a grassroots organization with a community orientation. The NCCS committed itself to renewed organizational efforts on the local level at its last board meeting. The organization plans to increase community outreach, a vital aspect of the NCCS mission, in areas that are underserved with regard to cancer advocacy. This mission, Ms. Stovall explained, is embodied in the NCCS' efforts to communicate with and coordinate many different groups on the national level.

Ms. Stovall provided some details on the consensus statement on health care reform drafted by six leading cancer consumer groups last December. The statement calls for universal coverage for people with cancer, detailing specific types of coverage; provides a

lengthy description of the types of clinical trials that the group believes are appropriate and must be covered; and emphasizes its belief that psychosocial issues, patient rehabilitation, home care, and hospice care are essential components of treating the entire patient. These collaborating groups are now known as the Cancer Leadership Council, which has played an effective role in the deliberations of the Health Care Reform Task Force.

Ms. Stovall stressed the NCCS' ability to work with various members of the oncology community, noting that representatives of the NCCS serve on the boards of the National Coalition for Cancer Research, the Consortium for Citizens with Disabilities, and the Consumer Federation of America. The NCCS has also participated in a coalition on smoking and health, the National Health Care Campaign, and meetings and conferences with the Oncology Nursing Society, the Association of Community Cancer Centers, the American Cancer Society, the American Society of Clinical Oncology, and the National Cancer Institute.

Ms. Stovall told the Board that the NCCS believes that the survivorship movement must employ all available resources and treat the whole person, that there is a model of constructive dialogue and cooperation that can assist medical professionals and policymakers while also benefiting survivors, and that the NCCS plays a vital role in solving the cancer problem in the United States as a national cancer consumers' organization. She explained that the NCCS has created a systematic way of transmitting the wisdom of cancer survivors and caregivers to those who are newly diagnosed. This shared information empowers survivors and involves them in making important decisions that will improve their quality of life.

On behalf of the NCCS, Ms. Stovall saluted all those working with the National Cancer Program and for the collaborative effort in cancer research and treatment during the past two decades. Despite the successes, Ms. Stovall identified the need for a "coordinated national enterprise" in the area of cancer survivorship. She congratulated the NCI for issuing an RFA to study adult survivors of cancer last February. Ms. Stovall expressed the NCCS' pleasure in seeing the National Cancer Program address survivorship as a phenomenon in and of itself, rather than as a byproduct of basic research in cancer treatment. She conveyed that it is of little significance for a patient to be medically successful if he or she is damaged psychosocially. She stressed the need for an increase in awareness and education regarding community acceptance of people with cancer, as well as the need to eliminate barriers to employment and gain universal access to insurance.

Ms. Stovall expressed the readiness of the NCCS to work with the NCI to improve the quality of life for people with all cancers. She mentioned the need to advocate more vigorously for funding those prevention and control initiatives whose funding decreased in the last decade. Ms. Stovall emphasized that this is a critical time to reevaluate and enforce the mission of the National Cancer Act. She added that it is crucial for all sectors of the cancer community to lay aside their different agendas and work together in a systematic way.

**Questions and Answers**

Dr. Lawrence thanked Ms. Stovall for her presentation and for her significant contributions to the meetings of the Subcommittee on Interactions With Voluntary Organizations.

Dr. Calabresi expressed his thanks to Ms. Stovall as well, and commented that since more than half of all cancer patients are being cured at present, this topic will be increasingly important in the future.

## V. SOCIAL FORCES AND TOBACCO CONTROL—DR. DAVID BURNS

Dr. Ihde introduced Dr. David Burns, Coordinator of the Developmental Pulmonary Research Clinical Laboratory and Medical Director of Respiratory Therapy at the University of California at San Diego. Dr. Burns has been instrumental in advancing the understanding of the relationship between American society and the tobacco plant. He has conducted research on environmental tobacco smoke and lung cancer. Dr. Ihde quoted a statement by Dr. Burns in his September 16, 1992, editorial in the *Journal of the National Cancer Institute*: "It would be a public health tragedy if 20 years in the future we are obliged to total the cost in human lives and suffering of our failure to act on scientific certainty." Dr. Ihde commented that these words speak for many who recognize the need to focus on future societal opportunities once strong scientific evidence has been established.

Dr. Burns began his presentation by stating that health care providers who trained in the latter half of the 20th century assume that lung cancer is a large part of the cancer problem. He related a story told by Dr. Alton Oxner, founder of the Oxner Clinic and one of the leaders of cardiothoracic surgery in the United States. While in medical school in the 1920s, Dr. Oxner and the entire third-year class were called out of the dormitory at night to witness an autopsy of a patient with lung cancer, because of the fear that the students might never see another case of this rare disease in their professional lives. Dr. Oxner concluded that there was an epidemic of lung cancer after seeing four cases of lung cancer in his first year of practice as a thoracic surgeon. Dr. Burns noted that thoracic surgeons currently see a far greater number of cases than four per year.

Dr. Burns pointed out that tobacco is the major, but not only, cause of lung cancer, and that lung cancer is currently the leading cause of cancer death in both men and women. He presented a plot graph illustrating tobacco use in the United States from 1890 to the present. Dr. Burns explained that tobacco has a long history in the United States, beginning with its status as a primary cash crop for the original 13 colonies. Since that time, he said, several technological advances have contributed to the regular use of tobacco. In 1886, a machine was invented to manufacture cigarettes. Also, the process of producing tobacco was changed to make it milder and change its pH. With this process, nicotine could not be absorbed through the oral mucosa and had to be inhaled into the lungs to be effective. Another critical advance occurred in 1900—the invention of safety matches. The most important element conducive to cigarette smoking was the introduction of mass marketing techniques in 1910. This represented the first demonstration of the ability to create a market for a product when there was no preceding demand or need for that product.

Dr. Burns presented a slide showing per capita consumption of cigarettes. Per capita consumption was 54 in 1900, peaking at 4,300 in 1963. The slide also depicted several social forces that influenced tobacco consumption. For example, an increase occurred during World War I (1914 to 1919), a major decrease took place during the Great Depression in 1929, and another increase occurred during World War II (1940 to 1945). The tobacco industry employed several tactics to bolster use, most notably by giving away tobacco products to men in the military and training nurses to show women how to smoke cigarettes so that they would not feel awkward or clumsy.

A major downturn in tobacco consumption occurred in 1954, at the time of the first major prospective studies. The tobacco industry, however, was able to confuse the public about scientific findings, and per capita consumption increased again. Release of the Surgeon General's Report on Smoking and Health and the resultant media attention caused another decrease in consumption in 1963 and 1964. Another abatement occurred from 1967 to 1970, when the Fairness Doctrine required antismoking spots on television; also, cigarette advertising was banned from the airwaves in 1970. Consumption again increased when the

tobacco industry appealed to Congress to order an end to the antismoking spots and won. The advent of the nonsmokers' rights movement also affected the consumption of tobacco on the level of social unacceptance.

Dr. Burns next presented a slide that depicted the prevalence of smoking in a birth cohort of individuals born during the period of 1910 to 1914. Examining prevalence among White males in this cohort, Dr. Burns pointed out, it becomes clear that by the time an individual reaches adulthood, he either is a smoker or will not become one. He stated that this has been true for White males for a long time, but it is not true for all groups in the U.S. population. This illustrates, he emphasized, that the risk or vulnerability period for tobacco use is during adolescence, when the purchase of cigarettes is illegal. In regard to White male birth cohorts from 1900 to 1964, Dr. Burns indicated that consumption peaked very early across the board. There has, however, been a steadily lower prevalence of smoking over time. Cohorts of White women were found to have begun smoking much later than men (in the 1930s and 1940s) and did not peak as high in prevalence, but also had a less significant downturn than men. Early cohorts of Black men, those born before 1910, had a lower prevalence of smoking, while later Black cohorts show a higher prevalence of consumption and lower significant downturns than Whites. Cohorts of Black females showed little increase in the early years and their trends were similar to those of White females.

The risk of tobacco use was recognized in the 1950s and it was believed that if the U.S. Government, the American Cancer Society, and other groups disseminated this information about risk, then people would change their behavior. A short while later, it became clear that smoking behavior would not be easy to change, and smoking cessation strategies began to focus on the individual. Much time, money, and energy were expended to define the perfect smoking cessation program, but it was soon realized that few people would actually participate in these programs. The success of the nonsmokers' rights movement in motivating people to quit smoking changed the emphasis of tobacco control to focus on social and environmental factors, such as the social acceptability of tobacco use.

Dr. Burns explained that the Community Intervention Trial for Smoking Cessation (COMMIT) project funded by the NCI focuses on the entire community. It maintains a focus on the individual, but uses interventions within the community to provide an inescapable message to quit smoking, in addition to resources and assistance to enable the individual to do so. The NCI has now progressed past the concepts defined in the COMMIT Project to the American Stop Smoking Intervention Study for Cancer Prevention (ASSIST), a project directed at altering the environment within which smoking initiation and cessation takes place as a means of facilitating a smoke-free society.

Dr. Burns explained that it is useful to conceptualize tobacco control in terms of the cycle of smoking initiation and the cycle of a dependent user. A nonsmoker will consider smoking, experiment, regularly smoke, and eventually become a dependent user. The dependent user will think about quitting, try to quit, experience some short-term success, fail, and either return to smoking or successfully quit.

Dr. Burns discussed two forces that steer adolescents toward dependent smoking—availability of cigarettes and advertising. According to a survey conducted in California, adolescent teenagers, particularly 16- and 17-year-olds, could easily purchase cigarettes. Other surveys revealed that 12-year-olds also have little difficulty buying cigarettes over the counter or from a machine. Dr. Burns pointed out the accessibility of tobacco products in American society and stressed that this availability presents a major opportunity for intervention, since those who do not begin cigarette smoking during adolescence are not likely to do so at all. Although most 10-year-olds would report that smoking is "bad for you," 25 to 35 percent of them eventually initiate smoking.

Teenagers in the California survey perceived smoking to provide relief from boredom and stress, promote excitement and relaxation, act as a social assist, and control weight gain. Dr. Burns presented slides of cigarette advertisements depicting or suggesting excitement, individualism, independence, confidence, autonomy, glamour, thinness, and sexual attractiveness. He stated that adolescents have continual, strong feelings of inadequacy, and suggested that the images in the advertisements presented diminish one's sense of inadequacy. Dr. Burns reminded the Board that the first experience with a cigarette is not usually biologically pleasing, but because the cigarette is useful for the aforementioned reasons, people overcome the unpleasantry.

Dr. Burns next discussed the appeal of cigarette advertisements to children. According to a survey in California, Marlboro was identified as the most heavily advertised brand of cigarettes; it is also the most heavily smoked cigarette among adolescents. Marlboro's nomination increased as the age at which adolescents initiate smoking most increased. The nomination of Camel, however, with its "Camel Joe" cartoon character advertising campaign, increased steadily as age diminished. Recognition of Camel Joe and Mickey Mouse were approximately equal among 5-year-olds, while most adults cannot recognize or name the cigarette character.

Dr. Burns emphasized that preventive measures, such as limiting access to tobacco, raising the cost of cigarettes, changing the image of tobacco use, restricting areas where smoking is allowed, and educating children within schools, cannot exist without the cooperation of the media. Independent of pharmacology, tobacco persists among adults because of its psychological and sociological utility—it is a useful behavior. The cigarette develops mood-altering properties with continued use and can eradicate negative sensations such as anger, frustration, or boredom. Final dependence occurs when the cigarette wears off, the nicotine level falls, and resultant disagreeable effects are experienced.

Dr. Burns discussed the challenge of overcoming the cycle of smoking. He reported that 30 percent of smoking Americans have made a serious attempt to quit smoking in the last 12 months. There has been success in motivation; what is now necessary is to enable people's success. Dr. Burns suggested that raising the tax on cigarettes is a possible solution. He added that California has increased its tobacco tax by $.25. Cigarettes in Canada now cost more than $5.00; this increase has had a substantial impact on cigarette consumption, especially among adolescents who have the least amount of disposable income. Restriction of smoking areas, especially in the workplace, is another viable solution.

Dr. Burns presented data, divided by racial groups, on cigarette smokers in California who had seen a physician in the past 12-month period. Approximately 36 percent of those smokers had never been told by a physician that they should stop smoking. Dr. Burns stressed that long-term success in smoking cessation is defined by social and environmental forces, but physicians can effectively motivate people to attempt to quit smoking.

Examining data on the effect of the major media campaign that occurred with the Fairness Doctrine from 1967 to 1970, Dr. Burns noted a substantial downturn in cessation following the removal of the antismoking advertisements. Although this indicated that the media role was not very successful, other data from California suggested that the media, in conjunction with the activities of the American Cancer Society and other agencies, could be effective in tobacco control.

Dr. Burns outlined what he referred to as the four pillars of tobacco control: 1) advocate for nonsmokers' rights; 2) change the social acceptability of tobacco use; 3) decrease the personal, psychological, and social utility of tobacco; and 4) limit the opportunity to learn to use tobacco or relapse from tobacco cessation. Data show that the relapse rate is twice as high in work environments that allow cigarette smoking. Dr. Burns suggested that a $2.00 per

pack increase in the price of cigarettes would probably decrease the prevalence of smoking in the United States by approximately 20 percent. He added that Canada has done an excellent job of limiting minors' access to cigarettes.

Dr. Burns concluded by expressing his hope that the tobacco industry will advertise responsibly. He suggested that the industry decide how to responsibly advertise a product that kills 40 percent of its users, many of whom are adolescents. Since independent, antismoking interventions have little effect, he advised that tobacco control must focus on the interdependence and synergy of such activities. Media campaigns must convince people to join smoking cessation programs, and these programs must be available. Science must substantiate nonsmokers' rights legislation. There must also be a focus on the environment in which smoking initiation and cessation occur.

Dr. Burns concluded that the most enlightening point he has discovered in examining the challenge of tobacco control is that one-third of smokers have made a serious attempt to quit smoking. It is imperative that the environment be structured so that it is possible for people who attempt to quit to realize their goal.

**Questions and Answers**

Ms. Zora Brown asked Dr. Burns which advertising campaigns are most effective in convincing people to quit smoking. She commented that she had seen one very effective advertisement in the middle of the night, but these types of ads do not run during prime time television and often run on independent television. Ms. Brown added that she believes advertisements to be the most powerful tool for cessation. Dr. Burns agreed with Ms. Brown, but added that no advertising campaign would be successful by itself. Media is effective, he stated, when used selectively, to set an agenda, and to reach specific target groups with specific issues. Dr. Burns explained that the tobacco industry has taught us that it is necessary to target advertising in order to be effective. Tobacco ads run primarily on MTV and on Spanish-language stations, targeting new and current smokers. Targeted advertising, combined with the community support of COMMIT and the policy effort of ASSIST, can have an enormous impact on long-term successful cessation.

Dr. Bettinghaus commented that advertising should be divided into two kinds of effort: advertising directed at cessation and advertising directed at prevention. He added that the States of Minnesota, California, and Michigan have produced a series of advertisements directed at prevention among children. Dr. Bettinghaus advised that public service announcements (PSAs) are not effective enough alone. Also, PSAs need to run during popular children's programs. Dr. Burns added that there is probably no advertisement that would be as effective as removing the Marlboro and Camel advertisements from the marketplace.

Dr. Lawrence asked how successful a significant national tax would be. Dr. Burns turned this question over to Mr. Alan Davis, Chairman of the Coalition on Smoking and Health. Mr. Davis stated that there is tremendous support for this initiative in Congress. Smuggling has become a problem in Canada since the cigarette tax increase in that country. Mr. Davis explained that the U.S. media is highlighting this potential problem, which had been a key strategy of the tobacco industry. He told the Board that he was invited by the Canadian Cancer Society to attend a press conference that preempted an announcement by the tobacco industry about the concern over smuggling and the need to reduce excise taxes. Mr. Davis proposed that if the United States raised its cigarette prices close to the Canadian price, there would be no incentive for smuggling. He stated that the next issue will concern Mexico, but he feels that this is a different issue because of the more heavily patrolled border between Mexico and the United States.

Mr. Davis explained that the tobacco industry is falsely suggesting that the tax increase would cause a loss of 760,000 jobs in the United States. The tobacco industry calculated that 2 percent of all jobs in Maine relate directly to tobacco; Mr. Davis pointed out that there is no tobacco industry in Maine. This study was conducted, he continued, by Price Waterhouse, a firm known to support incentives of the tobacco industry in the past. Mr. Davis reported that there is an attempt to obtain another prominent national accounting firm to review the data.

Dr. Yodaiken commented that a ban on smoking in the workplace would have a significant impact, but unless it is proven that passive smoke is a grave danger to workers, a complete ban would violate an individual's rights. Dr. Yodaiken told the Board that the Secretary of Labor has urged the Occupational Safety and Health Administration (OSHA) to develop a standard for passive smoking and some reasons why smoking should be curtailed, reduced, or completely restricted in the workplace.

Dr. Yodaiken suggested that the Board address a letter to the Secretary of Labor supporting the fact that passive smoking is a significant factor in carcinogenesis. He proposed adding that members of the Board would be willing to confirm this finding with scientific data and provide expert witnesses if a hearing were held. Dr. Calabresi requested that Dr. Yodaiken present this suggestion in the form of a motion. Dr. Bettinghaus offered to assist Dr. Yodaiken in writing the motion.

Dr. Sigal cautioned the Board about the Ashtray Standards, which essentially say that if there is proper ventilation in buildings or the marketplace, then smoking or passive smoking is no longer a problem. Dr. Burns commented that the Ashtray Standards are based on comfort rather than carcinogenesis. He added that there cannot be enough ventilation to reduce the risk of carcinogenesis. Dr. Sigal insisted that there be a clause about the Ashtray Standards in the motion because consultants on this issue contend that they have adjusted for smoking.

Dr. Calabresi commented that most hospitals have banned smoking entirely. He asked Dr. Yodaiken and Dr. Bettinghaus to write up this motion and present it to the Board for a vote during the second day of the meeting.

Dr. Correa mentioned a study conducted in Louisiana in which respondents who came to the hospital were asked if they had health insurance. Respondents reported that they were paying $1,300 per year for insurance, and yet they were spending $2,400 a year for alcohol and tobacco—mostly tobacco. Dr. Correa suggested that the patients should pay for insurance in increments if they choose to use these products.

Dr. Chan complimented Dr. Burns for his informative and powerful presentation and suggested that smoking cessation education should be integrated into grade school education. Dr. Burns agreed and added that antismoking advertisements directed at children in the late 1960s were effective, and that parents reported that their children influenced them to quit smoking.

## VI. MINIMAL ACCESS SURGERY/VIDEOTAPE—DR. EDWARD L. TRIMBLE

Dr. Chabner introduced Dr. Edward Trimble, a surgical gynecologic oncologist, who joined the NCI staff in 1992. Dr. Chabner explained that it is Dr. Trimble's responsibility to respond to opportunities to include research in surgical oncology in the extramural program, and that Dr. Trimble's presentation would focus on advances in laparoscopic surgery.

Dr. Trimble began by explaining that minimal access surgery, otherwise known as minimally invasive surgery or endoscopic microsurgery, is an approach that permits exposure of the operative field with a decrease in the surgical trauma associated with gaining that operative field. Minimal access surgery has been used with various approaches in the past, such as diagnosis and treatment of the oro- and nasopharynx, prostate, and bladder. Dr. Trimble pointed out that gastroenterologists routinely conduct esophagoscopies, gastroscopies, and duodenoscopies. He explained that it is now possible to use flexible colonoscopy, rather than rigid sigmoidoscopy, to remove polyps for biopsy. Gynecologists use minimal access techniques to evaluate the endometrial cavity in cases of infertility, treat excessive menstrual bleeding, and resect submucous fibroids. Dr. Trimble added that orthopedic surgeons routinely use arthroscopy on knee and ankle joints.

Recently, Dr. Trimble related, the use of minimal access surgery has been extended to include evaluation of the lungs, mediastinum, and both the intra-abdominal and retroperitoneal organs, such as the stomach, pancreas, liver, gall bladder, colon, kidney, ovary, endometrium, and cervix. With the aid of new imaging developments in terms of stereotactic biopsies, minimal access surgery is being used for conditions of the cerebrum and cerebellum.

Dr. Trimble described the advantages of minimal access surgery, including faster patient recovery, decreased time in the hospital, lower hospital expenses, quicker return to normal activity, and decreased incidence of wound complications. Based on prospective evaluations of laparoscopic cholecystectomy, patients who undergo a laparoscopic procedure are advanced to a regular diet and oral pain medications about 24 hours sooner than those who have a traditional open procedure. Dr. Trimble added that hospitalization is significantly decreased for patients who have a laparoscopic procedure, while morbidity for the two procedures is similar. In terms of cost-effectiveness, Dr. Trimble indicated that the laparoscopic procedure involves fewer days in the hospital. Operating room and recovery room charges are slightly higher for the laparoscopic procedure because it is a longer procedure and requires additional instrumentation. Overall hospital charges, however, are lower for patients who undergo the laparoscopic procedure, and these patients return to work sooner than patients who undergo traditional surgery.

Dr. Trimble then presented a videotape of a laparoscopic colon resection, courtesy of Dr. David Ota at the M.D. Anderson Cancer Center. Dr. Trimble remarked that, basically, the same techniques are used in the abdomen through the laparoscope as in open surgery. He explained that the patient in the video had presented with anemia and a tumor was found involving the right colon.

Dr. Trimble described the procedure being seen by the Board. The surgeon retracted the right colon from the right pelvic side wall and made an approach through the mesentery of the colon, excising the peritoneum over the mesentery. He used blunt and sharp dissection to isolate the vessel and ligate the major blood supply to the colon—the ileocolic artery and the right colic artery. Dr. Trimble noted that the last step was very similar to the technique used in open procedures. He explained that surgeons have found that the procedure can be completed more expeditiously if they can adopt similar techniques and use existing technical skills.

The surgeon then applied clips to one of the arteries. Dr. Trimble explained that there are generally three clips on the side that stays in the patient—two clips on the side coming out and a vessel loop or ligature that has been placed around the artery being clipped. At this point in a laparoscopic colectomy, Dr. Trimble explained, a mini-laparotomy is made and the segment of the bowel to be resected is removed from the abdominal cavity. The remnants of the mesentery are clamped and cut, and the remainder of the anastomosis is performed outside the abdominal cavity.

The isolated colon was clamped, cut, or transected, and stapled with a gastrointestinal stapling device. The reanastomosis was then performed, and Dr. Trimble pointed out that the Board was seeing a side-to-side functional end-to-end anastomosis using the gastrointestinal stapling device. The defect in the colon was closed using a stapling device, and the bowel was returned into the abdomen.

Dr. Trimble stated that minimal access surgery has been used in many cancers to diagnose malignancy, stage disease, assess operability, and perform definitive cancer treatment, but no prospective comparisons with standard surgery have been conducted in terms of cost, efficacy, and quality of life. He expressed concern that arthroscopic surgery may become the standard of care without conducting any comparisons.

The first laparoscopic cholecystectomy, Dr. Trimble explained, was performed in 1987 and not reported until 1989. In 1991, 2 years after the first case was reported, there were 17,000 cases of laparoscopic cholecystectomy. Dr. Trimble pointed out that this is probably a low estimate, due to inaccuracies in coding. He explained that there is concern that it will be difficult to recruit patients to trials requiring standard surgery and that third-party payers may not pay for standard surgery if minimal access surgery is found to be less expensive.

Dr. Trimble informed the Board that the Division of Cancer Treatment Board of Scientific Counselors will receive a proposal to conduct a 3-year evaluation of minimal access surgery in cancer treatment, with a first-year award of $750,000. Funding of four to six Phase III trials of laparoscopic versus standard surgery would be proposed. Possible examples are laparoscopic colectomy versus a standard open procedure or a laparoscopically assisted vaginal hysterectomy and lymph node sampling versus an open hysterectomy for patients with endometrial cancer. Cooperative agreement would be the mechanism, and multi-institutional consortia applying for the study must have the ability to perform statistical and surgical data management. Selection criteria would include the speed with which the trial could be completed, experience of the surgeons, and cost and quality-of-life evaluations.

Dr. Trimble explained that the cooperative agreement mechanism will allow input from the NCI and other Public Health Service agencies. The NCI can encourage collaboration between various interested groups and review the methodology and feasibility of the proposed studies.

Dr. Trimble concluded his presentation with a quote by Sir William Osler, who advised that "diseases that harm call for therapies that harm less." Dr. Trimble stated that it is worthwhile to try to preserve the efficacy of cancer treatments, while decreasing the cost and disability associated with those treatments.

**Questions and Answers**

Dr. Calabresi asked about the use of minimal access surgery for metastasis removal from the liver or lung. Dr. Trimble answered that there are some Phase II reports of resection of isolated lung metastases using the arthroscopic approach and isolated liver metastases using an endoscopic approach, but, currently, this success is limited to Phase II trials.

Dr. Wilson asked if the cooperative agreements would involve only laparoscopic colectomy. Dr. Trimble replied that the proposals are open; gynecologic oncologists and pediatric surgical oncologists are interested in similar trials, but procedures involving the colon are most ready for clinical trial.

Dr. Wells commented that, at times, a technology revolutionizes an approach to the point that it is impossible to conduct a randomized controlled trial. He pointed out that if the

laparoscopic procedure improves the diagnosis of metastatic disease, it would be an enormous advance. Resection of these lesions, he added, is important, but not as important as diagnosis.

Dr. Ihde related a story of a patient with metastatic carcinomas who had had a laparoscopic cholecystectomy because of right upper quadrant pain. The major finding missed in this case was carcinoma in the upper abdomen. This incident was similar to three other cases at the same hospital in 1 year. Dr. Ihde asked whether this error is a common problem. Dr. Wells responded that it is easier to see using laparoscopic technology than it is using open surgery to perform a cholecystectomy, though the surgeon cannot place a hand over the dome of the liver to find something using this procedure. Although there is always the possibility of missed cases, Dr. Wells concluded, this procedure as a screening technique for oncology will be more powerful than most current imaging techniques.

Dr. Day asked if there is less blood loss using minimal access surgery. Dr. Trimble answered that there seems to be less blood loss and less exposure to blood by the surgeons. Dr. Day inquired if there is also less need for transfusions. Dr. Trimble stated that there seems to be less of a need, but it varies according to the extent and type of procedure.

Dr. Calabresi asked whether any unique complications are associated with this procedure that do not occur with standard surgery. Dr. Trimble explained that this is merely a different approach and access, so the complications seem to be the same.

Dr. Lawrence commented that his colleagues who use laparoscopic techniques for colon resection have not experienced such striking improvements in length of hospitalization and time lost from work. He pointed out that these cases are not part of randomized trials and expressed concern that this technique is not as advantageous as cholecystectomy. He asked if the proposed cooperative agreement would be randomized and if there are any anticipated problems with informed consent procedures randomizing patients between laparoscopic and open colon resection. Dr. Trimble answered that randomized trials are preferred. He explained that the surgeons who have discussed the possibility of this study have related that they are familiar with both techniques and feel that they can communicate this information to their patients and recruit them to the trial.

After announcing the locations and times of the subcommittee meetings, Dr. Calabresi adjourned the morning meeting.

## VII. CLOSED MEETING—SPECIAL ACTIONS SUBCOMMITTEE

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 1,721 applications were received, requesting support in the amount of $299,162,509. Of those, 1,266 were recommended as being eligible for funding at a total cost of $200,765,546.

## VIII. EORTC COOPERATION IN DRUG DEVELOPMENT—DR. H. M. PINEDO

Dr. Chabner provided a brief overview of cancer research in Western Europe. Dr. Henri Tagnon, who trained in the United States at Boston City Hospital and then returned to Europe, was a key figure in the development of medical oncology and clinical cancer research in Europe. With Dr. Tagnon's support through the European Organization for Research and Treatment of Cancer (EORTC), other talented individuals were responsible for organizing a

clinical trial group that presently interacts very intimately with the NCI in terms of drug development. Dr. Chabner then introduced Dr. Herbert Pinedo, noting that he has been one of the most important people involved in the development of clinical cancer research in Europe. Dr. Pinedo worked at the NCI in the mid-1970s as a fellow in the Medicine Branch before returning to Holland. Dr. Pinedo is currently Clinical Research Director of the Netherlands Cancer Institute in Amsterdam and a professor at the Free University Hospital in Amsterdam. Dr. Pinedo, among others, was responsible for establishing the New Drug Development Office (NDDO) at the EORTC, which, every 2 to 3 years, holds a very important meeting in Amsterdam at which NCI staff and the European cancer research community share information and ideas related to new drugs. Dr. Chabner explained that Dr. Pinedo's presentation would focus on the structure and current research activities of the EORTC and clinical cancer drug trials in Europe.

Dr. Pinedo began his presentation by acknowledging the NCI's contributions to his professional success, including his participation in the European New Drug Development Program. Dr. Pinedo stated that the collaboration between the NCI and the EORTC started approximately 6 years ago, when an agreement was signed with the Division of Cancer Treatment in 1986. This collaboration in new drug development has resulted in major benefits for both organizations. Through this agreement, Europe has contributed more than 45,000 new agents to the NCI screens. The current rate of input remains at about 2,000 compounds per year, and more than 50 of these compounds have entered clinical trials in Europe. Dr. Pinedo explained that most of the expenditures for developing these compounds have been covered by three entities that work very closely: the EORTC; the NDDO in Amsterdam; and the Cancer Research Campaign (CRC) in the United Kingdom.

Dr. Pinedo then described the activities currently performed by the EORTC. He indicated that the EORTC was founded by Dr. Henri Tagnon in 1962. In the early years after the EORTC's foundation, the main cancer centers within the organization collaborated mostly on Phase III clinical trials and some Phase II trials; Phase I trials surged only during the past 10 years. Dr. Pinedo stated that during the early years of the EORTC, clinical research groups primarily collaborated with the organization; however, currently, a substantial number of basic research groups are also collaborating.

Dr. Pinedo discussed the main objectives of the EORTC and its structure. He explained that the EORTC is responsible for conducting, developing, coordinating, and stimulating cancer research in Europe. The EORTC is composed of a President (currently, Dr. Emmanuel van der Schueren), a Board, an Executive Committee to the Board, a General Assembly, and four Branches, of which the Research and the Treatment Branches are the largest. The New Drug Development Program is within the Research Branch, which is chaired by Dr. Tom Connors. The NDDO, in Amsterdam, is responsible for coordinating the work on new drug development within the EORTC.

The EORTC collaborates very closely with the CRC in the United Kingdom. Several groups within the EORTC are involved in this collaboration, including the New Drug Development Coordinating Committee, which was chaired until very recently by Dr. Paul Workman. The chairman of this Committee is elected by the General Assembly of the EORTC. Within this Committee there are preclinical cooperative groups, a clinical trials group, and data center personnel, among others.

The New Drug Development Coordinating Committee consolidates the introduction of new drugs into the clinic. The Committee meets every 3 to 4 months and Dr. Omar Yoder, Director of the NCI-Liaison Office in Brussels and a member of the Committee, supervises the scientific products of the NDDO. Dr. Yoder also organizes the EORTC's annual Early Drug Development Meeting and the biennial NCI/EORTC New Drug Meeting held in Amsterdam.

Dr. Pinedo mentioned that he founded the NDDO in 1984. The NDDO has 20 employees and three locations in Amsterdam—the main office is at Free University and the other offices are at the Netherlands Cancer Institute and the Comprehensive Cancer Center of Amsterdam. The present director of the NDDO is Dr. Rinus Lobbezoo.

Dr. Pinedo then described the responsibilities of the NDDO, including its involvement in the acquisition and development of new compounds, the initiation of new drug development projects, and coordination of preclinical drug design and early clinical development activities, including Phase II studies. The NDDO has also developed standard operating procedures for different aspects of new drug development. The NDDO strives to ensure the European framework, evaluation, and development of new compounds to reduce the time lag between the synthesis and clinical evaluation of compounds. For example, Dr. Pinedo explained, the development of taxotere was extremely fast in Europe, taking only 6 months to complete the Phase II studies. Dr. Pinedo added that the NDDO developed the guidelines for conducting the clinical studies and that the institutes involved in these studies are adhering strictly to those guidelines. Dr. Pinedo explained that it is very important to achieve acceptance of research results by regulatory authorities within the United States, such as the Food and Drug Administration (FDA), and within the European Community. He also stressed the importance of stimulating an exchange of ideas and concepts in cancer research and treatment.

Dr. Pinedo noted that the major partner of the EORTC NDDO is the NCI, and that without the NCI, the EORTC would not have achieved its current accomplishments. He also acknowledged other partners in the drug development program, including the CRC, the Dutch Cancer Society, an organization in Germany that is currently under development, the pharmaceutical industry, and several other research institutes.

The NDDO is involved in screening, rational design, and synthesis of analogs of the drug discovery program (e.g., a compound called temozolomide, which is the analog of mitazolomide). Dr. Pinedo explained that the NDDO is involved in formulation and has a formulation office in Amsterdam and a pharmacist, Dr. Beijnen, who is in charge of troubleshooting difficult compounds. Dr. Pinedo stated that the EORTC NDDO has production facilities as well, and that several companies and centers, including BIBRA in the United Kingdom, work with the EORTC performing toxicology and pharmacokinetic studies. The NDDO has also been in charge of the data management of the Early Clinical Trials Group (ECTG) and the Phase I and Phase II studies.

Dr. Pinedo stressed the NDDO's particular interest in xenografts. The NDDO coordinates the xenograft group of the EORTC, which includes six centers that perform studies of new drugs on their own xenografts (e.g., melanoma, ovarian, colon) and then come together to discuss their results.

The EORTC has never been formally involved with NCI's Phase I agents. Dr. Pinedo, however, expressed the EORTC's and CRC's interest in becoming NCI's partners with respect to Phase I studies. Dr. Pinedo then mentioned a new compound, fostriecin, which is a topoisomerase-2 inhibitor. This compound, Dr. Pinedo said, might be the first drug on which the EORTC will perform Phase I studies. The studies will be performed in Holland by a group interested in topoisomerase-2 inhibitors; the group has already submitted a letter of intent to the NCI and received NCI approval for the protocol. The NCI performed a site visit, and no problems were reported; thus, the studies should begin promptly.

Concerning the Phase II activities of the EORTC, Dr. Pinedo discussed the compound taxotere, the counterpart of taxol, which has been developed in France by Rhône-Poulenc Rorer. The Phase II studies were performed by several groups of the EORTC. Taxotere has been under study during the past year by the ECTG at 30 centers in 11 countries, including Israel. All of these studies have been monitored by the NDDO. Dr. Pinedo explained that the

NDDO staffs monitors who visit and review data files in the different centers participating in the study. He also noted that the drug companies are very impressed with the quality of the data that is being produced by the ECTG.

Dr. Pinedo remarked that the studies initiated last year with taxotere that were performed in breast, colon, gastric, neck, kidney, melanoma, nonsmall cell, small cell, and ovarian cancer reported very impressive activities. The toxicity profile of taxotere, which is slightly different from that of taxol, is manifested by edema of the legs. Impressively, taxotere's response rate in breast cancer has reached 70 percent; the response rate in ovarian cancer is approximately 30 percent. Dr. Pinedo expressed the EORTC's excitement with these results, as well as its hope that the NCI will be able to use its Phase II data, together with the data obtained from Phase II studies currently being performed in the United States, to continue the development of taxotere in this country.

Dr. Pinedo then presented a slide showing the accrual rate of the taxotere studies. He mentioned that approximately 400 patients were studied in the past year in the ECTG, which represented a huge task for NDDO in processing the abundance of data while maintaining its excellent quality.

Dr. Pinedo referred again to the close collaboration between the EORTC and NCI during the past two decades, and stressed that although both organizations have benefited from the collaboration, the EORTC has gained more. The EORTC has developed its own structure that provides high-quality data and complies with the NCI and FDA criteria.

Dr. Pinedo reiterated that the total contribution, to date, from the EORTC has been 45,000 compounds in the NCI screening process, with a current input of 2,000 compounds a year, and 50 compounds already in clinical trials. Europe has assumed all of the expenses. Dr. Pinedo showed a slide with some examples of drugs that have Investigational New Drug Application (INDA) approval by the FDA based on European data. One compound, 2'deoxy-5-azacytidine, is being used to treat acute leukemia. Phenylquinoline is an antimetabolite for which Phase I studies were conducted in Europe and, thereafter, in the United States. Taxotere is another compound for which Phase I studies were performed in both Europe and the United States. Other examples of drugs developed with major European contributions include: flavone acetic acid, which was initiated in the United Kingdom and appeared to have no activity in the Phase II studies; gallium nitrate; hexamethylmelamine; levamisole, which originated in Brussels, Belgium; and pentostatin, which was also initiated in the United Kingdom.

Dr. Pinedo then showed a slide containing examples of compounds planned for IND filing based on European data: aphidicolin glycinate; bryostatin, for which Phase I studies were conducted in Manchester, United Kingdom; clomesone; rhizoxin; and temozolomide, which has been studied in London. Dr. Pinedo said that temozolomide has been active in brain cancer and that the responses are very impressive. He stressed that this compound is very promising and that there is a need for the NCI to begin collaborative studies in the United States to develop this drug as rapidly as possible.

Dr. Pinedo gave some examples of compounds currently under European development that are of joint interest to the EORTC and the NCI, including topotecan and irinotecan (CPT-11), which is a topo-1 inhibitor from Japan that is being studied in Europe by Rhône-Poulenc Rorer. CPT-11 has provided very impressive responses in colon cancer in a study conducted in Paris. Another example is EO9, which was screened 2 years ago at the NCI and showed activity in a group of solid tumors. The EORTC continued development of the drug, and Phase I studies are currently being completed in preparation for initiation of Phase II studies. Carzelesin, Dr. Pinedo stated, has two analogs, one of which will be studied in Europe and the other in the United States. Another compound, ICI-1694, is a thymidylase synthetase inhibitor

that produces extensive toxicity; Phase I studies on this drug have concluded and it is currently in Phase II studies in Europe. Finally, Dr. Pinedo listed some compounds with proven activity that are currently being used by oncologists worldwide, including: cyclophosphamides; diphosphamides; adriamycin; VP-16; carboplatin; deoxycoformycin; taxotere; temozolomide; fostemustine; and levamisole.

Dr. Pinedo emphasized once again that the achievements of the EORTC would not have been possible without NCI's collaboration. He said that the CRC, NDDO, and the NCI meet once every 3 or 4 months to discuss and propose new studies and new compounds, and that the EORTC would like to maintain a long-term relationship with the NCI. The three organizations are currently making arrangements to expand the scope of the joint agreement. The EORTC is proposing that the NCI allow EORTC experts to review selected compounds that have been referred to the Biological Evaluation Committee. Dr. Pinedo stressed that the EORTC will sign any necessary confidentiality agreements to safeguard existing agreements between NCI and its compound suppliers.

Dr. Pinedo described a proposal for NCI in which he said that compounds selected by the EORTC under mutual agreement with the NCI may be further evaluated by the CRC and the EORTC. Preclinical test results on such compounds will be reported to the NCI after initial antitumor testing has been completed, and interim reports will be submitted to the NCI upon request. If a compound is considered to be of interest for clinical development, Dr. Pinedo continued, a developmental plan will be discussed jointly. NCI should have the first right of refusal for preclinical development and initiation of Phase I clinical trials on those compounds originating from the NCI screens. NCI will also have the option to participate in discussions with the potential drug sponsor at any stage. The major costs of the studies will be covered by the EORTC.

Dr. Pinedo concluded his presentation by stating that this proposal would facilitate the rapid evaluation of a large number of potentially active compounds and would assist the NCI in evaluating the new disease-oriented screen. The ultimate beneficiary, Dr. Pinedo added, will be the cancer patient.

**Questions and Answers**

Dr. Salmon asked whether the EORTC is extending its preclinical or clinical studies to any of the Eastern European countries or to those countries in the former Soviet Union. Dr. Pinedo responded that although the EORTC is exploring that possibility and that it is amenable to collaboration with any of these countries, there has been no success to date. The EORTC's first priority is to maintain the high quality of the Phase I and Phase II studies under the current heavy workload.

Dr. Salmon explained that his question was directed more toward a preclinical input by the Eastern European countries and not an input at a clinical stage. Dr. Pinedo replied that the EORTC is a small organization and that although they are interested in collaborating with the Eastern European countries, this would be a time-consuming task and is not, at the moment, a first priority of the EORTC.

Dr. Salmon asked Dr. Chabner about the status of temozolomide. Dr. Chabner answered that the NCI has been trying to bring the compound to the United States in a clinical trial. The Phase I studies in Europe were conducted using brain tumor patients, which was a novel approach, with the possible rationale of testing whether temozolomide is active in brain cancer. This compound is a 5-(3,3-dimethyl-1-triazeno)-imidazole-4-carboxamide (DTIC) analog that is spontaneously active and does not require metabolic activation, which is one major advantage. Data on this compound showed very impressive and consistent responses, both symptomatic as well as clear resolution of abnormalities on CAT scan; therefore, the NCI

has been very interested in it. Dr. Chabner explained that the initial effort of the NCI was to help the EORTC in the synthesis of large quantities of temozolomide for their current study in Europe. The NCI also assisted the EORTC in finding an American sponsor, Schering-Plough. The clinical trial should start in approximately 2 to 3 months. Dr. Pinedo commented that Schering-Plough has a new formulation for the compound and would like to perform an abbreviated version of the Phase I study using the European data. Dr. Chabner then added that the EORTC has not yet found a maximum tolerated dose for temozolomide; the maximum dose that has been used has caused some leukopenia. It is possible that by manipulating the schedule or by adding G-CSF, better results could be achieved.

Dr. Calabresi asked Dr. Pinedo whether he has any specific recommendations for the Board on how the NCI could help improve the collaboration between Europe and the United States. Dr. Pinedo replied that he would like to seriously discuss the proposal he just presented to the NCAB and to reach an agreement with the NCI. Dr. Pinedo also noted that the EORTC would like a more formal collaboration in terms of Phase I studies. The EORTC could perform Phase I studies with some of NCI's compounds and, reciprocally, NCI could perform Phase I studies with an EORTC drug in which they might be interested. Dr. Pinedo suggested that the NCI, the CRC, and the EORTC should meet to update the joint agreement signed in 1986.

Dr. Chabner commented that a revision of the agreement between the NCI, the CRC, and the EORTC is in the process of making the CRC and EORTC formal partners of NCI in the early phases of drug development. Until now, the EORTC and the CRC had the option of conducting Phase I studies on drugs for which NCI lacked the ability or interest to pursue in Phase I trials. This activity, however, has not taken place on a regular basis. The EORTC would like to participate in the NCI meetings and receive NCI reports about earlier phases of drug development, as well as to assume responsibility for the early stages of development of drugs that are not on NCI's high-priority list but are of interest to the EORTC. Dr. Chabner then expressed his support for achieving this formal collaboration with the EORTC and said that it is simply a matter of arranging the confidentiality aspects of the agreement. The legal aspects of the agreement are currently under revision by NCI.

Dr. Calabresi thanked Dr. Pinedo for presenting a wonderful overview of the EORTC's achievements.

## IX. PAPILLOMAVIRUSES: INVOLVEMENT IN CANCER AND PROSPECTS FOR VACCINATION—DR. DOUGLAS LOWY

Dr. Rabson introduced Dr. Douglas Lowy, Chief of the Laboratory of Cellular Oncology of the Division of Cancer Biology, Diagnosis, and Centers (DCBDC). Dr. Lowy first came to the NIH in 1970 as a research associate in the laboratory of Dr. Wallace Rowe, an outstanding, internationally known virologist. Dr. Lowy determined that halogenated pyrimidines could actually induce latent retroviruses, a major breakthrough discovery in the field of retrovirology. He became a dermatologist at Yale University and later returned to the NIH. Dr. Lowy's laboratory has been working on two projects: the *ras* oncogene and papillomaviruses. Dr. Rabson explained that Dr. Lowy's presentation would focus on the progress of his papillomavirus work.

Dr. Lowy began his presentation by listing three different aspects of papillomavirus infection to be discussed in his agenda—range of infection; pathogenesis, specifically related to cervical cancer; and development of reagents both for immunoprophylaxis of infection and for screening techniques for genital papillomavirus infection. Dr. Lowy noted that his presentation would also include the work being performed in the laboratories of Drs. De Paolo

and Howley. Dr. Lowy added that Dr. Howley was recently elected to the National Academy of Sciences, mainly for his research on papillomaviruses. He acknowledged several individuals within his laboratory, as well as his colleagues from NIH and elsewhere, for their important contributions.

Dr. Lowy explained that genital papillomavirus infection is a common sexually transmitted condition, with a prevalence of 5 to 40 percent among sexually active women. Infection with high-risk papillomaviruses is the most significant risk factor for developing cervical cancer, and 90 percent of cervical cancers contain human papillomavirus DNA. Dr. Lowy stated that the risk factor analysis conducted by Dr. Schiffman and other epidemiologists has revealed that papillomavirus infection is involved in approximately 15 percent of human cancers.

Dr. Lowy next presented some slides indicating the range of lesions induced by human papillomavirus infection. One slide displayed a child with external and internal genital infection; the next slide showed a larynx papilloma. Dr. Lowy explained that although the larynx papilloma is benign, it represents a high risk of airway obstruction in small children and, therefore, requires major intervention. Ordinary warts that occur on the hands are also benign, but, he noted, can be very devastating for the patient.

Dr. Lowy moved on to discuss genital papillomavirus infection, indicating that safe sexual practices can play an important role in the prevention of the disease. Dr. Lowy explained that the viral genetic information replicates in the upper layers of the epidermis, which may contribute to the relatively efficient sexual transmission of papillomaviruses. Once the viral DNA is replicated, the virus is packaged and extruded with the cells as they are released either into the vaginal fluid or into the air. The minor trauma associated with sexual exposure releases these cells and the virus is then transmitted.

Dr. Lowy observed that one of the most important advances in papillomavirus research over the last 15 years has been the recognition of the existence of multiple types of these viruses. Although more than 60 types have been described, papillomaviruses can be divided into three major groups: nongenital viruses, which are seen mainly in dermatology, and do not seem to have a malignant predisposition; viruses seen principally in a rare condition called epidermodysplasia verruciformis, which represents a unique susceptibility to chronic nongenital papillomavirus infection; and mucosal or genital papillomaviruses, which infect the genitalia and the oral and laryngeal areas.

Dr. Lowy stated that only a subset of people with epidermodysplasia verruciformis develop skin cancers, usually on areas exposed to the sun. Possibly, the papillomavirus infection and the sunlight act together to generate the squamous cell cancers. The important point with regard to epidermodysplasia verruciformis, Dr. Lowy said, is that only a subgroup of the papillomaviruses appears to be associated specifically with the cancers. Thus, infection with a particular subtype of human papillomavirus (HPV) appears to be necessary, although not sufficient to cause these cancers, since the sunlight seems to play a decisive role in the development of cancers in these particular patients.

With regard to genital papillomaviruses, Dr. Lowy explained that the viruses can be classified according to their cervical risk in the so-called low-risk HPV types, especially types 6 and 11, and the so-called high-risk HPV types, such as 16, 18, 31, and 33, which are more prevalent in cervical cancer. Dr. Lowy displayed a slide describing the different kinds of cervical lesions, ranging from the most benign, such as condylomas, to dysplastic lesions, intraepithelial neoplasias, and carcinoma *in situ* (or invasive cervical cancer). The low-risk HPV types are correlated mainly with benign lesions, and their prevalence is sparse in more dysplastic lesions and frank cancer. By contrast, the high-risk HPV types are identified in at

least 90 percent of cervical cancers; a high proportion of cell lines derived from cervical cancers contain papillomaviruses from the high-risk types.

Dr. Lowy explained that the cells derived from cervical cancers and grown in culture seem to depend on the continued expression of the papillomavirus genes, since the inhibition of the expression of these genes can actually kill some cell lines. The development of a therapeutic approach could take advantage of this observation by trying to either directly inhibit the expression of the papillomavirus genes or indirectly interfere with the action of the proteins encoded by those genes.

The structural viral genetic information is either deleted or not expressed in the cervical tumors or in cell lines derived from these tumors. However, there are two particular genes, *E6* and *E7*, which are preferentially retained and expressed in the cervical tumors and in the cell lines. Dr. Lowy indicated that a cell culture assay developed at NIH has shown that human keratinocytes—cervical or other genital region epithelial cells—can be immortalized with DNA from high-risk, but not low-risk, HPV types. This observation reflects the condition seen in cervical cancer; namely, that the high-risk (but not low-risk) HPV types are present.

Genetic analysis data, Dr. Lowy continued, have indicated that the *E6* and *E7* genes must be expressed together to produce immortalization—the extensive growth of epithelial cells, which, in turn, will proliferate indefinitely. By contrast, if only the *E6* gene is expressed, there will be almost no growth and the cells will eventually die, which is what normally occurs in ordinary epithelial cells. Similarly, if *E7* genes are expressed alone, the cells will barely grow and then will die. These data, therefore, imply a cooperation between the *E6* and *E7* genes, which are the two genes preferentially retained and expressed in the cancers.

Dr. Lowy stated that his laboratory has been trying to determine whether there are any biological differences between the high-risk and low-risk HPV types of both the *E6* and *E7* genes. Dr. Lowy said that they have found that both genes must be of the high-risk type in order to immortalize the cells. This would indicate that there are, in fact, major biological differences, both for the *E6* and the *E7* genes, between the high- and low-risk viruses. Dr. Lowy reported that Dr. Howley's laboratory has provided some important insights into some of those biological differences.

Dr. Lowy explained that the normal control of cell proliferation involves at least two different classes of genes: those genes that stimulate growth, often called proto-oncogenes; and those cellular genes that inhibit cell growth, often referred to as tumor suppressor genes. Apparently, the *E6* and *E7* genes work, at least in part, by inactivating these tumor suppressor genes. The *E7* gene causes inactivation by binding to the protein encoded by the retinoblastoma susceptibility gene. Dr. Lowy then showed a slide of a child with bilateral familial retinoblastoma. The rate-limiting step, Dr. Lowy added, for the development of retinoblastoma in children is the inactivation of both of the *Rb* alleles. *E7* in the papillomavirus inactivates the *Rb* allele in the cervical cells; however, this action is not sufficient to trigger the development of cervical cancer. This implies that there are also some biological differences between the retinal and cervical cells.

The *E6* gene binds to and inactivates a gene called *p53*—it encodes a protein that is 53 kilodaltons in size. Dr. Lowy then explained that Li-Fraumeni Syndrome, first identified at NCI, has an inborn mutation of inactivation of one of the two *p53* alleles. People with this syndrome are at increased risk of developing a variety of tumors. They are not, however, at increased risk of developing cervical cancer because if *p53* is inactivated by *E6*, there is no immortalization of the epithelial cells.

Dr. Lowy noted that the potential importance of the host response must also be considered in the pathogenesis of tumors. Investigators in Europe have recently reported that a

high proportion of women with cervical cancer have particular immunologic response genes that are significantly different from those of controls. It may be important then, in the long term, to try to identify individuals who are at particularly high risk.

Dr. Lowy gave another example to indicate the importance of understanding the consequences of host response. It was recently reported by Dr. Gerard Orf and his colleagues that only certain rabbits that had developed warts due to a rapid papillomavirus showed an early regression of these warts. This observation, he noted, appears to be associated with genes involved in the host response. Dr. Lowy concluded that understanding the host response is as important as understanding the etiologic agents involved.

Dr. Lowy then explained that in trying to relate multistep carcinogenesis with papillomavirus infection, the latter should be thought of as the early stages leading to inactivation of *Rb* and *p53*, which, in turn, sets the trigger for the development of cancer. He noted that if these cells are inoculated into animals, they do not give rise to tumors. Similarly, although women with cervical infection with a high-risk HPV are at a greatly increased risk of developing cervical cancer, the majority of them are not going to actually develop the cancer.

Several cellular genetic and epigenetic changes need to occur before the eventual development of cancer takes place. Dr. Lowy indicated that if an oncogene, such as the *ras* oncogene, is added to the immortalized cells, as has been done in Dr. De Paolo's laboratory, it will give rise to tumors. Activation of oncogenes in cells has been described in a variety of cervical cancers. Dr. Lowy emphasized that viral infection seems to be necessary, but not sufficient, to cause the development of cancer; other changes are also important.

Dr. Lowy pointed out that the high-risk HPVs are able to bind and inactivate *Rb* and *p53* much more efficiently than the low-risk types. This could provide a biochemical explanation for the biological difference between the high- and low-risk viruses discussed above.

Dr. Lowy then addressed the possibility of immunoprophylaxis against infection. Formal and inactivated papillomas containing papillomavirus can protect against challenge with bovine papillomavirus in the skin or vagina. It has been much more problematic, he said, to try to induce actual disappearance of existing lesions with these kinds of preparations. The resistance to challenge, Dr. Lowy explained, is related to the development of neutralizing antibodies (i.e., antibodies that are able to prevent infection).

When the major structural protein of the virus is expressed in bacteria, it induces only very low titers of neutralizing antibodies, compared with intact virus particles. Dr. Lowy noted that in his laboratory, a different cell system has been used to try to make papillomavirus particles. He indicated that his colleagues have used an insect virus system that infects insect cells and not mammalian cells. The advantage of this system, Dr. Lowy explained, is that any kind of gene can be introduced into the virus and a high level of expression of the proteins encoded by those genes can be obtained. Because insect cells, phylogenetically speaking, are much closer than bacteria to mammalian cells, the possibility of making material that is much more similar to mammalian cells is greater. The material prepared in such insect cells has already been approved for vaccine trials with HIV.

Dr. Lowy indicated that when the *L1* protein, the major structural viral protein, both from the bovine papillomavirus (BPV) as well as the HPV, was expressed in his laboratory, particles were found that were made in the nucleus and were indistinguishable from authentic particles. Making the HPV16 particles, however, was much less efficient than using the bovine particles. Dr. Lowy explained the rationale for using BPV, indicating that the BPV provided a source of infectious virus and, because a good cell infectivity assay was available

that was developed in his laboratory some years ago, it was possible to determine whether the virus-like particles were able to induce neutralization.

Dr. Lowy displayed a slide demonstrating that if rabbits were immunized with various preparations of the virus-like particles, the sera developed from the rabbits were able to neutralize BPV infection in a manner similar to the authentic virus particles. However, Dr. Lowy explained, if the virus-like particles are denatured before being inoculated into the rabbits, they will not induce neutralizing antibodies. Thus, the intact structure of the virus-like particles is needed in order to induce the antibodies.

Dr. Lowy reported that less success has been achieved in producing efficient particles with the HPV16 *L1*. HPV16 is the papillomavirus found in the majority of cervical cancers. Dr. Lowy reiterated that the problem was related to the *L1* gene that was being used, a gene cloned from a cervical cancer. When two different *L1* genes from earlier lesions were used instead, these genes were able to efficiently self-assemble. A DNA sequence analysis revealed that the *L1* gene derived from the cervical cancer had a point mutation, accounting for the 1,000-fold difference in efficiency of self-assembly. Dr. Lowy added that with the efficient *L1* genes, limitless amounts of the virus particles can be obtained.

Dr. Lowy concluded his presentation by suggesting some future directions for his research. He discussed the potential development of a serological assay for detecting papillomavirus infection. The advantage of this assay over the Pap smear is that the latter requires specialized personnel both for sampling as well as for analysis. In addition, the Pap smear has a false-negative rate of approximately 20 percent. The serological assay, on the other hand, would complement the Pap smear and, possibly, could be an automated assay. Dr. Lowy said that the assay might also have some implications in third world countries where cervical cancer is one of the leading cancers in women. He concluded that, although no effective serological assay currently exists, it may be possible to use the virus particles being produced in his laboratory in the development of such an assay.

Dr. Lowy concluded his presentation with a suggestion for a second potential application of his research. He recommended developing a vaccine to prevent benign or malignant papillomavirus-induced disease, with a strong emphasis on genital papillomavirus infection.

Dr. Calabresi thanked Dr. Lowy for his interesting presentation.

**Resolution**

The Board next discussed a resolution addressed to the Secretary of Labor, the Honorable Robert B. Reich, proposed by Dr. Yodaiken the day before:

> The National Cancer Advisory Board fully supports the Secretary of Labor and the Occupational Safety and Health Administration (OSHA) in any effort to control smoking in the workplace. The carcinogenic consequences of passively inhaled tobacco smoke are well documented and, therefore, passive smoking is a grave threat to all exposed workers.
>
> The Board will support standards which address indoor air quality and passive smoking in the workplace, and hereby offers to provide, through its individual members, any requests for scientific documentation. In addition, the Board undertakes to identify experts who would be willing to testify at any hearing that OSHA may hold on this subject.

One amendment was made before the Board unanimously approved the resolution: "The Board will support standards which address indoor air quality and passive smoking in the

workplace, and hereby offers to respond, through its individual members, to any requests for scientific documentation."

## X. REPORT ON INTERACTIVE RESEARCH PROJECT GRANTS (IRPGs)—DR. MARVIN R. KALT

Mrs. Bynum called Board members' attention to their copies of the recent program announcement describing investigator-initiated interactive research project grants published by the NIH. She stated that the IRPG represents a major victory for the NCI, since its efforts gained acceptance for this mechanism as a trans-NIH mode of supporting research project grants. Mrs. Bynum announced that Dr. Marvin Kalt would describe the NCI's experiences in achieving acceptance of the IRPG as a general mechanism.

Dr. Kalt began by describing the chronology of IRPGs. Responding to a request from Dr. Broder, NCI staff began developing a concept for the IRPG as an interactive R01 mechanism in the fall of 1991; this concept was then presented to the Boards of Scientific Counselors. Two NCI announcements were generated in January of 1992. One broad announcement (92-29) covered all NCI Divisions and required a minimum of three research project grants for the IRPG mechanism. A second announcement (92-57) was issued by the DCT and diagnostic radiology and essentially solicited IRPGs in that area. The first round of applications was reviewed in June of 1992. The second round of IRPG applications was received in October of 1992, at which time Mrs. Bynum presented the concept for consideration and adoption across NIH to the Extramural Policy Management Committee of NIH. In February of 1993, the third round of applications was received and preliminary funding decisions were made on the first round of applications. The NIH approved and published its broad area program announcement for IRPGs and the *NIH Guide to Grants and Contracts* in the last week of April of 1993.

Dr. Kalt explained that the major difference between the NCI version and the NIH-wide version of the IRPG concept is a reduction in the minimum number of projects required from three (NCI) to two (NIH-wide). There are also required budget tables that relate to the utilization of any shared resources that are proposed. Dr. Kalt added that there are standards of review practices for processing applications received by the Division of Research Grants (DRG) study sections, in terms of addressing the interactive nature of each of the applications.

Dr. Kalt explained that the IRPG is predicated upon the fact, at least within the NCI, that if one IRPG application is within the payline of the Institute, program staff and the Executive Committee would consider other applications within a single set that have received a rating of significant and substantial scientific merit for exception payment. He presented a slide showing the odds of at least one application making the payline, based on the number of applications submitted and the percentile payline. For example, the odds of 1 application making the payline are 1 in 4 at a 25 percent payline. Dr. Kalt explained that there would need to be a larger group of submissions to ensure that at least one application makes the payline. The greater number of independent applications submitted, however, lowers the probability that all of the applications would make the payline together. Dr. Kalt summarized that the odds of all applications within a single group of IRPGs making the payline are slim.

Dr. Kalt presented a slide showing the number of responses received for all of the program announcements and the first three RFAs. He noted that 139 applications have been received in response to the program announcements over 4 rounds and 216 applications in response to 3 RFAs, for a total of 355 applications. This number represents 10 percent of all the R01 applications submitted to the NCI. Dr. Kalt pointed out that almost all applications were new Type I applications. Thus, Dr. Kalt said, the IRPG struck a responsive chord in the

applicant community. He reported that 29 sets have been received in response to the program announcement and 64 sets in response to the 3 RFAs, for a total of 93 sets, with an average of 3 to 4 applications per set.

The only applications that have been funded, Dr. Kalt related, are from the May 1992 and January 1993 Boards. He pointed out that some applications in the January 1993 Board will be considered for exception funding later this fiscal year. Four of 9 applications were funded in the first round, 4 of 64 applications in the second round have been funded, and 4 diagnostic-imaging applications were funded. Dr. Kalt noted that the success rate ranges between 6 and 44 percent, although data for the success rate are not adequate at this time. He indicated that there will be a built-in success rate for the RFAs, which will exceed the success rate for individual R01s. Dr. Kalt reminded the Board that only partial data are being presented, since applications for the October Board in response to the program announcements were not included. He stated that 1 RFA was currently open, from which the DCPC will probably receive 78 applications. Dr. Kalt pointed out the utility of the RFA mechanism by noting that 96 new R01 applications were received in response to RFA 92-25 from DCT, which represents purely clinical research.

Dr. Kalt presented the percentile distribution of all IRPG applications reviewed by the Division of Research Grants in response to the program announcements. According to raw scores, he said, not many applications in the program announcement area are achieving fundable percentiles. These results, however, are comparable to the first two RFAs, a DCT RFA (92-25) concerning innovative systemic therapies and a DCBDC RFA (92-24) on the biology and immunology of breast cancer. Dr. Kalt noted that there are few top-scoring applications.

Dr. Kalt explained that a tailored review committee has been matched to the body of clinical applications received, and a substantial number of the applications have not been recommended for further consideration by the committee. He stated that there is no significant difference in the shape of the distribution of scores voted by either the DRG study sections or the hand-picked NCI initial review groups (IRGs). Dr. Kalt commented that he would not expect large improvements in the quality of responses until some amendments or competing continuing Type 2 applications are submitted.

Regarding IRPGs, Dr. Kalt noted that good priority scores have been randomly distributed in IRPG groups; they have not aggregated in individual IRPG packages. Only 1 or 2 of approximately 96 IRPG packages have had multiple well-scored applications in the same package. This issue has been a challenge for NCI program staff and the Executive Committee under both the straight program announcement and the RFA packages. Dr. Kalt indicated that this problem will limit the utility of the IRPG mechanism until investigators receive feedback from the first round of review, adjust their collaborations, and revise their applications.

**Questions and Answers**

Dr. Bettinghaus commented that investigators across the country believe that P01s are not well received, so many investigators switch applications originally intended to be P01s to IRPGs. Mrs. Bynum responded that approximately the same number of P01s and IRPGs were funded in 1992, and the same will probably happen in 1993. Dr. Kalt clarified that the NCI will "pay about the same percentage of success." Dr. Bettinghaus stated that, regardless of what actually happens, there is a negative perception in the field about P01s, which discourages many investigators from applying for P01 grants. Mrs. Bynum explained that in order to gain NIH-wide acceptance of the IRPG mechanism, the NCI defended the assertion that the P01 and IRPG are not surrogates. P01s and IRPGs, she continued, have different objectives and review criteria. Mrs. Bynum pointed out that the IRPG mechanism allows

younger investigators to pursue their own independent research grants, which probably attracted a large number of the applications.

Dr. Kalt mentioned Dr. Broder's suggestion in a recent paper published in *Cancer Research* regarding the program project portfolio, that the success rate for program projects is historically, and likely will continue to be in the future, greater than the success rate for R01 applications. Dr. Kalt added that a new population of investigators is submitting these interactive grants—not previously unsuccessful P01 applicants.

Because there is no guarantee of worker/investigator collaboration in the IRPG mechanism, Dr. Salmon commented that it will be difficult to conduct an evaluation to determine to what extent the interactiveness affects long-term cooperation that advances clinical efficacy. Dr. Salmon urged the NCI to create a means of evaluation before these grants come up for competitive renewal. Mrs. Bynum commented that the public document concerning this mechanism stated that the study sections conducting these reviews will receive common information (i.e., all applications will have a section that includes a distribution and a nature of interaction as part of the application). Also, there will be a specific written evaluation of the extent of the interaction in the summary statement so that staff can track activities during the life of the grant.

Dr. Mihich asked about the differences between the National Cooperative Drug Discovery Groups (NCDDGs) and the IRPGs. He questioned his belief that there is no financial rule for the IRPGs but there is a scientific interaction, and that IRPGs are individual, self-standing grants. Dr. Kalt explained that the NCDDGs are cooperative agreements that require substantial staff involvement in the collaboration and oversight of those awards. Mrs. Bynum added that, as part of a cooperative agreement, the investigators at the various institutions are obligated to have these interactions with NCI staff. This is not required of the IRPGs; thus, each of those components must have the capability to stand alone as an independent research project grant.

Dr. Mihich stated that the NCDDGs, as a mechanism, provide for shared resources among the components, but the IRPGs do not have this component. Given the interest in interactive science, he asked what would be possible in terms of providing interactive core funds within the IRPG. Mrs. Bynum explained that there is a provision in the IRPG mechanism for a small amount of support specifically to facilitate the interaction. The magnitude, she continued, would depend upon the Institute's determination of how much is needed to make it a cost-effective mechanism.

## XI. UPDATE ON LEADERSHIP INITIATIVES—DR. THOMAS GLYNN

Dr. Greenwald introduced Dr. Thomas Glynn, noting that the NCAB launched its first leadership initiative in the mid-1980s, and two other initiatives were subsequently started. He explained that the overall goal of a leadership initiative is to ensure that the entire population benefits from NCI-sponsored research and, in the long run, participates in the research. Dr. Greenwald then called upon Dr. Glynn, Acting Associate Director for the Cancer Control Science Program, to introduce the Program Director for each initiative.

Dr. Glynn stated that the leadership initiatives are unique at the NCI because they will be evaluated but are not research oriented in the standard sense. Leadership initiatives essentially apply research results in communities across the country, helping to fulfill the NCI's mandate to reduce cancer-related morbidity, mortality, and incidence. Dr. Glynn explained that the initiatives are currently targeting Black, Hispanic, and Appalachian

populations. He described the two goals of the leadership initiatives as: 1) to reduce cancer morbidity and mortality among specially targeted populations; and 2) to transfer cancer prevention and control research findings to community settings, build lasting community coalitions focused on cancer prevention and control, and actively engage community leaders in cancer prevention and control issues. Dr. Glynn added that the leadership initiatives act as consumers of the research funded and carried out by the Institute and attempt to ensure that it is implemented within the community at large.

Dr. Glynn introduced Mr. Frank Jackson, Director of the National Black Leadership Initiative on Cancer (NBLIC), the oldest leadership initiative.

**National Black Leadership Initiative on Cancer—Mr. Frank Jackson**

Mr. Jackson discussed the National Black Leadership Initiative on Cancer, which was organized in 1989. During its first 3 years of operation, the NBLIC established approximately 47 coalitions throughout the United States, targeting about 30 million Black Americans. Based on this model's success in targeting Blacks, the Hispanic and Appalachian programs were later initiated.

With the NCAB's approval and Dr. Glynn's guidance, the National Black Leadership Initiative has awarded three projects—the Minority Health Professions Foundation, the Howard University School of Social Work, and the University of Maryland-Eastern Shore—each with unique characteristics that complement one another and allow better access to Black Americans, especially those who live in rural areas. Mr. Jackson added that the Howard University project conducts a unique approach to the behavioral and sociological aspects of cancer outreach.

Mr. Jackson presented a map showing strategic locations of targeted regions and project sites. Original project sites are located in Los Angeles; Houston; Washington, DC; Atlanta; Chicago; and New York City. Other sites added in 1993 include those in Oklahoma; Baton Rouge and New Orleans, Louisiana; and Raleigh, North Carolina. Mr. Jackson explained that the National Black Leadership Initiative is currently more interested in enhancing existing coalitions than establishing new ones. Other program goals include extending outreach to rural Black America, assessing the effectiveness of other community outreach models, making appropriate adjustments to improve efficacy, and stimulating greater community leadership involvement, especially in areas that are difficult to access. Mr. Jackson emphasized the importance of community leaders in facilitating access to a community. A final goal of the Initiative, he continued, is to publish its findings of knowledge, attitudes, and behaviors.

Mr. Jackson then discussed current activities of the program, noting that the NBLIC publishes a quarterly newsletter, conducts annual cancer awareness campaigns, initiates community radon education projects, and collaborates on project activities. The Morehouse site is developing a smoking cessation self-help guide and, since his return as President of Morehouse, Dr. Louis Sullivan has initiated cancer education teleconferences with students at Historically Black Colleges and Universities, the first of which was held in April.

Mr. Jackson pointed out that the goals and objectives of the NBLIC correlate directly with those of *Healthy People 2000*. The National Black Leadership Initiative aims to reduce cigarette smoking, increase breast cancer screening, and develop and implement a national process to identify gaps in disease prevention and health promotion data. Mr. Jackson mentioned that no such data exist at the present time.

Mr. Jackson credited Ms. Veronica Chollette with laying the groundwork for the program, and presented some of the brochures that have been developed. Mr. Jackson noted

that one brochure, recognizing volunteers who work on the initiative, was a tremendous morale booster in the field. He mentioned another informative brochure that includes a tear-out card that can be placed in a rolodex file and a second card to use for requesting information. He also showed a copy of the Initiative's quarterly newsletter that is published and distributed nationwide.

Mr. Jackson then introduced Ms. Elva Ruiz, Director of the Hispanic Leadership Initiative.

**National Hispanic Leadership Initiative on Cancer (NHLIC)—Ms. Elva Ruiz**

Ms. Ruiz began with a brief overview of the National Hispanic Leadership Initiative on Cancer, noting that it targets large numbers of the Hispanic population and convenes researchers from different segments of this population who then target the segments that they represent. This Initiative includes two cooperative agreements—one at the University of Texas at San Antonio and the other, COSSMHO, in Washington, DC. Ms. Ruiz presented a map showing where the 22.3 million Hispanics targeted by the program are located in the United States. Target sites are strategically placed in areas with large Hispanic populations, primarily in the western section of the country. The sites are also located in areas that collectively contain the major Hispanic population groups within the United States, including San Francisco and San Diego, California; Brownsville and San Antonio, Texas; Miami, Florida; Chicago, Illinois; Brooklyn, New York; Washington, DC; and Puerto Rico.

Ms. Ruiz discussed the goals of the Hispanic Leadership Initiative, which include mobilizing national, State, and local leaders; building coalitions; stimulating cancer control data collection; identifying health risk factors; and assessing the efficacy of the interventions. She emphasized the importance of mobilizing national, State, and local leaders due to the Hispanic population's lack of a national health agenda and its inadequate representation at the national level to address such an agenda. Ms. Ruiz indicated that the NHLIC provides an opportunity for Hispanics to organize around cancer-related issues. The formation of coalitions, she continued, is a unique approach to empower the population to address their own health needs. Ms. Ruiz explained that representative data collection agencies have not adequately identified the Hispanic population for purposes of cancer data collection. She added that the NHLIC will add to the available baseline data and hopes to demonstrate that it is not difficult to collect data for this population. The NHLIC plans to assess the program's long-term interventions to determine their value in outreach intervention methods, as well as measure the impact of that outreach program on the targeted community.

Ms. Ruiz reported that the NHLIC was organized in October 1992. Since that time, nine program sites have been established, two of which are national centers in San Antonio and Washington, DC. The remaining seven sites are regional projects. The sites have been in the planning stages, conducting regional meetings and establishing liaisons with intermediary organizations. Ms. Ruiz stated that the first grantees' meeting would be held in Washington, DC, in May to exchange information; to begin development of a newsletter and a handbook describing the organization of the NHLIC, its goals and objectives, and its startup procedures; and to develop the project management system that will establish a uniform method of training volunteers at different sites, as well as establish uniformity in the collection of baseline data, the types of cancer awareness projects to be initiated, and the development of cross-cutting research plans.

Ms. Ruiz explained that the overriding mission of the NHLIC is to directly or indirectly advance and, possibly, surpass, the Year 2000 goals for the Hispanic population. For breast examinations and mammography, a goal would be to improve the baseline data, which are currently only 20 percent for women aged 40 and 18 percent for women aged 50 and over. Ms. Ruiz noted that although baseline data for Pap smears seems to be adequate, there is a

high incidence of cervical cancer in the Hispanic population. She questioned whether baseline data for Hispanics should be reconsidered. Ms. Ruiz suggested that one possible way to improve the health status of Hispanics is to increase sources of preventive and episodic health care, since more than 30 percent of Hispanics do not receive regular physician, clinic, or hospital care. She also suggested that it is necessary to increase the implementation of culturally and linguistically appropriate promotion programs. She maintained that because surveillance projects for the Hispanic population always seem to be projected for the future or because money is not available, Hispanics either are not included in these programs in large numbers or are not reached at all.

Ms. Ruiz concluded that the Hispanic Leadership Initiative on Cancer hopes to raise the consciousness of health care for Hispanics and obtain measurable outcomes in prevention and control for this population. She then introduced Ms. Nancy Simpson, Program Director of the Appalachian Leadership Initiative on Cancer.

**Appalachian Leadership Initiative on Cancer—Ms. Nancy Simpson**

Ms. Simpson began her presentation by displaying the new logo for the Appalachian Leadership Initiative, developed by Appalachian artist Margaret Gregg in conjunction with the program's four principal investigators. She noted that people like the informality of the logo, which is reminiscent of the crafts that are so popular in the Appalachian region.

Ms. Simpson named the recipients of this Initiative's four awards: Dr. Audrey Maretzki of the Cooperative Extension Food Service, Pennsylvania State University; Dr. Fred Butcher, Director of the Mary Babb Randolph Cancer Center in Morgantown, West Virginia; Dr. Gilbert Friedell, Director of the Cancer Control Program at the Markey Cancer Center in Lexington, Kentucky; and Dr. Barbara Garland of the North Carolina Cooperative Extension Service, North Carolina State University.

Ms. Simpson described the Appalachian region, which includes all of West Virginia and portions of 12 other States. It follows the spine of the Appalachian mountains, she continued, and includes approximately 20.7 million people. Ms. Simpson stated that the Initiative covers all of the Appalachian region, except the Appalachian portions of Mississippi and Alabama, which may be included in the program at a later date.

Ms. Simpson outlined the program's objectives, which include creating a network of cancer control community coalitions throughout Appalachia; developing, supporting, and disseminating regional cancer control outreach activities; stimulating cancer control data collection and research efforts and the dissemination of new findings; and evaluating the effectiveness of the project. Although each project has its own design, she explained, the targeting of low-income and rural communities is the priority of all the projects.

Ms. Simpson reported that this first year of the Appalachian Leadership Initiative's 5-year scope has been devoted to planning, establishing the 14 project sites, and developing a monograph on cancer in Appalachia. She explained that the Initiative's steering committee, composed of principal investigators and the senior project manager from each project, has requested that special workshops be held in conjunction with steering committee meetings. The first workshop was held in Lexington, Kentucky, and concerned community development and cultural sensitivity issues. Ms. Simpson noted that the next steering committee meeting will be held in September in West Virginia and will focus on communication strategies and the development of materials for low-income populations.

Ms. Simpson explained that this project is developing a quarterly newsletter similar to that of the NBLIC, and is working with the Cancer Information Service and the Office of Cancer Communications to develop a communications plan to coordinate communication

across all of the sites. Other activities include developing a list of key Appalachian contacts and a 5-year program plan.

Ms. Simpson related that the Appalachian Leadership Initiative is looking to the cancer prevention and control objectives defined in the *Healthy People 2000* reports to help guide and shape the program. These are risk reduction objectives focusing on the reduction of smoking, fat intake, and sun exposure, and increasing intake of complex carbohydrates and fiber. The program is examining objectives that relate to low-income and rural populations, since there are no specific objectives for the Appalachian region. Services and protection objectives include increasing tobacco cessation counseling, diet modification, cancer screening, clinical breast examinations and mammography, and Pap tests. There are also plans to increase fecal occult blood testing and sigmoidoscopy, and oral, skin, and digital rectal examinations.

Ms. Simpson concluded that this initiative includes four very active projects and that she looks forward to providing further updates at future Board meetings.

Dr. Glynn acknowledged the contributions of key staff members involved in the initiation of these projects: Dr. Marvin Kalt, for his work related to IRPGs; Dr. Claudia Baquet, who began the leadership initiatives; Mrs. Barbara Bynum, for her assistance in the startup of these projects; and Mr. Paul Van Nevel, for his ongoing support. He noted that this is an ambitious project that is targeting 60 million medically underserved Americans, and that his staff would enjoy making another presentation in approximately 1 year to report on the progress of the programs.

**Questions and Answers**

Ms. Brown asked Mr. Jackson what happened to the NBLIC's original awardees and why this year's three awards are in the same geographic location. Mr. Jackson replied that although the awardees are in the same area, they have complementary differences. One awardee, he explained, focuses on the behavioral and social behavioral aspects of the cancer message. Another is primarily a medical model, designed to implement screening programs and refer clients to either free or low-cost sites where they can obtain mammography or other types of screening. Ms. Brown then asked about the number of original grants and their locations and funding levels. Mr. Jackson answered that there was one award the first year. He explained that the original structure of the regions is intact, and the two new projects are designed to work synergistically with the existing projects. Mr. Jackson reported that funding increased by more than $200,000; funding for the project was $749,000 in 1992 and is $1.2 million for 1993.

Ms. Brown asked how outreach to rural Black Americans is being coordinated with Cancer Centers in nearby locations. Mr. Jackson answered that this issue has not been investigated yet. Most of the project's efforts have focused on identifying the strengths and weaknesses of the two projects to enable them to work together successfully. Dr. Greenwald commented that it will be important to build other types of research into the leadership initiatives after they are running smoothly; for example, investigative scientists might study cancers that are high risk for certain populations.

Ms. Brown then asked whether the Raleigh site of the NBLIC and the Raleigh site of the Appalachian Initiative coordinate activities or if they coordinate with other departments of the NCI. Mr. Jackson indicated that there are plans for the projects to work together and, possibly, plan a future conference or workshop to include all three initiatives.

Ms. Brown asked how the success of the NBLIC is being measured. Mr. Jackson answered that the current 3-year project is being asked to examine methods of measuring

coalition acceptance, success, and effectiveness. He noted that the first-year project was not asked to consider this issue.

Mrs. Bynum reminded the Board that creation of the NBLIC began with the NCAB. She added that the Board will be kept informed about the progress and accomplishments of this initial effort that was funded through one grant. By advertising for this current competition, Mrs. Bynum commented, Dr. Greenwald hoped to obtain better coordination of these regions while not disturbing the maintenance of the structure that has proven effective in forming regional coalitions.

Mr. Jackson commented that he is encouraged by the support and scrutiny of the program given by NCI staff, particularly Dr. Greenwald, Mrs. Bynum, and Dr. Broder.

Dr. Correa congratulated the staff on these initiatives and suggested that a leadership initiative for the Mississippi Delta be established. He commented that the Mississippi Delta is the poorest section of the country, and that this fact was acknowledged by a commission chaired by President Clinton while he was Governor of Arkansas. He added that maps produced by the NCI show a high-risk area around the lower Mississippi River. Because this new problem was not highlighted 20 years ago and has not been addressed, Dr. Correa suggested that the NCAB study this issue.

Dr. Sigal expressed her concern about low minority recruitment to clinical trials, particularly in the Washington, DC, metropolitan area, which has two cancer centers. She asked about any efforts of coordination that are in effect or should be enacted to ensure minority participation. Dr. Greenwald explained that there has been a special request for applications for minority community clinical oncology programs; he noted that there are 11 at present. All cooperative groups are required to show that they give attention to minority accrual, and this has been done with variable success. A new issue that will be examined, Dr. Greenwald continued, is evaluating centers for successful accrual.

Dr. Wilson asked Mr. Jackson to identify "community leaders"—whether they are medical, political, social, or other types of community leaders. Mr. Jackson explained that communities are accessed through community leaders. Principal investigators and their staffs maintain comprehensive lists of prominent people within a given community and make contact with them. Other contacts are made as a result of coalition activities, such as cancer survivors' support groups. Leadership, Mr. Jackson continued, is broadly defined and involves lay and professional people who have the ability to influence or encourage others.

Mrs. Bynum stated that she, Dr. Greenwald, and Mr. Jackson can provide information on the leadership initiatives to newer Board members, so that they can examine this project in its historical context; that is, from the time the idea was initiated in 1987. She commented that the country was divided into six regions arbitrarily; this division provided a framework for accessing communities. Mrs. Bynum added that Board members completed much of the initial legwork for the project themselves, and that hundreds of people effective in the role of "leader" have been identified. Mr. Jackson added that he brought extra copies of NBLIC documents for distribution.

## XII. SUBCOMMITTEE REPORTS

### Clinical Investigations Task Force

Dr. Michael Friedman, reporting for Dr. Calabresi, conveyed Dr. Calabresi's strong feelings about the problems of clinical investigation discussed at a recent meeting of the

American Society for Clinical Investigations. This subcommittee, Dr. Friedman reported, focused on the NCI's and the extramural community's perceptions of possible remedies for the support of clinical oncology research. The subcommittee recommends that a clinical oncology review committee be established by the DRG. Dr. Friedman explained that this subcommittee would like to meet with Dr. Jerome Green, Director of DRG, and other DRG staff as soon as possible to discuss the possibility of quickly establishing a clinical oncology review committee.

The subcommittee recognizes that reluctance on the part of the DRG to establish such a new committee and a mandate from the Executive Branch of the Federal Government to reduce the number of standing committees by one-third could pose potential problems with the recommendation. Dr. Friedman pointed out that some subcommittee members feel that this is a unique opportunity to establish the new committee because the DRG is currently reevaluating and reordering their review process.

The minutes of the Clinical Investigations Task Force were unanimously approved.

**Aging and Cancer**

Ms. Deborah Mayer reported that Dr. Margaret Holmes, Chief of the Cancer Centers Branch, DCBDC, NCI, presented results of a survey that was sent to all NCI cancer centers. The questionnaire obtained information on interests in geriatric oncology within the centers and on possible collaborations with geriatric programs funded by the National Institute on Aging or the Veterans' Administration. Dr. Holmes reported that of 41 currently funded NCI clinical centers, 8 have ongoing collaborations, 5 have ties to explore mutual interests, and an additional 11 would be interested in developing further collaborations.

A discussion ensued regarding how the NCI could foster such collaboration and increase the number of affiliations. Ms. Mayer mentioned some suggested possibilities, including R13 developmental conference grants, R21 exploratory grants, and P20 developmental grants, as well as an examination of ways in which the NIA and NCI could stimulate complementary activities.

Ms. Mayer reported that the subcommittee also continued a discussion from its last meeting about the accrual of cancer patients over the age of 65 to clinical cooperative groups and their underrepresentation in clinical trials. The subcommittee will continue to investigate this issue, examining care data. Ms. Mayer added that the subcommittee will explore the issues and identify gaps, but that it has no specific recommendations at this time.

The minutes of the Aging and Cancer Subcommittee were unanimously approved.

**Cancer Centers**

Dr. Sidney Salmon reported that the major topic of this subcommittee's discussion focused on membership on the cancer center review committee, potential conflicts of interest, and *ad hoc* review of those centers at which a member served on the parent committee. He explained that this topic was first raised at the Cancer Centers Directors Workshop in March 1993. The primary concern was the reluctance of center directors and other senior leaders to serve as members of the Cancer Centers Support Grant Review Committee if their own institution received an *ad hoc* review. Subcommittee members are concerned that the Cancer Centers Review Committee include significant representation of the cancer centers, and wish to avoid *ad hoc* review. The subcommittee feels that these goals can be accomplished if an appropriate percentage of the Cancer Centers Review Committee comprises cancer center directors and senior leaders, using shorter terms of membership when necessary. This

strategy, Dr. Salmon stated, might encourage center directors to participate more freely if they know that shorter-term commitments are possible and conflicts of interest can be avoided.

The subcommittee also suggested extending existing Cancer Centers Support Grants administratively to change their review cycles and avoid conflicts of interest. Dr. Salmon added that the composition of *ad hoc* committees could include former members of the Cancer Center Support Review Committee. He noted that Dr. Margaret Holmes will prepare a letter for distribution to cancer center directors addressing these strategies and showing that excellent review can be attained with little *ad hoc* review.

Other topics of discussion included tracking of the cancer centers budget, definitions of translational research, and the minority enhancement program discussed by Dr. Lemuel Evans and its potential for receipt by cancer centers based on their ability to compete. Dr. Salmon concluded the report by noting that Dr. Evans drafted a letter reviewing opportunities for breast cancer research that was recently sent to the cancer center directors.

The minutes of the Cancer Centers Subcommittee were unanimously approved.

**Environmental Carcinogenesis**

Dr. Pelayo Correa served as acting chairman for this subcommittee in Dr. Becker's absence. Dr. Correa reported that Dr. Brenda Edwards of the NCI Surveillance, Epidemiology, and End Results (SEER) Program reviewed the most recent statistics for brain tumors at the meeting. She estimated that there will be 17,500 cases of brain cancer and 12,000 deaths from this disease in 1993. There has been an increased incidence of, but a slight decrease in mortality from, brain cancer among persons under the age of 65, and incidence and mortality are both increasing among those over the age of 65. Dr. Correa noted that Dr. Edwards suggested that the increase in incidence could be attributed to improved imaging and diagnostic techniques. She also informed the group that brain cancer has two peaks—one in childhood and one in adults.

Dr. Jerry Rice, Chief of the Laboratory of Comparative Carcinogenesis, DCE, NCI, presented an overview of the causation of brain tumors in animals by viruses, x-rays, and chemicals. Dr. Correa stated that Dr. Rice emphasized x-rays and chemicals as important means of tumor causation. Dr. Rice addressed the question of transplacental carcinogenesis, noting that there are many indications in animals that this is an important route for factors that increase risk. For example, 150 milligrams of ethylnitrosourea will produce brain tumors in an adult animal, while the dose to produce similar tumors in the offspring is 3 milligrams. Thus, Dr. Correa emphasized, an adult tumor may have been induced during pregnancy.

Dr. Susan Preston-Martin of the University of Southern California School of Medicine reviewed the epidemiology of brain tumors. Dr. Correa related that brain cancer represents 2 percent of cancers in adults and 20 percent in children. There is a significant relationship between higher incidence of brain tumors and higher socioeconomic status among men, but not among women. Dr. Preston-Martin outlined three main classes of brain tumors: glial tumors, which are most often malignant; meningeal tumors, which are not malignant; and neural sheath tumors, the most important of which is the acoustic neuroma.

Dr. Preston-Martin reviewed the different risk factors for acoustic neuromas, one of which is x-rays. Dr. Correa reported that the best human data on this causation comes from Israel. Among 15-year-old Israelis exposed to treatment for ringworm infection, x-rays increased the risk 15 times for a neural sheath tumor, 9 times for meningiomas, and 2 times for gliomas. Trauma is another important factor for brain tumor causation. Dr. Preston-Martin presented statistics and cases in which trauma to the head was followed by the development of meningiomas. She also presented evidence that excessive noise will result in an increased

incidence of acoustic neuroma, and some biologic hypotheses regarding damage to hair (Schwann) cells. With the subsequent regeneration of surviving Schwann cells, there is an increased chance of DNA copying errors or fixation of previous mutations by DNA replication. Dr. Preston-Martin also emphasized the role of N-nitroso compounds that appear to be the most probable chemical carcinogen in man and produce cancer in animals.

Dr. Peter Inskip of the Epidemiology and Biostatistics Program, DCE, NCI, described the planned NCI case-control study on risk factors for brain cancer in adults in the United States, involving 800 brain tumor cases and 800 hospital controls (without tumors). The study will focus on occupational, medical, hormonal, dietary, and other lifestyle exposures, and inherited susceptibilities, in addition to cellular telephones. It will be conducted in four or five hospitals in urban areas.

The minutes of the Environmental Carcinogenesis Subcommittee were unanimously approved.

**Program Project Task Force**

Dr. Samuel Wells reported that the substance of this subcommittee's report relates to a motion concerning a 3-year trial of P01 peer review using a two-tier initial review system, made by Dr. Salmon and seconded by Dr. Day. The first tier would involve site visit teams composed of a combination of *ad hoc* reviewers and parent committee members, similar to the special review committees in having pertinent scientific expertise. All original competing applications normally would be eligible to receive a site visit or applicant interview. Site visit teams would provisionally score individual components and make tentative recommendations on the integration of the program. Parent review committees (ultimately to be chartered) would not normally re-review the science of individual components, but would focus on evaluation of the overall scientific program, its integration, synergy, innovation, and uniqueness and then assign the overall priority score of record. Dr. Wells stated that it would be necessary to charter three or four committees to provide the expertise needed to review the full range of P01 applications received by NCI. Alternatively, one committee with three or four subcommittees could be created as the single chartered "parent" panel.

Dr. Wells reminded the Board that this is a 3-year trial, and that there will be an interim report for the NCAB to monitor progress. The motion was passed unanimously.

Dr. Wells reported on the Task Force's final order of business—the release of updated P01 guidelines. The 1987 guidelines have been modified to reflect conformance to changes and NIH review policies in the 9/91 revised PHS 398 application kit. Dr. Wells pointed out that the changes are summarized on pages three and four of the 1993 draft P01 guidelines, which were distributed to Board members. He explained that the guidelines cannot be released without approval of the NCAB. Thus, Dr. Wells called for a vote of approval of the subcommittee report and the P01 guidelines.

Dr. Correa commented that he has received three documents concerning P01 review—a review of the 20 P01 applications performed as a ranking experiment for the current Board round, an evaluation of the Ranking Panel experiment, and another document essentially stating that another layer of review will not solve the problem of score compression. Mrs. Bynum explained that the proposed return to a chartered committee structure is in no way analogous to the P01 ranking experiment, in which the Panel was given separate and independent review criteria and was specifically proscribed from reviewing the science of the applications. The NCAB Task Force, she explained, is recommending the resumption of a method of peer review that was in place before the current *ad hoc* system and included consideration of the evaluation of programmatic aspects and those characteristics that define a P01 as an initial review.

Mrs. Bynum noted that the actions of the one-time-only P01 Ranking Panel merely indicated that superimposition of criteria that are not normally, and never were, part of the initial review process seemed not to have any beneficial effect. She surmised that the experiment failed because it was difficult for the panelists to compartmentalize or refrain from reflecting on their view of the raw merit of the science, as opposed to the more global criteria of synergy, relevance, and importance of the questions being asked. Mrs. Bynum clarified that Dr. Salmon's suggestion, in effect, would empower the parent committee with the right to make changes based on other issues. It was noted that since the NCAB has some responsibility for these considerations as well, staff will be careful to formulate a structure for the new parent committee(s) that will provide a better rank ordering but not impinge on the Board's prerogative to make programmatic recommendations.

Dr. Correa posed the problem of assigning a project on molecular carcinogenesis and a project on social aspects to one review group. Mrs. Bynum replied that by reverting to the two-tier initial review process employing a standing parent committee, the scientific imperatives would be fully addressed initially, separate from the overall parent committee consideration. She emphasized that science will not be shortchanged in any mode presented. Mrs. Bynum stated that the Task Force felt that a return to the two-tier review would be the best way of achieving some ranking introduction of program project consideration, as well as considerations in the state of the science and the NCI program. Dr. Wells added that concern about heterogeneity of P01 grants and obtaining a fair overview was discussed at length and was a point of debate. He stated that fair overview depends on the consistency of the committee. Annual tracking and the 3-year review of the process would lessen any potential downside risk.

Dr. Broder stated that the need to decide on funding priorities among different disciplines is not unique to P01s, but is within the structure of all research project grants. It is sometimes necessary after peer review has been completed to weight percentiles for grant topics to develop funding priority. Dr. Broder expressed his concern, nevertheless, about human bias of certain proposals by peer reviewers. Peer review, he said, is supposed to gauge the scientific priority of a grant on some relative scale. Dr. Broder stressed the importance of prioritization. He restated the peer review committee's goal of trying to adhere to the scientific ranking priority in making funding decisions. It is important, Dr. Broder emphasized, to encourage people to make choices among closely ranked alternatives, and that, in the absence of competition, applications reviewed one at a time often cannot be accurately ranked. Dr. Broder noted that the program project portfolio is excellent and has a high success rate. He stated his concern that the recommended system will need to address the issue of encouraging reviewers to provide scientific priorities by rank ordering applications in some useful way.

Dr. Salmon announced that he had to leave the meeting, but he would vote in favor of the parent committee motion. On a separate point, he indicated that Dr. Correa appropriately noted the apparent dichotomy between the evaluation performed in the Ranking Panel experiment and the recommendation of the initial review group, but the evaluation system used by the Ranking Panel specifically stated that science was not to be re-reviewed. Dr. Salmon stated that the Ranking Panel did not appear to incorporate the science and relate the applications to one another, but looked only at the scores and somehow rank ordered the applications on the basis of the stated criteria. The Ranking Panel experiment did not result in a significant change because of the Panel's inability to relate new scientific merit to the various fields. The experiment had been done because the subcommittee felt that this process might lead to decompression of scores and deserved to be viewed only as an experiment. Dr. Salmon noted that only the summary statements, not the grants themselves, were reviewed.

Dr. Wells called for a vote on the motion and report. The minutes of the Program Project Task Force and the motion for new P01 guidelines were approved with one opposing vote.

**Information and Cancer Control**

Ms. Marlene Malek reported that the grant application deadline for the regional breast cancer summits was May 7, 1993. She announced that a number of major summits and an additional number of mini-summits will be funded. Peer review of applications was scheduled for June, with awards to be made between August and September. The summits will occur between October 1993 and June 1994. Ms. Malek said that a successful workshop for potential applicants was held earlier this year with more than 80 participants.

Ms. Malek stated that Dr. Ed Sondik, Deputy Director of the Division of Cancer Prevention and Control, briefed the subcommittee on *Healthy People 2000*, a set of Department of Health and Human Services goals related to health promotion, health protection, and disease prevention. Dr. Sondik told the subcommittee that the NCI is the lead agency for coordinating efforts to meet the report's cancer goals. The NCI's Year 2000 objectives have been integrated into the *Healthy People 2000* goals. Ms. Malek announced that the subcommittee decided to organize a 2-hour meeting in September to review progress toward achieving both Year 2000 and *Healthy People 2000* goals. Dr. Sondik, she said, indicated that new SEER data, as well as new information from the National Health Interview Survey, may be available by the September meeting and will serve as indicators of progress.

Because the NCI Year 2000 objectives have been integrated into the *Healthy People 2000* goals, Ms. Malek told the Board that the subcommittee unanimously voted in favor of renaming the subcommittee "Information and Cancer Control," instead of Information and Cancer Control for the Year 2000.

Ms. Malek reported that several members of the subcommittee suggested repeating the series of public participation hearings that the Board conducted in 1987 and 1988. The 1987-1988 meetings, she explained, were designed to allow the Board to collect information on non-Federal efforts to achieve the Year 2000 goals and to identify gaps in those efforts through testimony. Ms. Cecile Johnson of Prospect Associates reported on evaluations of the 1987 and 1988 hearings, which were conducted in 1988 and 1992 and consisted of interviews with Board members who ran the hearings and individuals who testified. The evaluations showed that the hearings had met the first objective of informing NCAB members about community programs, but it had been too early to judge the extent to which the hearings had reached the second objective of raising public awareness. The subcommittee voted unanimously not to recommend another round of hearings, after weighing the expertise, amount of resources, and time required to carry out such a venture, and the potential benefits. Ms. Malek reported that Dr. Bettinghaus suggested that instead of conducting hearings, the Board should encourage financial support for Cancer Centers to collect information on how well cancer control is being addressed at the community level.

Ms. Malek conveyed Dr. Bragg's statement that the scientific debate on mammography screening guidelines is confusing to the public. Dr. Bragg added that it is important to emphasize that screening has great benefit for women over the age of 50.

The minutes of the Information and Cancer Control Subcommittee were unanimously approved.

**Interactions With Voluntary Organizations**

Dr. Walter Lawrence reviewed the subcommittee meeting held on April 19, 1993, which brought together representatives of voluntary organizations to discuss steps to enhance NCI communication with outside groups. He reported that representatives were present from the American Cancer Society, Us Too, the Cancer Control Research Network, Candlelighters, and the National Coalition for Cancer Survivorship. Dr. Lawrence noted that a representative of the National Alliance of Breast Cancer Organizations did not attend but sent an excellent report.

Dr. Lawrence reported that the group recommended that the NCI conduct a needs assessment of the organizations as a first step in determining appropriate communications mechanisms. The list of organizations to be contacted for this assessment would be broadened to include as many potentially relevant groups in the database as possible.

All subcommittee members endorsed the idea of a needs assessment survey. They reviewed a draft version of the survey and recommended changes and additions. The next step, Dr. Lawrence stated, is to ask the Office of Communications to conduct the mail-in survey this summer, analyze the results, and present the findings to the subcommittee at the September meeting. The subcommittee will then make recommendations to the full Board.

Dr. Lawrence explained that by approving the subcommittee's minutes, the Board would also be approving the process of this survey. The minutes of the Interactions With Voluntary Organizations Subcommittee were unanimously approved.

**Minority Health, Research, and Training**

Ms. Zora Brown reported that this subcommittee had an extensive agenda for its meeting. There was not enough time to discuss involvement of minority institutions and investigators in breast cancer research and training, collaboration with other NCAB subcommittees to broaden minority participation across the board, and the relationship between health care reform and minority health research and training. However, Dr. Vincent Cairoli presented an update on a draft NIH notice for Phase II of the Minority Recruitment Plan requirement on Institutional Training Grants. Ms. Brown explained that this notice will clarify the NIH policy for recruiting and training underrepresented minorities and will change the emphasis of peer review procedures from "an adequate plan" to an evaluation of actual progress and success. Beginning with the September 10, 1993, receipt date, she continued, principal investigators must provide data on the ethnic/racial distribution of students in the department, and information on those applying, offered admission, appointed, and completing the training program. Also, annual progress reports must contain recruitment and retention data.

Ms. Brown told the Board that the subcommittee welcomed the plan to evaluate progress in recruiting and retaining minority trainees, but members expressed concerns about implementation and actions to be taken in instances of noncompliance or lack of progress during noncompeting years. One member suggested that the NIH should follow the same rules that it requires universities to follow.

Ms. Brown reported that Dr. Lemuel Evans provided an informational update on the Minority Enhancement Award concept approved at the February 1993 NCAB meeting. An RFA for this concept is under development and will be published during this fiscal year, with awards anticipated for fiscal year 1994.

Ms. Brown related that the issue of expanded minority involvement in breast cancer research and training was discussed. It was noted that existing mechanisms, including career

awards, could be used to encourage individual participation in research and training targeted to breast cancer.

Problems related to minority patient accrual to clinical trials were pointed out, especially in the Washington, DC, area. Dr. Robert Frelick described the success in recruiting minority patients in a clinical trial program based in Chicago (Hyde Park) and suggested that this program should be studied carefully for possible duplication. This idea was recommended as a possible motion but was tabled due to a lack of available discussion time.

Regarding concerns about nonimplementation of the new procedure to evaluate progress in recruiting minority trainees, Mrs. Bynum reminded the Board that the Cancer Training Branch (including Dr. Cairoli) presented options for addressing noncompliance in the first phase a couple of years ago. She added that these options, such as funding for a shorter period of time than recommended by IRG, are in the presentation of a plan. Mrs. Bynum recommended that Dr. Cairoli and Dr. Evans form an approach for dealing with nonconcurrence in Phase II for NCAB review. Ms. Brown stated that this suggestion would be helpful, and added that this subcommittee will try to meet before September to develop suggestions.

Dr. Wilson commented that he was impressed with the University of Chicago's recruiting success and suggested a presentation for the next subcommittee meeting on the university's recruitment procedures and statistics. Dr. Wilson added that it might be possible to invite a representative from the University of Chicago to speak about this procedure.

Dr. Day suggested having a presentation on plans for recruitment of minorities and underserved populations by various institutions and cooperative groups.

The minutes of the Minority Health, Research, and Training Subcommittee were unanimously approved.

**Planning and Budget Task Force**

Dr. Erwin Bettinghaus called the Board's attention to two different meeting reports of the Planning and Budget Task Force—one from the May NCAB meeting and the other from a meeting in Chicago on March 24th where the Bypass Budget was discussed.

Dr. Bettinghaus expressed the subcommittee's agreement with Dr. Broder's suggestion that the Bypass Budget should be a scientific document that expresses the actual scientific needs of the NCI. Dr. Bettinghaus added that the committee feels strongly that the science should be presented clearly, coherently, and consistently, and should reflect the progress of particular program areas. He explained that he reviewed the last nine Bypass Budgets and found little continuity in the documents prior to 1994. Thus, on behalf of the committee, Dr. Bettinghaus strongly congratulated Dr. Judith Karp and Dr. Daniel Ihde for introducing consistency into the production of the 1994 and 1995 Bypass Budgets. He added that the 1996 Bypass Budget will follow the current pattern for readability and continuity. Dr. Bettinghaus concluded that specific suggestions for the 1995 Bypass Budget are included in the March 24th and May 4th minutes.

The minutes of the Planning and Budget Task Force were unanimously approved.

**Women's Health and Cancer**

Dr. David Bragg reported, in Mrs. Johnson's absence, that the May meeting of this subcommittee focused entirely on breast cancer. Ms. Iris Schneider informed the committee about the Institute of Medicine's report on the Department of Defense's $210 million breast

cancer funding. The report was submitted to the DOD and will be made public at the end of May. Dr. Bragg explained that the National Breast Cancer Coalition is supporting the NCI 1994 bypass request for breast cancer, but will also lobby for continued funding for a breast cancer research program in the DOD, which is not included in the President's budget request for 1994.

Dr. Bragg stated that the largest portion of this committee's report consists of a summary of the January conference on Breast Cancer in Younger Women (women under the age of 40). About 6.5 percent of all breast cancers occur in this age group. Dr. Bragg described unique factors of breast cancer in this subpopulation. Although there are conflicting data, stage for stage, the prognosis for younger breast cancer patients appears to be less favorable than for older women. Dr. Bragg reported that findings regarding the timing of surgery during the menstrual cycle and follicular phase of the cycle were presented and warrant further investigation.

Dr. Bragg reported that evaluating surgical ovarian ablation, as opposed to hormonally induced ovarian ablation, was suggested at the conference. Dr. Bragg noted that further attention and additional funding are needed for investigating the psychosocial impact of breast cancer in younger age groups and educating health care providers who are not always well informed about the incidence and management of breast cancer, especially in younger women.

Dr. Bragg reported that Ms. Brown expressed concern about the rising incidence of breast cancer among young African Americans. She emphasized the importance of educating this population and health care providers about the evaluation, risk factors, and workup of breast cancer in this group. The subcommittee, Dr. Bragg stated, expressed similar concern about the confusing debate about the role of mammography in breast cancer detection. The controversy over screening younger women has led to reduced utilization of mammography among women over the age of 50. On behalf of Dr. Bragg, this subcommittee urged the Subcommittee on Interactions With Voluntary Organizations to help disseminate a focused and positive message about the role of mammography.

Dr. Day asked whether there was any discussion about estrogen replacement at the January conference. Ms. Brown answered that this topic was discussed; there was no definitive conclusion about whether estrogen replacement should be recommended to younger women.

The Board unanimously approved the minutes of the Women's Health and Cancer Subcommittee.

## XIII. NEW BUSINESS

Dr. Day pointed out that the proposal for health care reform will probably be presented prior to the next NCAB meeting. He emphasized the importance of the leadership initiatives and their significance to health care reform. From the perspective of the research community, Dr. Day stated, reimbursement for screening or health care is a key item on the future health care agenda. He added that this topic was discussed in the Planning and Budget subcommittee meeting because the next Bypass Budget may have to allocate a substantial amount of money for payment of clinical trials not reimbursed by third parties under health care reform. Dr. Day stressed that someone must pay for health care costs if clinical research is to continue. Thus, Dr. Day requested that the best cost information or best estimates be obtained from cancer centers, cooperative groups, and other sources. He stated that this is an important request, and these figures should be examined at the September NCAB meeting. Dr. Day concluded that

this Board has an obligation to express its concerns about features of the plan that may have adverse effects and endorsement of positive features. Mrs. Bynum assured Dr. Day that this request will appear as an action item of this meeting and that the Executive Committee and Dr. Calabresi will recommend the best method of addressing this issue. Dr. Wells suggested that this topic appear as an agenda item at the next meeting. Dr. Sigal agreed with Dr. Wells, and encouraged the Board to be more proactive on this issue and form a vehicle with which it can express its priorities.

Dr. Chan requested that the NCI prepare a plan of the impact of committee reductions on the review process. Mrs. Bynum explained that there have been no reductions thus far, because the NIH is awaiting a response to its submission to the Office of Management and Budget. The individual Institutes, she continued, have been asked to justify the continuation of the extant advisory committees and identify which committees could be terminated within this fiscal year. The issue of creating new committees has not been raised. Mrs. Bynum noted that Secretary Shalala expressed her support of peer review or whatever is required to conduct this aspect of the NIH. Mrs. Bynum agreed to Dr. Chan's request to provide the NCAB with information on this subject.

## XIV. ADJOURNMENT

There being no additional business, Dr. Wells thanked the group for their participation and adjourned the 86th National Cancer Advisory Board meeting at 12:18 p.m.

_____ _____

Date Dr. Paul Calabresi, Chairman