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

Summary of Meeting
January 10-11, 1995

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]
January 10-11, 1995

The National Cancer Advisory Board (NCAB) convened for its 93rd regular meeting at 8:00 a.m., January 10, 1995, in Building 31, C Wing, 6th Floor, Conference Room 10, National Institutes of Health (NIH).

NCAB Members

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

President's Cancer Panel

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

Alternate Ex Officio NCAB Members

Dr. Robert Delap, FDA
Dr. Marilyn A. Fingerhut, NIOSH
Captain Bimal C. Ghosh, DOD
Dr. Aparna Koppikar, EPA
Dr. Lakshmi C. Mishra, CPSC
Dr. Gerald Poje, NIEHS
Dr. Raymond L. Sphar, DVA
Dr. P. C. Srivastava, DOE
Dr. Ralph Yodaiken, DOL

Members, Executive Committee, National Cancer Institute, NIH

Dr. Samuel Broder, Director, National Cancer Institute
Dr. Edward Sondik, Acting Deputy Director, National Cancer Institute
Dr. Jerry Rice, Acting Director, Division of Cancer Etiology
Mr. Philip D. Amoruso, Associate Director for Administrative Management
Dr. Marvin R. Kalt, Director, Division of Extramural Activities
Dr. Bruce A. Chabner, Director, Division of Cancer Treatment
Dr. Peter Greenwald, Director, Division of Cancer Prevention and Control
Dr. Alan S. Rabson, Director, Division of Cancer Biology, Diagnosis, and Centers
Mrs. Iris Schneider, Executive Secretary, Asst. Director for Program Operations and Planning

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

Liaison Representatives

Dr. John Currie, American Association for Cancer Education, Inc.
Dr. Edwin A. Mirand, Association of American Cancer Institutes
Ms. Margaret Foti, American Association for Cancer Research, National Coalition for Cancer Research
Dr. Marc E. Lippman, American Association for Cancer Research
Dr. Robert Martuza, American Association of Neurological Surgeons
Ms. Kerrie B. Wilson, American Cancer Society
Dr. John Laszlo, American Cancer Society
Dr. Robert W. Frelick, Association of Community Cancer Centers
Dr. Stanley Zinberg, American College of Obstetricians and Gynecologists
Dr. Bernard Levin, American Gastroenterological Association
Dr. Edward P. Gelmann, American Society of Clinical Oncology, Inc.
Dr. Stanley Order, American Society of Therapeutic Radiologists
Mr. James Kitterman, Candlelighters Childhood Cancer Foundation
Ms. Linda Johnson, Oncology Nursing Society
Ms. Pearl Moore, Oncology Nursing Society
Ms. Dorothy J. Lamont, National Cancer Institute of Canada
Dr. J. David Beatty, National Cancer Institute of Canada
Dr. James H. Brown, National Science Foundation
Dr. Tracy Walton, National Medical Association
Dr. Marston Linehan, Society of Urologic Oncology
Dr. Jeffrey Norton, Society of Surgical Oncology, Inc.

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

Dr. Barbara Rimer called to order the 93rd meeting of the National Cancer Advisory Board. She wished everyone a happy New Year and welcomed a new member, Dr. Kay Dickersin, to fill the Board's last vacancy. She noted that Dr. Dickersin, an epidemiologist at the University of Maryland, was appointed through her affiliation with the National Breast Cancer Coalition (NBCC). Dr. Rimer acknowledged Dr. Dickersin's importance to the Board—both as a representative of the NBCC and as a scientist.

Dr. Rimer introduced guests representing a number of respected organizations and societies dedicated to cancer education and research, as well as Federal agencies whose activities impact cancer-related issues. She welcomed the members of the public and asked them to express their views on items discussed during the meeting by writing to Dr. Marvin Kalt, Executive Secretary of the Board, within 10 days of the meeting.

Dr. Rimer referred to the meeting dates set for 1995, noting that they are spread more evenly throughout the year than they were in 1994 and that while 3-day meetings are scheduled, it is hoped that they will not require more than 2 days each. She announced that efforts will be made to start the May meeting at midday to accommodate the west coast members and requested that the Board notify Dr. Kalt as soon as possible if there are conflicts with any of the scheduled meeting dates. She also requested that Board members inform Dr. Kalt by the end of the coffee break of any grant applications they wished to discuss.

Dr. Rimer called for approval of the minutes of the December meeting, which were unanimously approved without change. She emphasized the need for those present to attend the full meeting to ensure a quorum of 10 voting members. She stressed the fullness of the meeting's agenda, the need for adherence to allotted speaking times, and the importance of speakers' use of their microphones for purposes of transcribing the minutes.

Dr. Rimer announced that following lunch, a full schedule of subcommittee meetings would be held, as listed in the agenda, followed by a closed session. As an overview, she informed the Board that the meeting would include grant review, regular presentations, and special presentations on BRCA1, a melanoma antigen, the Arizona Cancer Center, the National Action Plan on Breast Cancer, and a presentation by Dr. Edward Bresnick of the American Association for Cancer Research (AACR).

Dr. Rimer introduced Dr. Harold Freeman, Chairman of the President's Cancer Panel (PCP), to update the Board on the last PCP meeting.

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

Dr. Freeman began his presentation by recognizing Ms. Visco for her representation of the PCP at the December NCAB meeting in his absence, explaining that he was serving as the Chair on a component ad hoc meeting of the President's Cancer Panel to examine the Federal

Trade Commision's (FTC's) cigarette testing method. He stated that he would discuss the reasons for that meeting and its resulting recommendations.

Dr. Freeman indicated that in 1967, the Federal Trade Commission began testing cigarettes for tar and nicotine content using a standardized, machine-based protocol developed by the FTC itself. This protocol was later broadened to include the measurement of carbon monoxide. Design changes over the years, including the use of ventilated tobacco rods and filters, improved filtration, use of more porous cigarettes, increased use of reconstituted tobacco seeds, and manufacturer additives, have resulted in a lowering of smoke constituents, as measured by the FTC-based method.

Dr. Freeman explained that during the 1980's, preliminary questions were raised by both public health officials and tobacco industry sources about the accuracy of the FTC method to measure tar, nicotine, and carbon monoxide in these redesigned cigarettes—whether these testing methods actually duplicated human smoking behavior. In 1983, the FTC announced that their testing method did understate the values for smoke constituents in cigarettes and, consequently, the FTC testing laboratory was closed. Dr. Freeman explained that under the continued oversight by the FTC, the responsibility for the complex and costly testing programs was assumed by the Tobacco Institute on behalf of the cigarette manufacturers.

Dr. Freeman pointed out that due to the concerns regarding the limitations of the current test system, Rep. Henry Waxman, at the time the Chairman of the House Subcommittee on Health and the Environment, asked the National Cancer Institute (NCI) to convene a meeting of experts to review and make recommendations on the accuracy and appropriateness of the FTC's methods for determining the relative tar and nicotine content of cigarettes. The FTC, also recognizing these same concerns, requested that the NCI convene a meeting to examine how tar and nicotine ratings are determined, and to respond to suggestions made by public and private health groups that such ratings, relating to the differing reported levels of tar and nicotine, may mislead customers about the risk of smoking. Dr. Freeman indicated that over 26 experts in health, pharmacology, toxicology, chronic disease epidemiology, social and behavioral science, medicine, and addiction research, as well as representatives from the tobacco industry, were invited to present and comment regarding the validity of the FTC test method.

The panel assembled for this ad hoc meeting comprised 11 experts who were asked to respond to three questions: 1) Does the evidence presented clearly demonstrate that changes are needed in the current FTC protocol for measuring tar, nicotine, and carbon monoxide and, if so, what changes are needed? 2) Should constituents other than tar, nicotine, and carbon monoxide be added to the protocol? 3) Does the FTC protocol provide information that is useful to consumers in making decisions about their health?

Based upon their review of the FTC method, the committee came to the following conclusions: 1) the smoking of cigarettes with lower machine-measured yields has a small effect in reducing risk of cancer caused by smoking, no effect on the risk of cardiovascular disease, and an uncertain effect on the risk of pulmonary diseases; and 2) reducing the machine-measured tar yield from 15 milligrams of tar to 1 milligram of tar does not reduce relative risk equivalently. The FTC test protocol was based on cursory observations of human

smoking behavior, while real smoking behavior is characterized by wide variation. This results in similar wide variations in tar and nicotine exposure (i.e., smokers who switch to lower tar and nicotine cigarettes frequently increase the number of cigarettes they smoke, thereby negating any potential health benefit).

Based on these findings, Dr. Freeman continued, the committee recommended that the use of the FTC protocol be changed to measure and publish information on the range of tar, nicotine, and carbon monoxide yields that smokers should expect from cigarettes sold in the United States. He indicated that this information must be clearly conveyed to the smoking public with a simple graphic representation on each pack of cigarettes and on all cigarette advertisements. He pointed out that the representation between tar, nicotine, and carbon monoxide measurements should in no way imply a 1:1 correspondence with disease risk. Equally important, it was recommended that all such information be accompanied by public education to alert smokers that individual exposure depends on how a cigarette is smoked (i.e., individuals who smoke low-dose cigarettes can get doses equivalent to the high-dose cigarettes by puffing more deeply or covering the holes in the cigarette filter). The benefits of switching to lower-yield cigarettes are small when compared with the benefits of quitting. This factor should also be illustrated. Dr. Freeman explained that the committee advocated continued Federal oversight of cigarette testing, and that such testing should continue to be performed by the tobacco industry at its expense.

The committee also concluded that issues surrounding the FTC protocol are extremely complex and require ongoing involvement of Federal health agencies, including the National Cancer Institute, National Institutes of Health, the Food and Drug Administration (FDA), and the Centers for Disease Control and Prevention (CDC). Further, regardless of the testing method and use, any such system should be reexamined at least every 5 years to determine whether the testing regimen is keeping pace with changes in smoking technology, and whether it remains useful to the smoker in conserving health risks. This reexamination process will require that any changes made in cigarette design that affect yield must be clearly communicated to the appropriate Federal agency.

Dr. Freeman then addressed the third issue posed to the panel. When considering how much information regarding cigarette components to convey to the public, the committee recommended that no levels of smoke constituents other than tar, nicotine, and carbon monoxide be published at the current time. However, it would be appropriate for each package and advertisement to contain a listing of other hazardous components of tobacco smoke, classified by toxic effect.

The committee noted that information from the testing system is useless to smokers unless it is readily available to them. Information regarding constituent levels in smoke from generic and other less-advertised, or underadvertised, brands is currently not consistently available and must be made available to the smoking public. In this context, Dr. Freeman stated, the committee concluded that brand names or classifications such as "light" and "ultra" represent health claims which should be regulated and represented in fair balance with an appropriate disclaimer. Finally, Dr. Freeman stated, the available data presented during the course of the meeting suggested that smokers misunderstand the FTC test data and underscored the need for an extensive public education effort.

The committee also emphasized the need for additional research regarding smoking behavior and measurements, including: 1) the extent to which smokers of lower tar and nicotine cigarettes are less likely to attempt to quit smoking; 2) the extent to which biomarkers other than nicotine derivatives are correlated with machine-measured yields of the same substances; 3) how smoking topography in ethnic groups differs and what this implies for health and consumer education; and 4) the development of a system to help smokers gauge where their individual smoking behavior places them on the dose continuum.

Finally, Dr. Freeman pointed out that a full report of the ad hoc panel's concerns and recommendations is being prepared for approval by the President's Cancer Panel and will subsequently be available to the public.

Questions and Answers

Dr. Correa asked for an explanation of the FTC oversight process and its guarantee of protection.

Dr. Freeman explained that the cigarette constituent testing has been performed for a number of years by the tobacco industry due to the high Government expense involved. He stated that Federal experts view the testing as accurate. He further explained that the testing is undertaken by several tobacco companies and, because of industry competition, the FTC believes that the testing is sound. Although the testing is sound, Dr. Freeman indicated a limitation in that the process is carried out through a machine-based protocol. He explained that individuals smoke differently than machines (i.e., people may puff more deeply on the cigarette and/or cover the holes in the filter). These characteristic differences may lead individuals who smoke low-dose cigarettes to receive doses equivalent to those found in the high-dose cigarettes. Thus, the data gathered by machine cannot be extrapolated to the general population.

Dr. Yodaiken asked whether the information that is disseminated to American smokers will also be given to smokers in countries to which the tobacco industry exports cigarettes. Dr. Freeman explained that this issue has not been discussed, although it is a topic worth considering.

Dr. Sigal asked what the next step will be with the recommendations that have been developed. Dr. Freeman responded that since Congressman Waxman is no longer Chair of the House Subcommittee on Health and the Environment, it is uncertain what will happen at the Congressional level. He stated that this is an issue that involves the health of the American people—individuals need to know what they are smoking. He stressed that the Federal Trade Commission seems to be driven by the concept of truth in advertising and may find that the method used to advertise cigarettes contains false and misleading information. Finally, Dr. Freeman indicated that the Food and Drug Administration is currently considering possible methods for regulating tobacco to improve the constituent levels and quality of cigarettes.

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

Marking the occasion of his 25th, and last, address to the National Cancer Advisory Board as Director, Dr. Broder stated that he considers his most important accomplishment as NCI Director to be strengthening the role of clinical research. One of the most difficult challenges, he noted, was the fact that investigator-initiated clinical research could not be easily supported within the current NIH grant-making format. The choice, Dr. Broder observed, was to fight the study section system or develop appropriate adaptive functional processes to address the problem.

In a series of slides, Dr. Broder provided examples of several Requests for Applications (RFAs) that were aimed at achieving a balance between the needs of basic researchers and clinical researchers. These covered the total spectrum of cancer research, including issues related to survivorship, tissue banking, development of novel agents, therapies for breast cancer, cancer prevention and control, and gene therapy.

Summarizing recent National Cancer Institute staff changes, Dr. Broder mentioned that Dr. Bruce Chabner will be leaving in May 1995 to join the staff of Massachusetts General Hospital. Following the retirement of Dr. Richard Adamson as Director of the Division of Cancer Etiology, Dr. Broder announced, Dr. Jerry Rice, Associate Director of the Frederick Cancer Research and Development Center (FCRDC), has been appointed as Acting Director. Dr. Broder reported the announced retirement of Dr. Herb Blatner as Chief of the Viral Epidemiology Branch, Dr. Robert Gallo as Chief of the Laboratory of Tumor Cell Biology, Mr. Nick Olimpio, Division of Cancer Prevention and Control Administrative Officer, and Dr. Ken Brow as Chief of the Research Facilities Branch and the Centers, Training, and Resources Program.

On a happier note, Dr. Broder continued, Dr. Judith Karp has been appointed as Assistant Director for Applied Science. She will be responsible, he explained, for identifying areas of basic and preclinical discoveries that can be translated into clinical applications. Dr. Karp received her M.D. from Stanford University, served as an associate professor at Johns Hopkins University, and specialized in leukemia growth factors and therapies for leukemias of all types. An NCI staff member since 1990, Dr. Karp has served as Editor-in-Chief of the Institute's Bypass Budget document.

Turning to recent developments in cancer statistics, Dr. Broder reported that from 1989 to 1992, there was a clear decline in the breast cancer death rate among American women. The death rate among White women declined by 6 percent, the largest short-term decline since 1950. While the decline among White women applied to virtually every age group, the decline for those in the 30 to 39 age group was nearly 9 percent between 1989 and 1992 and roughly 18 percent between 1987 and 1992. It is believed that several factors are involved in this decline, including adjuvant therapy, breast cancer awareness and screening, and changes in risk factors. For the very youngest women—those in their 30's—Dr. Broder suggested that adjuvant chemotherapy has almost certainly played a major role.

Unfortunately, Dr. Broder stated, African American women have not experienced a similar decline. Other examples of diseases for which there is a differential course of progress, he added, include prostate, cervical, colorectal, and head and neck cancers, as well as diabetes, hypertension, asthma, fetal distress, and many others. Dr. Broder noted that a key mission of the National Cancer Institute is to address the differential hardships that cancer and other diseases present for minority populations.

Although breast cancer still causes immeasurable suffering, Dr. Broder stated, these new statistics provide the basis for cautious optimism concerning progress against breast cancer. The research programs supported by NCI, he noted, have contributed and will continue to contribute to the reduction of deaths and suffering caused by this disease. Dr. Broder cited as examples the 20-year history of progress in adjuvant therapy, the much-debated clinical alert issued by Dr. Vincent DeVita in 1988, and the more recent consensus conference.

Turning to cancer-related news, Dr. Broder reported that a new drug, Navelbine, has received Food and Drug Administration approval as one of the first new treatments for non-small cell lung cancer in 20 years. Clinical trials have shown that this drug, used alone or in combination with cisplatin, prolongs patient survival. Dr. Broder pointed out that lung cancer is the leading cause of cancer deaths in the United States and that non-small cell lung cancer accounts for about 75 percent of all lung cancer deaths.

Dr. Broder announced that the NCI is preparing for Congressional appropriation hearings; House hearings are expected in March and Senate hearings, soon thereafter. The new Chair of the House Appropriations Subcommittee for labor, health, human services, education, and related agencies is Mr. John Porter of Illinois. The Senate group with the same responsibilities is chaired by Senator Arlen Specter of Pennsylvania. Dr. Broder mentioned that a more detailed report would be presented later during the meeting by Ms. Dorothy Tisevich of the NCI Legislative Affairs Office. He added that the NCI will need to articulate carefully the fact that cancer research is essential to the agenda of both political parties and forcefully resist the tendency to use NCI resources as an administrative reserve to meet shortfalls in other areas.

Dr. Broder stressed the fact that progress against cancer is made only when there is a balance in NCI's research programs. The three foundation stones for progress are basic research, clinical trials—in both prevention and treatment—and cancer centers. In the normal course of events, he observed, the focus changes as achievements or problems occur in one area or another; there is a constant process of stress and adjustment, accompanied by quiet work and heightened scrutiny. Dr. Broder stated that, as NCI Director, he has found it useful to stress the importance of clinical research when speaking to basic researchers and to stress basic research when speaking to clinical researchers. It is important, he said, for both groups to avoid a kind of narcissistic arrogance concerning the necessity of their own domains.

Dr. Broder observed that one's perspective changes on becoming NCI Director, whether one comes from within the Institute or from outside. He suggested that it is difficult, before assuming this post, to see how large and strong, and yet—paradoxically—how fragile the Institute is. He used the metaphor of a redwood tree, which is gigantic in size but has a surprisingly delicate root system. Part of the delicate ecosystem of NCI, he said, is the

American public. He described as brilliant and inspired Mary Lasker's concept concerning the response of Government researchers to human suffering and the expansion of this concept into a one-to-one linkage of research to specific diseases through categorical Institutes. Dr. Broder stated that, every day, people suffering from cancer look to the National Cancer Institute; for them, the value of research is immediately understood and intuitively obvious.

The strength of the NIH, Dr. Broder continued, is that it supports and shelters the categorical Institutes. He asserted that what is good for the NIH is good for the NCI, and *vice versa*; the agencies, he stated, are part of the same research body politic. Dr. Broder emphasized that the inherent genius behind the establishment of the categorical Institutes—of which the NCI, founded in 1937, was a prototype—is clear and should be held in the highest regard.

Commenting on the bipartisan rush to downsize Government, Dr. Broder warned against blaming Government workers for doing their jobs and stated that we should be careful not to eliminate the things that can only be done as core Government functions. It is easier, he said, to weaken or destroy an NCI or an NIH than to create a new one. A surgeon would point out that if you cannot look carefully where you are cutting, you can harm the patient; it does not matter, Dr. Broder added, whether the person doing the cutting is a friend or a stranger.

Dr. Broder noted that everything being done by the NCI is occurring because intelligent peer groups or astute members of the public have asked that it be done. Everyone at the Institute, he said, must be extraordinary in their abilities. Dr. Broder stated that his hope is that the next Director of NCI can be the last Director, because the research mission of the Institute—learning to cure and prevent cancer—will have been achieved.

In discussing transitional processes, Dr. Broder stated, it might be useful to consider the concepts expressed by the contemporary social philosopher, Judith Viorst, in her book *Necessary Losses*. He quoted briefly from the book:

"When we think of loss, we think of the loss through death of people we love, but loss is a far more encompassing theme in our life, for we lose not only through death but also by leaving and being left, by changing and letting go, and moving on. And our losses include not only our separations and departures from those we love, but our conscious and unconscious losses of dreams, impossible expectations, illusions of freedom and power, illusions of safety."

The book, Dr. Broder continued, describes such losses as necessary for personal growth and maturity. This is equally true, he suggested, for organizations. Dr. Broder said that while one person is not indispensable to an organization, people collectively are irreplaceable. While each person makes a unique contribution, the uniqueness is, paradoxically, possible only when there is change and renewal, and a welcoming of new spirits.

Dr. Broder mentioned that he is the tenth Director of the NCI and has served under three Presidents. He said he has had the privilege of working with an exceptional set of employees and advisors during his tenure, and thanked his colleagues and advisors individually and collectively for all they have given to the Institute. Referring to the NCAB, he expressed doubt that any public or private agency has been served by better men and women who have given so much and received so little in return. Moreover, he added, the NCI

has a truly exceptional group of grantees, more committed to the Institute than most grantees of comparable organizations. The NCI, Dr. Broder noted, also has strong private organizations and articulate consumer advocates behind it. He thanked all of these supporters, including those who have served on the NCAB, other advisory committees, and Boards of Scientific Counselors (BSCs).

Dr. Broder commended the NCAB, and particularly Dr. Paul Calabresi, who chaired the Subcommittee to Evaluate the National Cancer Program (SENCAP), for its report *Cancer at a Crossroads: A Report to Congress for the Nation.* He thanked Dr. Barbara Rimer for her insight and skill in succeeding Dr. Calabresi as Chair of the NCAB. He also thanked Dr. David Korn, who served as NCAB Chair before Dr. Calabresi. He thanked and expressed his admiration for the members of the President's Cancer Panel, including Ms. Frances Visco and Dr. Henry Pitot, and especially PCP Chair Dr. Harold Freeman. Dr. Freeman's experience, compassion, and rigorous intellect, Dr. Broder added, have made a unique contribution. He taught the cancer research community that poverty is a carcinogen and that it will be no easy task to remove this carcinogen from our society.

Dr. Broder suggested that it takes all participants meeting in mutual respect to ensure the health of the Institute. There are tensions, he acknowledged, but they are healthy. He noted that in the body, tension strengthens muscles, and in an organization, dynamic tension and challenges are essential to scientific progress.

Speaking for himself and others who are leaving, Dr. Broder stated that devotion to the NCI is a lifelong affliction. NCI employees, he said, feel that it is an honor to work for the Institute. They love the larger universe of the NIH, he added, but feel a sense of purpose from the NCI's mission to prevent and cure cancer.

Questions and Answers

Dr. Rimer asked whether Dr. Broder had any data on changes in breast cancer mortality for Black women. Dr. Broder said that there is a slight hint of a downward trend, but that there is a differential effect that is not being seen among African American women. He suggested that representatives of the Surveillance, Epidemiology and End Results (SEER) Program prepare a detailed presentation for the next NCAB meeting.

Dr. Rimer stated that the NCAB wished to express its appreciation to Dr. Broder for all that he has done during his tenure as NCI Director and to express its sadness that he will be leaving. She asked Dr. Paul Calabresi to say a few words.

Dr. Calabresi said that he first came to know Dr. Broder about 8 or 10 years ago, when he served as Chair of the Division of Cancer Treatment's Board of Scientific Counselors. Dr. Calabresi said that Dr. Broder always created extra work for him by proposing honors for individuals, committees, or prestigious societies, and asking for endorsements or letters of recommendation. He was struck, he continued, by the fact that Dr. Broder was always proposing honors and recognition for others, and never pushed his own agenda. Dr. Calabresi said that he saw the same trend when Dr. Broder became NCI Director. His agenda was a simple one—to do his best against cancer and for people. However, Dr. Calabresi noted,

Dr. Broder was not a spokesman concerning cancer alone, but made it clear that the NCI cannot survive without a strong NIH. Dr. Broder supported the other Institutes and showed an altruistic and balanced approach toward the NIH as a whole. Dr. Calabresi expressed his admiration for Dr. Broder's role as a team player.

Dr. Calabresi suggested that Dr. Broder's major contribution to the National Cancer Program (NCP) has been his balanced approach. He cited Dr. Broder's support for research on gene therapy, his interest in translational research as shown by his support for the Specialized Programs of Research Excellence (SPORE) program, and his role as a strong proponent of clinical research. NCI, he said, has a very strong clinical research program as a result of Dr. Broder's leadership and commitment to bringing basic findings to the clinic. He also mentioned Dr. Broder's efforts in the area of chemoprevention.

Dr. Broder's legacy, Dr. Calabresi concluded, is that of a leader steeped in basic science combined with a strong commitment to clinical investigation and translational research. He expressed three wishes in connection with Dr. Broder's departure: that his successor be as balanced, showing the same interest in basic, translational, and applied research; that Dr. Broder will join the NCAB as a member from the private sector; and that he and others present will see the end of cancer as a major public health hazard. He thanked Dr. Broder for his leadership and wished him luck in his new endeavors.

Dr. Rimer stated that Dr. Calabresi did a beautiful job in summarizing Dr. Broder's contributions to the National Cancer Program, and echoed his wish that Dr. Broder join the NCAB in the next round of appointments. She expressed her regret at having worked with Dr. Broder for such a short time, expressing her high regard for his commitment to scientific truth during the debate concerning mammography. She said that the Board will miss his wit and wisdom and his unwavering commitment to the National Cancer Program.

Dr. Rimer presented Dr. Broder with a wrapped gift, and shared with members that the inscription on the gift is from the writings of Goethe: "Daring ideas are like chessmen. Moved forward, they may be beaten, but they may start winning a game."

IV. NEW BUSINESS-SESSION I—DR. BARBARA RIMER

Dr. Rimer notified the Board of a request by Dr. Bresnick, of the AACR, to be considered an *ex officio* member. She asked the members to consider the request after hearing Dr. Bresnick's presentation, and reserve debate for the formal new business section on the following day. Dr. Kalt noted that the *ex officio* membership of the NCAB is codified in the Public Health Service Act, necessitating an act of law to effect any changes. In response to Dr. Rimer's request for new business items, Dr. Yodaiken raised the issue of formation of an *ex officio* subcommittee for later discussion. There being no further items of new business to discuss, Dr. Rimer turned the meeting over to Dr. Kalt to discuss the proposed RFA.

Presentation by Dr. Marvin Kalt

Dr. Kalt explained that there is an extramural program at NCI in his Division that deals with minority biomedical issues. Those involved with this program have proposed an RFA to address the challenges mentioned by Drs. Freeman and Broder of underrepresentation of minorities in clinical trials and of poverty in relation to illness. The proposal for conference grants, "Regional Conferences for Increasing Representation of Minorities in NCI Clinical Trials," was described in a handout to the Board and scheduled for presentation at the next day's new business session.

Dr. Kalt explained the concept of the proposed RFA in further detail. The program is intended to support regional conferences on methods of increasing minority recruitment and retention in clinical trials. It will follow a workshop format for program development, planning, and implementation to incorporate current knowledge of barriers to recruitment and new recruitment strategies. The program seeks to encourage cooperation among minority community organizations, cancer centers, clinical cooperative oncology groups, and medical institutions with national recognition and access to substantial numbers of minorities. Dr. Kalt predicted five awards would be made at a total cost of $125,000 and asked the Board to consider the concept for approval at the next day's meeting.

There being no further new business to discuss, Dr. Rimer asked Ms. Iris Schneider to introduce Dr. Susan Blumenthal and Ms. Frances Visco to discuss the National Action Plan on Breast Cancer.

V. NATIONAL ACTION PLAN ON BREAST CANCER—MS. FRANCES VISCO AND DR. SUSAN BLUMENTHAL

Ms. Iris Schneider introduced the next two speakers, whom she described as national leaders in the fight against breast cancer. One of the speakers, Ms. Frances Visco, is a member of the President's Cancer Panel and a partner in the Philadelphia law firm Cohen, Shapiro, Plisher, Shiekman, and Cohen, as well as a breast cancer survivor. She is a member of the board of the National Breast Cancer Foundation and the PCP's Special Commission on Breast Cancer, and was elected as the first president of the National Breast Cancer Coalition (the Coalition). Ms. Visco played a vital role in organizing the December 1993 Secretary's Conference, which was convened to begin development of a national action plan for breast cancer. She is currently acting as cochairperson of the committee responsible for development and oversight of the implementation of the Secretary's National Breast Cancer Action Plan (the Action Plan).

Ms. Schneider also introduced Dr. Susan Blumenthal, who is the Deputy Assistant Secretary (Women's Health) in the Department of Health and Human Services (DHHS), as well as an Assistant Surgeon General with the United States Public Health Service (PHS). Ms. Schneider indicated that Dr. Blumenthal has a long history of involvement with women's health and breast cancer. She was formerly chief of the Behavioral Medicine and Basic Prevention Research Branch of the National Institute of Mental Health (NIMH); cofounder, scientific director, and vice president of the Society for the Advancement of Women's Health

Research; and has been active in numerous health- and mental health-related organizations and societies. Dr. Blumenthal currently oversees, coordinates, and promotes programs, policies, and activities regarding women's health for the entire PHS. She is the top Federal official involved with coordinating and implementing the Action Plan.

Ms. Schneider pointed out that the Action Plan is a collaborative effort between Federal officials, private-sector representatives, and consumer advocates, and involves numerous public and private institutions at various levels. Dr. Rimer announced that questions for these two speakers would be accepted at the conclusion of both presentations.

Presentation by Ms. Visco

Ms. Visco began her presentation by summarizing the key points she would address, including the history and background of the Action Plan, as well as details of its structure and steps for implementation. She credited consumer activists with providing the impetus for the Action Plan. The Coalition, whose efforts were vital to recent increases in appropriations for breast cancer research, circulated a petition requesting that a national plan of action against breast cancer be developed and collected more than 2.6 million signatures to support this initiative. The petition specifically cited the formation of a collaborative strategy to reduce breast cancer incidence as quickly as possible by involving leaders in the consumer community, Government and private research, private industry, and other Governmental areas. The hope was that these leaders could meet, share ideas, and formulate a national plan, including goals and action steps. Ms. Visco indicated that members of the Coalition were aware that they were seeking an unprecedented and extremely challenging plan.

Ms. Visco informed members that on October 18, 1993, the Coalition presented the more than 2.6 million petitioned signatures to the President, First Lady, and Secretary of DHHS, Dr. Donna Shalala. She reported that the President offered his commitment to support the petition's request. He charged Secretary Shalala with leading the development and implementation of the Action Plan. Ms. Visco stated that she worked in collaboration with Dr. Ruth Kirschstein, Deputy Director of NIH, Ms. Jan Hedetniemi, Coordinator of the Secretary's Conference on Breast Cancer, Office of the Director, NIH, then Surgeon General Jocelyn Elders, and Dr. Vivian Pinn, Associate Director, NIH, to plan the Secretary's Conference, and begin drafting the Action Plan. She explained that they met with a group of Government and non-Government representatives and developed a list of individuals who would be invited to participate in the conference. They also established and appointed cochairs to lead 10 working groups focusing on areas in basic, applied, and translational research; consumer and provider education; health care policy; access to health care; and service delivery.

Ms. Visco continued by informing members that the conference was held on December 14, 1993, in Bethesda, Maryland, and that the 300 participants represented an equal proportion of the private and public sectors. She reported that she worked with Dr. Francis Collins, National Center for Human Genome Research, to guide the working group on basic science. Ms. Visco characterized the actions of her working group as extremely successful in that they accomplished the goal of the conference—sharing ideas. She contrasted the events of the conference with those of other, more typical hearing formats, in which formal presentations are made, questions are asked, and the meeting is then adjourned, without follow-on application of information. During this conference, she stated, after a few presentations in the morning, the

entire day was dedicated to sharing ideas and expertise, and building a consensus in terms of action items. Ms. Visco noted, for example, that within the basic science group, consumer representatives probed researchers to determine what they needed to be able to answer the urgent questions about breast cancer.

Ms. Visco indicated that priorities emerged from the working group discussions, which were presented during the afternoon. Later that evening, the chairs of the working groups met with a facilitator to develop a rough framework for the Action Plan based on these priorities. This draft was submitted to DHHS, which worked with the Coalition to make the document more formal and readable for the public, and was published as the proceedings of the conference. Ms. Visco emphasized that these were the initial steps, and the challenge was to then use that document to implement the outlined Action Plan.

Under the leadership of Secretary Shalala, the chairs of the working groups were reconvened in June 1994 at DHHS to discuss implementation of the Action Plan, methods for coordinating the process, and strategies for handling the tensions inherent to a partnership involving the public and private sectors. Ms. Visco expressed satisfaction regarding the outcome of the meeting, noting that a consensus was achieved on six priorities that were to receive immediate focus. She remarked that these priorities primarily targeted areas that were not being sufficiently addressed by other institutions involved in the effort to eradicate breast cancer. Ms. Visco emphasized that all representatives, from both the private and public sectors, had an equal vote in which priorities were chosen.

Ms. Visco summarized the six priorities that were identified. The first was to develop an "information superhighway" to disseminate information about breast cancer and breast health to consumers, researchers, and providers. Second was to establish comprehensive resource banks of biological materials—a need expressed by the basic science working group, since currently available resources were insufficient. The third priority was to ensure consumer involvement in establishing research priorities at all levels, not just in an advisory capacity. The remaining priorities included expanding the scope and breadth of biomedical and behavioral research related to breast cancer etiology, implementing a comprehensive plan for addressing the needs of those individuals identified as carrying breast cancer susceptibility genes, and increasing access to clinical trials by decreasing barriers to participation.

Ms. Visco informed members that planning groups were created for each of these six priorities, with the eventual goal of establishing working groups that could outline action steps for implementing each of these priorities. To this end, each of the planning groups was charged with developing a list of individuals who should be a part of the working group for their priority, as well as developing a framework to organize action items.

Ms. Visco reported that, currently, planning groups have submitted lists of suggested working group members, and frameworks for action steps are beginning to be developed. She explained that she and Dr. Blumenthal, in conjunction with others, are modifying the lists of recommended working group members to ensure that they reflect an equal partnership between public- and private-sector individuals from diverse backgrounds. This process has been completed among all but two planning groups. A steering committee has also been established to handle challenges that emerge during the process, such as how to involve private industry

groups that are not represented in specific working groups and identify which pharmaceutical firms should be included in this process.

Ms. Visco concluded by thanking all those individuals who participated in the petition campaign and the Secretary's Conference. She expressed her belief that the project will ensure advances in the fight against breast cancer. Ms. Visco also requested that NCAB members volunteer time to work on the Action Plan and provide suggestions regarding the potential role they can play. She added that others in both public and private industry are already volunteering.

Presentation by Dr. Blumenthal

Dr. Blumenthal began her presentation by thanking all those individuals who have been involved in developing and implementing the Action Plan and expressing her hope that collaborative efforts will continue. She thanked Dr. Ruth Kirschstein and Ms. Jan Hedetniemi for fulfilling their vital roles in developing the Secretary's Conference. Dr. Blumenthal also commended Dr. Broder on behalf of the DHHS for the extraordinary leadership, energy, and compassion he has contributed to the battle against breast cancer. She added that he has created a legacy of wisdom and determination that will continue to inspire efforts to reduce the effects of breast cancer, and that he will be missed greatly when he leaves the NCI. She expressed hope that he will continue to work with her office in the fight against breast cancer.

Dr. Blumenthal praised Ms. Visco as one of the nation's most experienced and dedicated activists in the fight against breast cancer. She remarked that she is proud to serve as the nation's first Deputy Assistant Secretary for Women's Health. Dr. Blumenthal explained that this new position was initiated to address the negative effects that the disparities in both biomedical and behavioral research and access to health care services have had on the health of American women. She characterized the last 5 years as having the largest focus on women's health in the nation's history. Dr. Blumenthal reported that in 1990 the public became aware of the disparities in terms of the lack of research on women's health issues, the failure to analyze data by gender, and the scant number of senior female researchers in the nation's Federal and academic research institutions. She indicated that the PHS Office on Women's Health (OWH) functions to: coordinate and stimulate efforts to increase access to health care services for women; improve education regarding health care issues among women; promote women's health training among health care providers; foster and support basic, clinical, and epidemiological women's health-related research; and support the recruitment, retention, and promotion of women within medical research and other health-related fields. Dr. Blumenthal informed members that the OWH also works to encourage collaborations that support the current focus on women's health issues among Government agencies, consumer and health care professional groups, and private industry. She cited breast cancer as one of the nation's and OWH's top health priorities.

Dr. Blumenthal then moved to a discussion of recent activities toward implementing the Action Plan. She reiterated the innovative nature of this Plan and described it as a public/private partnership that was called for by the President and established by the Secretary of the DHHS. She stressed that the collaborative nature of the Plan is unprecedented and that its designers are committed to involving representatives from Government agencies, consumers, health care professionals, researchers, the media, Congress, and private industry.

Dr. Blumenthal summarized the progress of the planning groups during the past few months, including the identification of the six priority action areas described by Ms. Visco; the establishment of Federal coordinating groups for agencies of DHHS and other Federal Departments, such as the Department of Energy (DOE), the Environmental Protection Agency (EPA), the Department of Defense (DOD), and the State Department; and the creation of a national inventory of all Federal activities in breast cancer. Dr. Blumenthal mentioned that NCAB members could sign a list to receive a copy of the inventory.

Dr. Blumenthal then briefly discussed the six planning groups, each of which is chaired by two individuals, one from the public sector and the other from the private sector to ensure an equitable balance in the collaborative efforts. She indicated that the goal of the Information Superhighway planning group is to utilize the latest telecommunication and technologic advances to disseminate information regarding breast health and cancer to researchers, consumers, and health care providers. The group has met with private industry leaders, consumers, and Government representatives to identify opportunities for improved information dissemination, including the development of an interactive video and multimedia interventions, formulation of possible strategies for targeting underserved populations, and discussion of ways in which the information superhighway can be used to promote diagnostic and treatment interventions. Dr. Blumenthal added that the group has identified both short- and long-term issues that it will address through its activities. The group has also begun to explore the possibility of creating an Information Action Council, which would include consumers, Government representatives, and private-sector members, particularly from telecommunications industries. These activities will increase the education of the public, as well as health care providers, in terms of breast cancer prevention, screening, and treatment. Dr. Blumenthal recognized Drs. Kay Dickersin and Fred Goringer for their efforts as cochairs of the Information Superhighway planning group. This information was inadvertently omitted during the presentation regarding that group.

Dr. Blumenthal informed NCAB members that the efforts of the second planning group, focusing on the development of a comprehensive biological resource bank and patient data registry, were cited as a critical action area. This group's activities have included co-sponsorship of a conference with NCI to discuss available biological resources, as well as the ethical, legal, and technical issues surrounding the establishment of national banks. The pooling of data and tissues through the bank would allow researchers to utilize a wider spectrum of samples in their work, as well as allow increased access to such tissues. This may act to enhance research regarding the etiology of breast cancer. Dr. Blumenthal commended the actions of Dr. Alan Rabson, the public-sector cochair, and Dr. Susan Love, the private-sector cochair of this planning group. She added that during the cosponsored conference, the following topics were discussed relating to the establishment of the bank: specific data and tissue resources that will help researchers explore breast cancer prevention, diagnosis, and treatment; suggestions for the structure of the bank; mechanisms for collecting and aggregating data and tissues; the legal and ethical implications of tissue and data collection for a resource bank; and strategies for ensuring equitable sharing of resources among researchers.

Dr. Blumenthal explained that the third planning group is acting to ensure consumer input into service delivery, education, and research. She cited the efforts of Ms. Visco as well as some members of the NCAB who have worked hard to ensure that consumers are involved in all levels of policy development. Dr. Blumenthal emphasized that including consumers in

policymaking will be critical to the development of innovative strategies for eradicating breast cancer. She recognized the efforts of Ms. Jan Hedetniemi and Ms. Jane Reese-Coulbourne, Director, National Breast Cancer Coalition, Washington DC Chapter, in leading this group.

The fourth planning group is focusing on fostering research in breast cancer etiology. Dr. Blumenthal commented that in view of the increase in the incidence of breast cancer and the lack of a definitive cause of the disease, this area is a priority. The group's efforts will focus on expanding the scope and spectrum of biomedical and behavioral research regarding breast cancer etiology. She reported that the group has reviewed ongoing research efforts in both private and public institutions and created an inventory of current breast cancer etiology-related research projects supported by NIH and DOD, which will allow the group to identify gaps in research that should be targeted in the future. Dr. Blumenthal remarked that this group has emphasized environmental causes of breast cancer and genetic and environmental interactions that may be linked to breast cancer initiation. She reported that their next activity will involve compiling an inventory of research currently being conducted in the private sector. Dr. Blumenthal thanked NCI's Dr. Susan Sieber, the public-sector cochair, and Ms. Nancy Evans, the private-sector cochair, for their work. She added that the group is discussing the possibility of designing a standard questionnaire probing exposure to risk factors for breast cancer, which may be incorporated into future etiologic research and clinical trials.

Dr. Blumenthal indicated that a fifth planning group is working to develop innovative strategies to make clinical trials available to a wider spectrum of women, to recruit larger numbers of women from all minority groups by decreasing barriers to participation and to retain these women in the trials once they have begun participating. She stated that the group has reviewed current practices in terms of protocol design as it relates to patient recruitment and retention. She thanked the Planning Group cochairs Dr. Leslie Ford, NCI, and Ms. Zora Brown, NCAB Board member.

The final planning group is concerned with addressing the needs of individuals carrying breast cancer susceptibility genes. The ability to identify these genes mandates that a comprehensive plan be established to ensure that these women receive counseling and advice regarding preventive interventions. Also, the range of clinical and legal issues raised by testing for genetic susceptibility will be addressed. Dr. Blumenthal thanked NCI's Dr. Francis Collins and Ms. Mary Jo Kahn, private-sector cochair, for their work in leading this group's efforts.

Dr. Blumenthal indicated that the next step will involve forming the actual working groups by designating the chairpeople and members of each one. Once these groups have been established, they will develop work plans to guide their activities for the next 1 to 2 years and present a budget for these efforts.

Dr. Blumenthal also highlighted the efforts of the Federal Agencies Breast Cancer Coordinating Group, which, as mentioned earlier, involves members from every agency in the Government. They have identified three priorities they will address, in addition to those already outlined: improved access to and recruitment of women for breast cancer diagnostic services, particularly for the underserved and those over age 50; establish breast cancer tissue and patient data registries, particularly in the State Department and the Department of Veterans' Affairs, since employees of these Departments are not receiving the services they

need; and focus on environmental influences that lead to breast cancer and how these factors interact with genetic susceptibility.

Dr. Blumenthal cited several Federal achievements regarding breast cancer during the last year. She reported that the FDA issued regulations for implementing the Mammography Quality Standards Act of 1992, which requires Federal inspection and certification of all mammography facilities, equipment, personnel, and practices. This act will help to provide safe, accurate, and reliable mammography for the entire nation. Dr. Blumenthal also mentioned the clinical and consumer practice guidelines for mammography that were developed by the Agency for Health Care Policy and Research (AHCPR) and are available by making a free telephone call. These guidelines are designed to educate both health care providers and patients about mammography facilities and procedures. Dr. Blumenthal also highlighted the efforts of the DOD, which recently announced that it will support some 430 breast cancer research grants with $200 million in funding. Basic, clinical, and health outcomes research exploring breast cancer prevention, etiology, and treatment will be conducted under the auspices of these new grants. She commented that the DOD has been a strong participant in the activities of the Action Plan. Dr. Blumenthal also pointed out the efforts of the EPA to examine the role of pesticides, pollutants, and other environmental factors in breast cancer etiology. Recently, the EPA convened a national conference on the interaction between environment and women's health, which included a special focus on breast cancer research. Dr. Blumenthal also commended the activities of the Centers for Disease Control and Prevention. She informed members that by the end of the year, the CDC will offer free mammography for low-income, older, and minority women in almost every State, as a part of the PHS National Breast and Cervical Cancer Early Detection Program. Finally, Dr. Blumenthal praised the comprehensive research efforts of the NIH, which she indicated have resulted in numerous advances increasing the survival and quality of life of many women who develop breast cancer. Dr. Blumenthal charged that there is still much work to be done to eradicate breast cancer, particularly in the arena of breast cancer etiology and prevention.

Dr. Blumenthal stated that the DHHS has also formed a coordinating group, which has identified priorities for health care delivery, policy, and research. To advance research, the DHHS coordinating group will explore issues related to setting standards for National Tissue Resource Banks; establish comprehensive cancer registries that are centralized and accessible to all researchers; and explore the possibility of debt foregiveness for health care providers who complete 2 years of research training and agree to complete 2 years of breast cancer research. The group will also work to increase research efforts on environmental causes of breast cancer and methods for improving breast cancer detection.

Other efforts related to service delivery may include: developing a public/private resource directory; improving coordination of breast health education programs between public and private sectors; increasing participation of special populations in prevention programs; creating a clinical trial registry that is accessible to the public; and extending the scope, impact, and credibility of breast health education programs, possibly through a multi-organization approach. DHHS efforts in terms of health care policy will focus on involving advocacy groups and women with breast cancer in establishing research and service delivery priorities, and developing and distributing breast health-related information. Dr. Blumenthal added that this group indicated its commitment to increasing coordination among Government agencies in terms of breast cancer activities to avoid repetitive work and foster the

development of innovative strategies. She indicated that the group repeatedly emphasized its desire to coordinate breast cancer activities with private-sector groups.

Dr. Blumenthal thanked Dr. Edward Sondik and Dr. Samuel Broder for their expertise and resources that have advanced the efforts of the Action Plan. She also recognized other NCI staff, including Drs. Paulette Gray and Suzanne Haynes, Ms. Kathy Crosson, and Ms. Anne Middleswarth, for their work on the Action Plan. Dr. Blumenthal commented that $10 million has been allocated to support efforts related to the Plan in FY95. This money will support activities and priorities identified by the public/private partnership-based working groups, since they hold great promise for developing a creative and coordinated approach that will have a major impact on breast cancer.

Dr. Blumenthal summarized some of the future activities related to the Action Plan, including the establishment of a steering committee that will develop policies and an agenda for future Plan-related efforts. She also reported that funding for the working groups will be granted and a long-term implementation plan and grant program will be developed. A strategy for communicating Plan-related activities and soliciting involvement of the public and health care providers will also be created. She added that an evaluation component will be developed to assess progress in attaining the goals of the Action Plan.

Questions and Answers

Dr. Rimer began the discussion by inquiring about the NCAB's involvement in establishing priorities for the $10 million allocation. Dr. Blumenthal indicated that the steering committee would begin a discussion on how to distribute the funding within the next 2 weeks and that these decisions would then be presented to the Board. Ms. Visco stated that the appropriation is specifically designated for the Action Plan, not for the NCI. She reiterated Dr. Blumenthal's point that the steering committee will help to establish research and service delivery priorities based on the input of the related working groups. To avoid having to establish a new bureaucracy, research priorities will be funded through the NCI process. It has not yet been determined whether funds from the $10 million allocation will be used to meet research priorities or if they will seek separate NCI funding for research efforts. Dr. Blumenthal emphasized that it is the Secretary of DHHS' intent to fund the Action Plan efforts and that this will be accomplished through money allocated to NCI. She added that input regarding funding of these priorities from NCAB members and NCI staff is welcome, and that since many of these individuals are participating in the working groups, they are already actively involved in establishing funding priorities.

Dr. Salmon asked whether, in light of the desire to avoid duplicative efforts, existing resources such as the Cancer Information Service (CIS) and Physician's Data Query (PDQ) guidelines will be used to meet some of the Action Plan goals. Ms. Visco replied that the Information Action Council's goal is to more effectively use existing resources and to increase awareness of these resources among the public and health care providers. Ms. Visco cited an information superhighway partnership already in existence between the Government and private industry in North Carolina, which may be used as a prototype for future efforts.

Dr. Salmon asked Ms. Visco to clarify what is meant by the term "information superhighway." She explained that all communicative media, such as telephones, televisions,

Internet, and CIS are a part of the information superhighway. Dr. Blumenthal added that the telecommunication revolution will allow every home in the nation to be connected to a fiberoptic line that can disseminate health information. Through television, individuals will be able to communicate with their health providers and educators. Advances in telemedicine will utilize this link to transport mammography and biopsy findings from distant units to allow interpretation at urban sites. Dr. Blumenthal concluded that the Information Superhighway working group will explore not only these future avenues of health information communication, but will also focus on existing resources, such as the National Cancer Program, to see how they may be widened in terms of scope and impact on women and health care providers.

Dr. Dickersin reemphasized that members of the Information Action Council are not trying to reinvent information resources and added that most of these individuals are already working to address the goals of this working group. For example, Ms. Sue Hubbard, who administers the PDQ guidelines, and Ms. Lois Ann Colaianni, who works with the Library of Medicine, are involved with this group. Dr. Dickersin presented an initiative under way in the Maryland Library, called SAILOR, which provides free public access to and guidance through the Internet system. She stated that since many people may not go to the library, it is important to cultivate means other than Internet for delivering information (i.e., through telephones, televisions, and written materials) to the public. Dr. Dickerson commented that this was the motivation for changing the Information Superhighway working group's name to the Information Action Council. Dr. Rimer supported this decision.

Dr. Sigal queried about the feasibility of attaining debt forgiveness for breast cancer researchers during this Congressional year and whether they have considered involving other groups in achieving this goal. Ms. Visco indicated that there is debt forgiveness for AIDS researchers. She answered that they are uncertain of the feasibility of this measure being accepted by the current Congress.

Dr. Freeman asked for clarification of how access to treatment will be improved, particularly among the 38 million uninsured Americans. Ms. Zora Brown, one of the cochairs of the working groups, addressed this question by stating that there is not yet a complete plan for providing treatment to those women who are diagnosed with cancer through screening efforts. There is a collaborative effort under way in Washington that is exploring methods to fund treatment for these women. She indicated that an approach is being designed by Action Plan participants, that may serve as a model for the rest of the country; however, the means by which uninsured women will be funded are still uncertain. Dr. Freeman reiterated the importance of finding a way to provide treatment, which seems to be the inevitable next step following cancer screening. He stated that "mammograms do not cure cancer, they make a diagnosis." If the efficiency of screening is increased, then the access to treatment must be improved as well. Ms. Brown asserted that it is already an issue, and that while hospitals are not turning away women entirely, they are not providing services until the cancer develops into later stages. Dr. Blumenthal supported the importance of increasing access to new screening and treatment services; otherwise, she stated, all research and other efforts will have been wasted. Dr. Freeman stated that he is encouraged by the high level of political involvement breast cancer is receiving.

VI. LEGISLATIVE UPDATE—MS. DOROTHY TISEVICH

Ms. Tisevich, legislative liaison for the NCI, presented an update on the composition and outlook of the 104th Congress and an overview of certain Congressional priorities for this session.

Ms. Tisevich reminded the Board of her update at the December meeting in which she presented the anticipated changes in committees that would affect the NCI. She stated that many decisions have been made since then regarding party representation and membership, but some areas of uncertainty remain.

With respect to NCI's authorizing committees, Ms. Tisevich said that Senator Nancy Kassebaum (R-KS) is chairperson and Senator Edward Kennedy (D-MA) is the ranking minority member on the Senate Committee on Labor and Human Resources. The Committee's new members are all Republicans: Senator Bill Frist (R-TN), Senator Mike DeWine (R-OH), Senator Spencer Abraham (R-MI), Senator John Ashcroft (R-MO), and Senator Slade Gorton (R-WA).

Ms. Tisevich noted those members no longer on the Committee. The Democrats lost three seats on the Committee: Senator Howard Metzenbaum (D-OH) retired and was succeeded by Senator DeWine, who defeated Dr. Bernadine Healy and others vying for the Republican nomination for this Senate seat; Senator Harris Wofford (D-PA) lost his re-election bid; and Senator Jeff Bingaman (D-NM) vacated his seat on the Committee.

Ms. Tisevich recounted similar changes in the House of Representatives. The NCI's authorizing committee, formerly known as Energy and Commerce, is now the Commerce Committee. Representative Thomas Bliley (R-VA) is chairperson; Representative John Dingell (D-MI), former chairperson, is now the ranking minority member.

The Subcommittee on Health and the Environment has jurisdiction over the NCI. Ms. Tisevich pointed out that its new chairperson, Representative Mike Bilirakis (R-FL), was responsible for introducing the amendment to authorize NCI at the full bypass level of funding during the last reauthorization cycle. Representative Henry Waxman (D-CA), former Subcommittee chairperson, is now the ranking minority member. Ms. Tisevich noted the significant turnover in the Subcommittee's makeup through the addition of several new Republicans and the loss of several Democrats. Three Democratic slots on the Subcommittee have not yet been filled.

Ms. Tisevich updated the Board on changes in the membership of NCI's appropriations committees as well. The Senate Appropriations Committee chairperson is Senator Mark Hatfield (R-OR), but the ranking minority member has not yet been named. Ms. Tisevich named some of the new Republican members—Senator James Jeffords (R-VT), Senator Richard Shelby (R-AL), Senator Robert Bennett (R-UT), and Senator Judd Gregg (R-NH)—who filled slots awarded to the Republicans because of the party's majority status.

The Subcommittee on Labor, Health and Human Services, and Educational Related Agencies is now chaired by Senator Arlen Specter (R-PA), and former chairperson, Senator Tom Harkin (D-IA) is the current ranking minority member. Senator Patty Murray (D-WA)

lost her seat on the Subcommittee, but is still a full Committee member. Other Democrats on the Subcommittee are expected to return, but Ms. Tisevich cautioned that decisions are not yet final.

Ms. Tisevich reviewed the changes in the House Appropriations Committee. Representative Bob Livingston (R-LA) is the new chairperson, and former chairperson, Representative David Obey (D-WI), is now the ranking minority member.

The House Subcommittee on Labor, Health and Human Services, and Education is now chaired by former ranking minority member, Representative John Porter (R-IL), with Representative Obey as current ranking minority member for the Subcommittee as well as the full Committee. Ms. Tisevich noted the dramatic changes in membership that accompanied the new Subcommittee slots awarded to the Republicans as the majority party. Representatives Henry Bonilla (R-TX) and Bill Young (R-FL) are the only previous Republican members of the Subcommittee. Representatives Ernest Istook (R-OK) and Dan Miller (R-FL) were freshmen during the 103rd Congress, and Representatives Frank Riggs (R-CA) and Roger Wicker (R-MS) are freshmen of the 104th Congress; all are new to the Subcommittee. Representative Helen Bentley (R-MD) resigned in order to run for governor, but lost in the primary election.

Ms. Tisevich covered the four Democratic losses to the Subcommittee. Representative Neal Smith (D-IA) lost his bid for reelection; Representatives Jose Serrano (D-NY) and Rosa DeLauro (D-CT) dropped off due to their junior status and the few available seats; and Representative William Natcher's (D-KY) passing left an unfilled vacancy.

Ms. Tisevich reminded the Board of her description at the December meeting of the Republican Congressional agenda iterated in the "Contract with America," and informed Board members that a copy was included with the legislative update. Many of the following items were voted upon on the first day that the House convened: the ban on proxy voting in committees, open committee meetings, subjecting the legislative branch to laws that apply to other Federal and non-Federal agencies, and the super-majority requirement for tax increases.

The House and Senate introduced a total of 275 bills on the first day, which, Ms. Tisevich informed the Board, were included in the legislative update. Topics covered include a balanced budget amendment, health care reform, consolidation or elimination of Federal programs, unfunded mandates legislation, a line item veto, and Congressional procedural issues. In addition, Ms. Tisevich noted that many reductions have been implemented in committees and staff. Three House committees were abolished and their functions absorbed by other committees.

Ms. Tisevich said that her office plans to track only those bills relevant to biomedical research or the National Cancer Program and bring them to the attention of the Board. She also pointed out the summary of Congressional activities since the last NCAB meeting that were included in the legislative update and offered to answer questions.

Dr. Rimer remarked that Ms. Tisevich's role will be especially important in the upcoming months to assist the Board in understanding the new direction of the legislature. She announced a 20-minute break, and asked the next speakers to limit themselves to their

allotted times to allow for a longer lunch. Before recessing the meeting, Dr. Rimer recommended that the Board read an article on the benefits and costs of screening and treatment of early breast cancer that includes a suggestion for a benefit package for cancer that includes screening women under the age of 50. The article also proposes a different method of follow-up for cancer patients.

VII. MELANOMA ANTIGEN: AN UPDATE—DR. STEVEN ROSENBERG

Dr. Bruce Chabner introduced Dr. Steven Rosenberg, Chief of the Surgery Branch, Division of Cancer Treatment (DCT). Dr. Chabner indicated that Dr. Rosenberg is at the forefront of the identification of tumor-specific antigens, a crucial element for the success of immunologic approaches for the treatment of cancer.

Dr. Rosenberg explained that the identification of tumor-specific antigens is critical for the development of vaccines against cancer. Successful vaccine approaches against other diseases have carefully examined the molecular nature of the antigens involved in each particular immune response.

Dr. Rosenberg stated that human tumor immunology studies confront three critical questions: 1) whether unique antigens that are capable of inducing an immune response are actually present in human cancer cells—as demonstrated in murine and other experimental tumors; 2) if specific antigens are indeed present in human tumors, whether manipulation of the immune system can cause the rejection of established human cancers; and 3) whether immunization against tumor-specific antigens can be used as an approach for cancer prevention. Dr. Rosenberg indicated that evidence supporting a positive response to the first two questions derives from studies using interleukin-2 (IL-2). This molecule does not have a direct impact on cancer cells but, rather, its immunologic effects are mediated through the alteration of the host immune response to cancer. Dr. Rosenberg explained that 283 patients with advanced disease (melanoma and kidney cancer) have been treated with IL-2 in the Surgery Branch; approximately 7 percent of these patients have exhibited a complete regression of their established malignancies, and another 10 to 15 percent of patients have exhibited a partial regression of at least 50 percent. The majority of patients who experienced a complete regression have remained disease free for more than 5 years. These results may have a great impact on survival for those patients who respond to IL-2 treatment. Dr. Rosenberg indicated that a challenge in human tumor immunology has been to improve upon this low incidence of responses. These studies, however, have demonstrated the basic principle that tumor regression can be mediated by strictly altering the patient's immune system.

Dr. Rosenberg referred to the work performed by Dr. Thierry Boon and colleagues. These investigators identified a melanoma-specific antigen, MAGE-1, using lymphocytes from a melanoma patient that had been immunized multiple times over the course of 3 years with mutagenized cancer cells after the resection of his tumor, and with no further evidence of malignancy. This is the only patient in the world that has reacted with MAGE-1 or any other antigen of the MAGE series; no other patient has generated a natural T-cell response against MAGE antigens.

Dr. Rosenberg indicated that in search of approaches that would improve upon patients' response to cancer (melanoma) immunotherapy, his group initiated a series of studies with tumor-infiltrating lymphocytes (TILs), which are lymphoid cells that infiltrate solid tumors. TILs can be grown by removing a cancer nodule from a patient and culturing suspensions of lymphocytes infiltrating tumors in medium containing IL-2. Approximately 50 percent of patients with advanced melanoma respond to TILs that recognize unique antigens on fresh and cultured cancer melanoma cells; these TILs are identified by their ability to lyse cancer cells or specifically secrete cytokines when cocultivated with autologous tumors. In addition, these TILs are capable of mediating therapeutic effects. A recently completed pilot study in which grown TILs were reinfused into patients demonstrated that approximately one-third of patients with advanced malignant melanoma exhibited tumor regression. An equal response rate was observed in patients who had previously failed to respond to IL-2 therapy. Dr. Rosenberg stated that the TILs proved to be the key to identifying the molecular nature of tumor antigens in their studies.

The strategy for cloning genes that encode antigens involved in tumor regression has consisted of first identifying TILs that are known to recognize antigens that are widely shared among tumor cells. Thus, the basic hypothesis behind this approach is that by using TILs that are known to mediate tumor regression, identification of antigens of therapeutic significance might be enhanced.

Dr. Rosenberg displayed a series of slides illustrating the response of a melanoma patient to treatment with TILs. The patient, a 25-year-old man, exhibited multiple melanoma deposits in subcutaneous and intraperitoneal tissue as well as in the liver. The tumors in this patient rapidly regressed after treatment with TILs. This population of TILs was then used in the gene cloning efforts. A cDNA library was made from the patient's tumor and this library was then transfected into an antigen-negative cell line that expressed the appropriate major histocompatibility complex (MHC) restriction element (human leukocyte antigen [HLA]-A2). This approach involves transfecting the genes one by one until the gene of interest is identified by assaying the ability of the transfectant to stimulate a response from the same TILs that caused tumor regression. Along the course of this study, however, the COS-7 cell line was used as a transient system to transfect pools of genes instead of one gene at a time. From 13,000 individual genes that were transfected in the course of 3 years, two genes that encode tumor-specific antigens were identified from this patient: MART-1 (melanoma antigen recognized by T-cells) and gp-100. The complete DNA and protein sequences of MART-1 and gp-100 have been identified; MART-1 is a 118-amino acid protein, whereas gp-100 is a larger protein. MART-1 is not expressed in normal tissue with the exception of very low levels present in human retina (which contains melanocytes). However, no ophthalmologic effects have been reported in any patient treated so far with MART-1.

Dr. Rosenberg indicated that the MART-1 gene is not expressed in any tumor other than melanoma. The gene was present on 26 of 26 fresh melanomas and on 11 of 14 tissue culture tumor lines tested. In addition, 7 of 7 normal melanocyte lines also expressed the MART-1 gene. This latter finding suggests that the tumor has broken tolerance to this normal differentiation antigen present on melanocytes. Evidence supporting this hypothesis derives from the long-term observation that a statistically significant percentage of melanoma patients treated with immunotherapy (IL-2) develop vitiligo; these patients are reacting against antigens on normal melanocytes as part of their immune response against the tumor. In contrast, no

signs of vitiligo have been reported in patients with metastatic renal cell cancer treated with IL-2. Moreover, signs of vitiligo have only been reported among melanoma patients who have responded to immunotherapy, further suggesting that the MART-1 antigen is critical for the response (tumor regression) of patients with melanoma.

Dr. Rosenberg noted that unlike antibodies that recognize three-dimensional regions on intact protein molecules, T-cells recognize processed peptides that result from the degradation of proteins. The processed peptides are presented on the surface of the tumor cell on the groove of an MHC molecule. Thus, three molecules are critical for the recognition of the antigen by the T-cell: the T-cell receptor, the immunodominant peptide that results from the antigen degradation, and the MHC molecule that presents the processed peptide.
Dr. Rosenberg indicated that his research has focused on attempting to identify the immunodominant peptides of the melanoma antigens recognized by T-cells. As a result of a large screening process, one 9-amino acid peptide from MART-1 and two 10-amino acid peptides from gp-100 were identified as the only immunodominant peptides recognized by a patient's TILs. Additional gp-100 epitopes have been recently identified; thus far, a total of five 9- and 10-amino acid epitopes have been recognized. Fourteen melanoma-specific TIL lines have been derived from 14 HLA-A2-positive patients. Thirteen of the 14 cell lines recognized the MART-1 immunodominant peptide and 4 of the 14 recognized the gp-100 antigen.

Dr. Rosenberg stated that other melanoma-specific antigens have recently been identified, including tyrosinase, restricted by HLA-A24, and gp-75, restricted by HLA-A31. The complete sequences of tyrosinase and gp-75 have been determined and an immunodominant peptide of tyrosinase has been identified. Dr. Rosenberg indicated that the TIL approach for identifying melanoma-specific antigens has recently been applied to identify specific antigens associated with tumors other than melanomas. Presently, TILs derived from approximately one-fourth to one-third of breast cancer patients can be identified. These TILs recognize unique breast cancer antigens presented by Class II MHC molecules. Dr. Rosenberg referred to some studies in which secretion of cytokines (GM-CSF) by TILs was only observed when the TILs were incubated with the autologous tumor (breast or ovarian cancer cells) but not peripheral lymphocytes, Epstein-Barr virus (EBV)-transformed human B lymphocytes, or allogeneic tumors.

Dr. Rosenberg listed a number of potential approaches for cancer immunotherapy based on the ability to molecularly identify tumor-specific antigens. He explained that the TILs used for immunotherapy can be sensitized *in vitro* to the immunodominant molecules that have been identified on the tumor-specific antigens, thus enhancing their antitumor activity. These TILs could then be adoptively transferred to the patient. *In vitro* sensitization techniques similar to those used in viral systems for sensitizing peripheral blood lymphocytes (PBLs) have been developed from a tumor-bearing patient to the 9-amino acid immunodominant MART-1 peptide in a medium containing low doses of IL-2. Dr. Rosenberg indicated that the cells can be expanded up to 100,000-fold within a period of 5 to 6 weeks. Investigators from the Surgery Branch have demonstrated that *in vitro* sensitized cells are 50- to 100-fold more potent than TILs in recognizing and lysing tumors. Dr. Rosenberg noted that a regulatory approval is under way for using the MART-1 peptide-sensitized cells in cancer immunotherapy.

A second potential approach is to genetically modify lymphocytes or other killer cells to improve their capacity to recognize tumor-specific antigens. This approach requires, first, the identification of the T-cell receptors that recognize the tumor-specific antigens. Dr. Rosenberg indicated that his group has isolated the alpha and beta chains from the T-cell receptors that recognize the MART-1 and gp-100 antigens. These receptors have been cloned and sequenced, and inserted into lymphocytes which have subsequently been demonstrated to recognize the MART-1 antigen. A third approach is to transfect the genes encoding the alpha and beta chains of the T-cell receptors. Dr. Rosenberg stated that antitumor reactivity has been conferred to cells by using this approach. The implication, however, would be to transfect the genes into autologous bone marrow stem cells to provide the host with large quantities of antitumor effector cells. All differentiated effector cells, lymphocytes, and neutrophils might bear the receptor that recognizes the tumor-specific antigen. Dr. Rosenberg explained that this potential approach to cancer immunotherapy is being actively pursued by his group.

Dr. Rosenberg indicated that another application for molecularly identified tumor-specific antigens is to actively immunize against these molecules using recombinant viruses that encode the tumor-specific antigens. Dr. Rosenberg described studies currently in progress involving this approach. Since the tumor-specific antigens identified so far are human antigens, they cannot be used to study mouse tumors. Therefore, a mouse model (PA15 mastocytoma) has been developed. This is a colon carcinoma transfected with a model tumor antigen. A number of viral vaccines, including vaccinia, fowl pox, and adenovirus, that express the model tumor antigen are being developed. These vaccines can be used for experimental studies to assess the generation of T-cells against the tumor antigens or can be used in adoptive or active immunotherapy models. Results of these studies indicate that the different types of viruses generate cytotoxic T-lymphocytes (CTLs) against the model tumor antigen. Recombinant viral vaccines that express the tumor antigen plus a costimulatory molecule (e.g., B-7) or IL-2 have also been tested in mouse models. These molecules have been shown to improve the ability of the viruses to immunize against the tumor antigens. IL-2, B-7, and ICAM-1 were shown to be the most effective, among a large number of cytokines and other molecules, in reducing established lung metastases in mouse models. Dr. Rosenberg indicated that recombinant vaccines—with fowl pox, vaccinia, and adenovirus—expressing both MART-1 and gp-100 have been generated.

Dr. Rosenberg concluded his presentation by referring to the opportunities that the identification of tumor antigens has provided to cancer immunotherapy. Large quantities of purified tumor antigens can now be obtained by expressing them in *Escherichia coli*, Baculovirus, or yeast. Similarly, large amounts of immunodominant peptides can be obtained by *in vitro* synthesis; these peptides can then be used for direct immunization or incorporated into viral vectors for subsequent use in immunization. Dr. Rosenberg indicated that a series of clinical protocols has been approved to immunize with either MART-1 immunodominant peptide in adjuvant, or with vaccinia, fowl pox, and adenovirus expressing MART-1 or gp-100 alone or with IL-2. Regulatory approval of these protocols is under way.

Questions and Answers

Dr. Salmon asked Dr. Rosenberg whether circulating levels of MART-1 or antibodies against MART-1 have been detected in any melanoma patient that could account for therapy failure. Dr. Rosenberg indicated that his group has recently developed a sensitive polymerase chain reaction (PCR) technique to identify MART-1 and gp-100 as a potential diagnostic approach to identify melanoma. Dr. Rosenberg stated that circulating tumor cells have been identified using this PCR technique; the development of an ELISA assay to detect circulating MART-1 or anti-MART-1 antibody is in progress.

Dr. Broder congratulated Dr. Rosenberg for his revolutionary work and strongly recommended evaluating these immunotherapy approaches (for melanoma and, when available, for breast cancer) in an adjuvant setting as soon as proof of safety of the vaccines is obtained. He also asked Dr. Rosenberg whether he believes that this work could have been performed in any setting other than the NCI intramural program, without access to the clinical center, by himself or any other investigator. Dr. Rosenberg indicated that the resources that were available for rapidly taking the preclinical data and applying them in the clinical setting were extremely facilitated by the opportunities the NIH offers in translational research.

Dr. Goldson asked Dr. Rosenberg whether translational research could be implemented in patients with retinoblastoma, since Dr. Rosenberg showed that MART-1 is slightly expressed in human retina. Dr. Goldson added that since genetic predisposition is an important factor in retinoblastoma, immunization would potentially play an important role in preventing this malignancy. Dr. Rosenberg indicated that although he has not conducted any work related to retinoblastoma, with sufficient effort, TILs or CTLs raised *in vitro* against retinoblastoma antigens could be identified that would further facilitate the use of these immunotherapy approaches against this particular disease.

Dr. Pitot asked Dr. Rosenberg whether patients are screened for expression of MHC antigens before they are treated with TILs, since there are tumors that have lost the ability to express these molecules. Dr. Rosenberg indicated that only 4 of approximately 40 identified melanomas do not express Class I MHC molecules. In addition, most other tumors, including colon cancer, express Class I MHC molecules but have lost the ability to express Class II MHC molecules; gamma interferon can be used to upregulate these antigens. Dr. Rosenberg noted that a clinical trial currently in progress involves treatment with interferon gamma to upregulate MHC antigens prior to administration of IL-2 or TILs.

Dr. Calabresi asked Dr. Rosenberg whether the described melanoma antigens are present on both amelanotic and melanotic melanomas. Dr. Rosenberg stated that a small percentage of the melanomas studied were amelanotic and expressed MART-1.

Dr. Bishop referred back to the studies that suggested that the tumor (melanoma) has broken tolerance to the normal differentiation antigen present on melanocytes and asked Dr. Rosenberg to comment on how immunization against tumor-specific antigens would be successful in cancer prevention if tolerance has not been broken before the malignancy is evident. Dr. Rosenberg indicated that it is not clear how tolerance is broken against MART-1 and gp-100. One clue is that a tumor expresses 10 to 100 times the amount of antigen

compared with normal melanocytes; thus, it may be a quantitative phenomenon of antigen overexpression that leads to breaking of tolerance. Dr. Rosenberg pointed out that the critical question in this regard is why a tumor grows if tumor-specific antigens exist and specific T-cells against these antigens are generated. He stressed that the answer to this question might provide the best clinical application for tumor-specific antigens, since there is evidence that suppressive factors exist at the tumor site. The presentation of tumor-specific antigens on normal cells—away from the tumor environment—could provide the means for performing immunizations that the tumor itself could not produce while growing. Dr. Rosenberg indicated that, perhaps, this will be an effective approach to immunize against tumor-specific antigens and an overall approach for cancer prevention.

VIII. REMARKS OF THE PRESIDENT, AACR—DR. EDWARD BRESNICK

Dr. Edward Bresnick, President of the American Association for Cancer Research (AACR) began his presentation by providing a detailed background of the AACR. The AACR comprises 10,000 members, making it the oldest and largest cancer research organization in the United States. Dr. Bresnick noted the academic background of its membership—57 percent of AACR members have a Ph.D. and 45 percent have an M.D., indicating that a number of members hold multiple degrees. The degree specialties of the investigators are diverse, encompassing all facets of research. The mission of the AACR, Dr. Bresnick continued, is to further cancer research through communication, such as the annual meeting of the AACR, special conferences, and various AACR journal publications, including the most recent, *Clinical Cancer Research,* made available in December 1994. The AACR also furthers its communication efforts by fostering public education, science, education, and training. Dr. Bresnick indicated that the purpose of his presentation was threefold: 1) to emphasize the severity of the NCI's funding crisis; 2) to discuss the lack of appreciation of the National Cancer Institute's achievements; and 3) to offer novel strategies and alternatives to combat these crises.

Dr. Bresnick referred to the tremendous progress of cancer research in recent years, but pointed out that Federal funding barriers have hampered research efforts. Reduction in grant funding has not only hindered research efforts, it has hampered efforts to attract scientists into cancer research, and research in general. Referring to a slide, Dr. Bresnick documented the general downward progression in the grant success rate. The percentage of grant proposals funded in FY 1994 was only 22.2 percent, as compared with 40.1 percent in 1971, when the National Cancer Act was adopted. He stressed that research efforts that would substantially impact the cancer program are not being performed due to the decreasing allotment of Federal funding. In addition to the decreases in the number of grants funded, those competing grants that receive funding suffer a 10 to 13 percent decrease in the amount of approved funding per year. As a result, grants that have been approved for a 4-year period may sustain a 30 to 40 percent decrease in overall funding. Dr. Bresnick pointed out that the new Congress is committed to deficit and spending reductions and if a balanced budget amendment is adopted, it will require a reduction in domestic spending of at least 28 percent. Dr. Bresnick emphasized his belief that this additional reduction would severely impact the National Cancer Program.

Next, Dr. Bresnick addressed his belief that the National Cancer Program has not adequately communicated its achievements to its consumer constituencies. Ineffective dissemination of information has lead to a lack of public recognition of the research achievements under the National Cancer Program. The National Cancer Program's fundamental research has yielded important knowledge applicable to cancer, as well as knowledge of other disease areas such as AIDS, cystic fibrosis, adenosine deaminase deficiency, arthritis, Duchenne muscular dystrophy, and aging, to mention only a few. Dr. Bresnick cited the December issue of *Science* in which DNA repair was regarded as the process of the year. The fundamental research on cell biology and biochemistry that led to advances in DNA repair was largely supported by the NCI but, because of ineffective communication, NCI's role remains unrecognized.

The impact of the National Cancer Program in other areas has also not been adequately expressed, Dr. Bresnick continued. For example, cancer centers are an important component in the "war on cancer," contributing to improvements in survival and the quality of life for cancer patients. The NCI promoted the concept of such centers. The NCI has fostered translational research—taking basic laboratory findings and applying them to the areas of prevention, early diagnosis, and treatment. The NCI has developed new approaches in the area of prevention; for example, the concept of chemoprevention is being tested in high-risk populations. Finally, the NCI has been an important force in mobilizing the resources of industry, academia, and Government towards common goals. For example, the development, manufacture, and distribution of the drug taxol was largely orchestrated by the NCI. These represent only a few of the success stories of the National Cancer Program.

Dr. Bresnick briefly alluded to the perception among the extramural community that there is a move to dismantle the National Cancer Program, to reverse the National Cancer Act. He contended that the AACR strongly supports the precepts of the National Cancer Act, with the Director of the National Cancer Institute reporting, in all matters except budget, to the NIH Director. He indicated that excessive micromanagement and fragmentation have decreased the flexibility available to the Office of the NCI Director and the NCI Director's ability to respond to new leads with appropriate resources.

As strategies for the future, Dr. Bresnick stressed the importance of better communication with consumer constituencies, particularly legislators and their aides. He stated that 45 percent of legislators in the House of Representatives are in their positions for less than 2 years and not many of them may know about the progress that has been achieved through the National Cancer Program. It is imperative for effective communication to take place to ensure that the successes in research are recognized. Also, it is imperative to effectively communicate novel findings to the public, survivors and noncancer individuals, to reclaim their faith in the National Cancer Institute and the National Cancer Program.

Another approach, Dr. Bresnick continued, to combat the crises facing the National Cancer Program is the development of a better Bypass Budget document. Dr. Bresnick stated that the Bypass Budget must include an executive summary that represents the NCI's achievements and the needs and opportunities for further research on specific cancers. He emphasized the need for a more extensive lay summary, expanding on what has been performed and indicating new avenues of opportunity and the methods that are required to pursue those avenues. He stressed the need for a more detailed reference document that

interprets the technical writing into a more generalized summary to enable lay readers to easily summarize and interpret the findings. Finally, the Bypass Budget must justify research needs more appropriately in order to reduce the disparity between what is being requested and the actual appropriated budget.

Dr. Bresnick indicated that in order to carry out these novel strategies and mechanisms of action, it is imperative that unified leadership be established. He challenged the National Cancer Advisory Board to assume a stronger leadership role, hold hearings, review programs, make recommendations, and speak on behalf of the cancer community. He also recommended that approved grants be funded at a 33 percent success rate, an increase of approximately 10 percent. He further stated the need for establishing a mechanism for the professional societies embodying the scientific expertise of the cancer community, e.g., AACR and ASCO, to provide input on programmatic goals and priorities of the NCI. It is essential for the National Cancer Advisory Board to have a regular conduit to and from the cancer research community. Dr. Bresnick indicated that because it is the largest society of basic and clinical cancer researchers, the AACR would appreciate the opportunity to function in this capacity as an *ex officio* member of the National Cancer Advisory Board. (This is not possible by mandate.)

A final strategy Dr. Bresnick espoused is an economic one—quantifying the contributions of medical research. For example, he stated, 40 years have been added to the life expectancy of individuals with testicular cancer due to improvements in its cure rate. The estimated economic benefit is $166 million annually, at a total investment over 17 years of only around $56 million. A similar economic approach should be documented for other cancers, even those for which cures have not yet been achieved.

Dr. Sigal stated her agreement with most of Dr. Bresnick's remarks; however, she explained that organizations such as the AACR, NCCR, and ASCO must assume a collaborating role and take initiatives to aid in the development of a more effective public relations effort. She explained the need for a cohesive effort by all of the cancer associations affected by the funding crisis and stated the importance of revising the Bypass Budget.

Dr. Broder commented on the conflict between the NIH administrative structure and the NCI substructure created by the National Cancer Act of 1970. He stated that while the leadership of NIH is not and has not been in dispute with the NCI, the creation of the National Cancer Act institutionalized a form of conflict by deviating the NCI administration from the standard chain-of-authority structure set in all Government agencies. He pointed out, however, that certain types of conflict may be productive, stimulating intellectual advance and creativity. Dr. Broder noted that the NIH Director's ambivalent view of the NCI is an administrative reality. He also alluded to the creation of certain specialized NCI authority expectations created by the National Cancer Act. He explained that although these specialized authorities exist, the standard Government chain-of-authority requirements still exist and the NCI needs to come to terms with this fact.

Dr. Broder indicated that the Bypass Budget is a reflection of scientific opportunities and professional needs which makes it unrealistic to expect the Bypass Budget to develop effects annually. He further stated that the statute establishing the Bypass Budget was developed for the purpose of writing a scientific needs budget and not a document that would

be considered acceptable by the public. He concluded that the Bypass Budget is simply a means of articulating scientific research opportunities.

Finally, Dr. Rabson commented on Dr. Bresnick's request for NCI's participation in the public relations involving the executive summary. He stated that the NCI does not have the authority to undertake such a task but he indicated that the AACR and the Coalition for Cancer Research can indeed assume this position and responsibility.

IX. UPDATE: BRCA1 GENE AND BEYOND—DRS. ROGER WISEMAN AND MARY-CLAIRE KING

Dr. Rimer acknowledged Drs. Mary-Claire King and Roger Wiseman as two distinguished visitors who have both made tremendous contributions in this area and asked Dr. Alan Rabson to provide a brief introduction. Dr. Rabson began by praising Dr. Wiseman as an example of the type of young scientist who can come out of university research training programs. He noted that Dr. Wiseman had an opportunity as a young scientist to work with Drs. Jim and Betty Miller, two of the giants in American cancer research. Dr. Wiseman is currently with the National Institute for Environmental Health Sciences, where the BRCA1 gene discovery was made.

Next, Dr. Rabson introduced Dr. Mary-Claire King, a true scientific leader. He noted that she majored in mathematics at Carleton College and received her Ph.D. from the University of California at Berkeley, where she worked with Dr. Alan Wilson, a great scientist who helped establish the field of molecular population genetics. Dr. King has continued her research at Berkeley and her goal over the past 20 years has been to put together what is known about the epidemiology of breast cancer, breast tumorigenesis, and molecular genetics, in order to identify genes responsible for breast cancer, both in women with inherited susceptibility to the disease and among women at risk for breast cancer for purely environmental reasons. Dr. Rabson explained that while Dr. King's group did not first clone BRCA1, she and her associates mapped the gene for chromosome 17q21, making it possible for several groups to apply the technology that ultimately led to cloning in 1994.

Presentation by Dr. Wiseman

Dr. Wiseman indicated that his presentation would focus on the development of both mutation screening techniques and animal models for BRCA1, a gene responsible for inherited predisposition to breast and ovarian cancer. He explained that recent efforts have been directed towards finding meaningful applications (for the general public) of the new information regarding mutations on BRCA1 as well as understanding the function of this gene.

BRCA1 is composed of more than 5,700 nucleotides and exhibits at least 22 coding exons that are spread out over a large portion of the genomic DNA. Dr. Wiseman explained that mutation screening of BRCA1 has been a difficult task due to the number of identified mutations and because virtually all mutations seem to be able to inactivate the gene. He indicated that his research has focused, in part, on attempting to improve the mutation screening techniques, including direct DNA sequencing.

Dr. Wiseman stressed that mutation screening techniques exhibit significant limitations and are far from becoming automated or applied on an industrial scale. The screening, therefore, of an individual's BRCA1 gene is still a major research project. Dr. Wiseman indicated that, until recently, major efforts have been guided towards the use of single-strand conformation analysis in an attempt to simplify the localization of mutations rather than relying on direct DNA sequencing, a relatively expensive technique. Single-strand conformation analysis involves denaturing simple polymerase chain reaction products that will subsequently acquire sequence-specific structural conformations. The single strands are then run on gels and their differential migration is determined. This approach has been applied by several groups to analyze the BRCA1 gene of approximately 100 families who had a high probability of carrying germ line mutations. Only 31 mutations were identified in this study, suggesting that genes other than BRCA1 exist or the technique is less sensitive than projected.

Dr. Wiseman pointed out that another observation derived from initial mutation screening studies seems to indicate that the majority of identified mutations on BRCA1 appear to generate truncated proteins. Recent efforts have, therefore, focused on the development of protein truncation assays. This approach involves generating a protein from a PCR product. *In vitro* transcription is performed on PCR products containing the bacteriophage T7 transcriptional promoter (introduced by the forward PCR primer) that is recognized by a T7 RNA polymerase. The synthesized mRNAs are added to reticulocyte lysates to generate a protein (labeled with ^{35}S-methionine) through *in vitro* translation. Qualitative analysis of the proteins by gel electrophoresis will reveal whether truncated proteins other than the wild type BRCA1 are present. Dr. Wiseman referred to an example of a patient with ovarian cancer and indicated that the patient had a germ line frameshift mutation that resulted in a truncated mutant protein. Dr. Wiseman explained that truncated proteins result from the addition or deletion of base pairs from the coding sequence of a gene which cause a change in the reading frame of the mRNA; this, in turn, leads to premature termination as the result of introduction of a stop codon in the new reading frame. Dr. Wiseman indicated that this assay confronts numerous technical and economic problems. Issues to be addressed include the maximum size of the PCR product that can be used with this approach. In addition, the reageants for the assay are fairly expensive.

Another screening technique called carbodiimide mismatch modification that has the potential to detect all types of mutations is in the early stages of development in Dr. Wiseman's laboratory. This new technology involves a chemical reaction that is based on the fact that carbodiimide reacts with both guanine and thymine residues when they are mispaired. Since the DNA polymerase cannot get past the block presented by the carbodiimide adduct, a truncated oligonucleotide results that is detectable by gel electrophoresis. The reliability level of this technique, however, appears to vary with sequence context; its final analysis may reveal an 80 percent effectiveness with numerous false-negative cases.

Dr. Wiseman noted that few clues regarding the function of BRCA1 have been derived from the gene product structure. Only one motif on the protein structure appears to exhibit functional significance; a ring finger at the amino terminus of the molecule coordinates two atoms of zinc through a single histidine and a series of cysteine residues. These types of sequences have been identified in at least 30 other proteins so far. Dr. Wiseman stated that BRCA1 may be a transcription factor that interacts with DNA in a sequence-specific manner to either activate or inactivate a specific series of genes that act downstream of BRCA1. Dr.

Wiseman indicated that studies have been initiated to identify such specific DNA binding sequences. He also pointed out that major efforts in his laboratory have focused on characteristics of the homologous murine gene to facilitate preclinical studies. While the BRCA1 gene appears to be highly conserved at the ring finger region, the gene's sequence homology between the two species diminishes dramatically after the amino terminus. Dr. Wiseman stressed the importance of performing homologous recombination studies to introduce defective forms of BRCA1 into the mouse germ line and obtain insights on the gene's function even when poor sequence conservation exists between species. Generation of three-dimensional structures—at least of the zinc finger domain—is being actively pursued in collaboration with the structural biology group at NIEHS.

Dr. Wiseman concluded his presentation by stating that BRCA1 seems to act as a tumor suppressor gene, since most mutations—which truncate the protein—correlate with a loss of gene function.

Presentation by Dr. King

Dr. King stated that the BRCA1 gene was recently cloned (fall 1994) and portions of its sequence will soon be publicly available for investigators to pursue their own research with this gene. She then explained that the original rationale for studying breast cancer in families was based on the hypothesis that cancer is always genetic in the context that it always involves alterations in DNA (although cancer is only occasionally inherited). Dr. King explained that 21 years ago when she initiated this research, the hypothesis formulated was that predisposition to breast and/or ovarian cancer could be inherited—this hypothesis has now been confirmed experimentally. Thus, research was aimed to evaluate families which have inherited this predisposition with an attempt to identify the genes which in this case were inherited in an altered form (i.e., inherited mutations). The overall goal of these studies has been to gain some understanding of the processes involved in ovarian and breast carcinogenesis both in women with inherited susceptibility to the disease and in women at risk for breast cancer due to environmental factors.

Dr. King remarked that the ability to accurately identify women at inherited high risk of developing breast cancer becomes undermined by the currently limited ability to prevent or treat this disease. Therefore, the present goal is to apply the information available on BRCA1 to develop proper prevention, early diagnostic tools, and treatment regimens.

Dr. King indicated that the remainder of her presentation would focus on the epidemiology of BRCA1, the mutations of the gene, and the speculative role that BRCA1 might play in carcinogenesis. She explained that mutations on BRCA1 have been found throughout the coding region. The only homology of BRCA1 with other genes appears to be at the zinc finger motif. Regarding the epidemiology of this gene, Dr. King indicated that women whose mothers and sisters are free of breast cancer have a risk of developing the disease of approximately 1 percent by age 50 and 9 percent by age 80. The risk of developing the disease is somewhat higher for women whose mothers and sisters have been diagnosed with breast cancer after the age of 50. In contrast, the risk is considerably higher for women whose mothers and sisters were affected at an early age (<40). Dr. King explained that one interpretation of these data is that in some families, who represent a subpopulation of families in the United States, there is indeed an inherited predisposition for developing breast cancer

which may or may not be inherited by a particular woman in that family. If this woman inherits the predisposition, her risk to develop the malignancy will be extremely high; however, if she does not inherit the predisposition, her risk will be that of the population as a whole. This interpretation proved to be correct.

Referring to the Cancer and Steroid Study performed at the NCI, Dr. King indicated that several epidemiologic remarks were suggested on the basis of statistical analysis of approximately 4,000 families. The first states that although breast cancer might only be attributable to inherited susceptibility in 5 to 10 percent of patients, women who carry the susceptibility alleles (inherited as an autosomal dominant trait) will have a risk of developing breast cancer of 86 percent by age 70. The second remark indicates that the risk of developing breast cancer by age 70 among women in the same families who did not inherit the susceptibility alleles is the same as that of the population as a whole. The third remark states that women carrying the susceptibility alleles will also have an increased risk for developing ovarian cancer. The best population-based estimates of ovarian cancer risk among women who carry BRCA1 mutations indicate a 10 percent risk by age 60. Dr. King pointed out that there is no consensus among investigators regarding this estimate; many suggest that the risk is substantially higher. She also stated that a more accurate estimate of ovarian cancer risk can be presently determined and this information will soon be publicly available. The final remark states that most cases in which more than one family member develops breast cancer occur by chance and are not due to inherited predisposition.

Dr. King pointed out that with the advent of linkage data in 1990 and subsequent years, the predictions inferred from the epidemiologic analysis were verified. Specifically, the risk of developing breast cancer among women who inherited the BRCA1 mutations is very high, approximately 60 percent by age 50 and over 80 percent by age 80. Similarly, women in the same families who did not inherit the susceptibility alleles have a 10 percent risk of developing the disease by age 80. Dr. King noted that the families in these studies were selected for having high risk of developing breast cancer and, thus, may not be representative of BRCA1 mutations as a whole. BRCA1 mutations conferring moderate, rather than severe, breast cancer risk have not yet been identified, but can now be sought.

Even though the lifetime risk of developing breast cancer among women who carry BRCA1 mutations or who have a substantial family history of breast cancer is remarkably high (44 percent for a woman whose mother and sister or two sisters were diagnosed before the age of 40), the risk of developing the disease in the next 10 years is low (2 percent) for women with the same family history (highest-risk families) but who are under the age of 20. Dr. King noted that these estimates are based only on epidemiologic data.

Dr. King presented a table illustrating the estimated probabilities of developing breast or ovarian cancer due to inherited mutations on BRCA1 under various scenarios. She indicated that these numbers represent rough estimates extrapolated from high-risk families and, therefore, precaution is advised for making strong inferences about them. The probability that a patient diagnosed with breast cancer before the age of 40 carries a mutation on BRCA1 is estimated to be 6 percent when no family history of breast and/or ovarian cancer exists. A similar probability has been estimated for a woman diagnosed with ovarian cancer before the age of 50 with no family history of breast and/or ovarian cancer. In contrast, the probability of developing breast and/or ovarian cancer due to inheritance of BRCA1 mutations is

substantially higher if a family history of two sisters or mother and daughter diagnosed with breast and/or ovarian cancer exists. The risk becomes increasingly higher when the family history involves three or more cases of breast cancer and ovarian cancer is present as well. Dr. King stated that these data also reflect a significantly higher incidence of breast cancer compared with ovarian cancer. While multiple cases of breast cancer can occur within a family simply by chance, the simultaneous occurrence of breast and ovarian cancer within the same family becomes a much greater indication that inherited susceptibility is involved.

Dr. King indicated that the age at cancer onset as well as the development of ovarian and/or breast cancer appear to be independent of the mutation site on the BRCA1 gene; that is, the type of cancer and the age at which the cancer will develop cannot be predicted from the mutation site. Dr. King remarked that most cancer-related mutations on BRCA1 are frameshifts or nonsense mutations leading to premature termination of the protein and conferring high risk. Missense mutations also occur on the BRCA1 gene that destroy the zinc-binding motif; these mutations also confer high risk.

Dr. King presented a number of examples of families exhibiting BRCA1 mutations to illustrate the complexity of this gene. In the first case, she indicated that most patients in the family who were affected with breast or ovarian cancer carried a mutant gene; however, two family members with breast cancer did not present BRCA1 mutations nor linkage to BRCA1. While a 73-year-old woman within the same family carries a BRCA1 mutation and has remained cancer free, her daughter died of breast cancer at age 33. It is unknown whether the daughter carried a BRCA1 mutation. To complicate matters even further, an unusual event is also present in this family; men with prostatic cancer also carry the BRCA1 mutation characteristic of their female relatives. Dr. King stated that the potential role of BRCA1 in inherited predisposition to prostatic cancer is unclear. The second example illustrated a family in which a tumor sample from the mother was not available but her four daughters had developed breast cancer and three of them had also developed ovarian cancer. The four daughters carried a mutation on the BRCA1 gene leading to a truncated protein. Each of the daughters has one daughter, all of whom have been found to carry the wild type gene; thus, none of the granddaughters inherited the BRCA1 mutation. The following example illustrated the opposite phenomenon; namely, a family in which all women with breast cancer presented a mutation on BRCA1 that also led to a truncated protein. Several women in this family, however, are at risk (carry the mutation) but have not yet developed the disease. It is unknown whether these women will soon develop the malignancy or the particular mutation they carry confers lower risk. Dr. King noted that this mutation has been found in multiple families, and it will be interesting to determine whether these families have the same original ancestry. Dr. King added that all patients with this type of mutation also carry a specific allele at a near polymorphic marker.

Dr. King referred to BRCA1 mutations involving the zinc-finger motif. The replacement of thymine by guanine produces a change in the amino-acid sequence (cysteine is changed for a glycine) which ultimately produces the loss of the zinc-binding motif; this mutation generates a protein that is not capable of binding to DNA. Another type of mutation that has been identified on BRCA1 is a splicing mutation at the intron-exon boundaries that alters splice sites, thus activating regions which originally had no function; these regions become cryptic acceptor splice sites.

Twelve of the 20 families being studied by Dr. King's group have exhibited BRCA1 mutations. She indicated that the remaining families exhibit a wild type coding sequence on the BRCA1 gene. The putative promoter sequence at the 5' end and the splice junctions immediately adjacent to the normal exons are also wild type. Although the BRCA1 mutation site for these families is still unknown, the complete genomic sequence of BRCA1 is currently being generated (more than 80,000 base pairs). Access to the genomic sequence will certainly assist in the determination of such mutation sites.

Dr. King noted that other genes in addition to BRCA1 exist that are related to inherited breast cancer (e.g., BRCA2). Of the families studied so far by her group, 22 have exhibited either direct mutations on BRCA1 or linkage to BRCA1; three have shown linkage to BRCA2 on chromosome 13; and two have exhibited linkage to the estrogen receptor. Nine families have shown none of the above. Dr. King stated that the biologic significance of these observations is unclear. The families that do not exhibit the above observations could reflect a combination of BRCA1 mutations that result in noninherited breast cancer. Similarly, these families could reflect a coexistence of BRCA1 and BRCA2. Dr. King mentioned that according to the data obtained so far, BRCA1 appears to be more involved in inherited breast cancer than BRCA2; however, this remark does not imply that BRCA1 is a better target for intervention if both genes are involved in the same pathway.

Two lines of evidence suggest that BRCA1 is a tumor suppressor gene. The first is indicated by the loss of normal alleles of BRCA1 in inherited breast and ovarian cancer. These tumors are hemizygous for BRCA1; in all cases, with no exception, the allele that is lost is the surviving normal allele and the one remaining is the mutant one. The second line of evidence is indicated by a decreased expression of BRCA1 in invasive breast tumors. These findings will be published in *Nature Genetics* in the near future.

Dr. King concluded her presentation by referring to a gene identified by Dr. Donnie Black which is located 295 base pairs from BRCA1. This gene was identified using antibodies against the CA 125 antigen, a tumor marker, and is transcribed from the DNA strand opposite BRCA1. Although the biologic significance of this gene (CA 125-related gene) in relation to either CA 125 or BRCA1 is unknown, Dr. King speculated on the role that it might have in relation to BRCA1. The first assumption that has to be made is that when the normal BRCA1 transcribes and the translated protein binds to DNA (a promoter), BRCA1 not only regulates its own expression but also that of the CA 125-related gene. If this assumption is true, when BRCA1 has a mutation resulting in a truncated protein or destruction of the zinc-binding motif, and the normal allele has been lost, there is no BRCA1 gene binding to the promoter, so the production of the CA 125-related gene is no longer under control and its product is now elevated. If this second assumption is also true, two possibilities exist: 1) the CA 125-related gene plays an important role in relation to BRCA1 and, thus, its increased expression will have important consequences in tumorigenesis; and 2) the CA 125-related gene has no effect on BRCA1, but its increased expression enables it to be a reliable tumor marker when BRCA1 is destroyed.

Questions and Answers

Dr. Day indicated that he would like to discuss with Board members the ownership of the technologies described in Drs. Wiseman and King's presentations. Dr. Rimer replied that this issue will be included on the next meeting agenda.

Dr. Freeman asked Dr. King whether there is a relationship between prostate and breast cancer and what is the proportion of prostate cancer patients exhibiting BRCA1 mutations. Dr. King replied that the proportion of patients with prostate cancer exhibiting BRCA1 mutations, which are either somatic or inherited, is not known but is currently being investigated at Johns Hopkins University. She also indicated that strong evidence supports an epidemiologic relationship between prostate and breast cancer. Female relatives of men with prostate cancer are at the same risk of developing breast cancer as are relatives of women with breast cancer diagnosed at the same age. Thus, prostatic cancer (in the father) is as good a predictor of breast cancer risk in an offspring as is breast cancer (in the mother). Dr. King remarked that the same is true in the opposite situation; male relatives of women with breast cancer are at elevated risk of developing prostatic cancer.

X. CLOSED SESSION

A portion of the first day of the meeting was closed to the public because it was devoted to a meeting of the Special Actions Subcommittee. A total of 1,040 applications were received, requesting support in the amount of $212,424,710. Of those, 1,040 were recommended as being eligible for funding at a total cost of $190,668,432.

XI. DRG: CLINICAL RESEARCH UPDATE—DRS. MARVIN KALT, JEANNE KETLEY, PAUL CARBONE

In his introduction, Dr. Kalt noted that it is obvious that clinical research is a high priority of the Board. Dr. Kalt stated that the Division of Research Grants (DRG) formed a Clinical Research Study Group to analyze practices in reviewing clinical research. He noted that the group has reached some preliminary conclusions and would be presenting them to the Board. Dr. Kalt informed the Board that Dr. Jeanne Ketley is Chief of the Clinical Sciences Review Section of DRG and Executive Secretary for the Clinical Research Study Group and Dr. Paul Carbone is Director of the Clinical Cancer Center at the University of Wisconsin and an NCI alumnus.

Dr. Carbone began his presentation by defining some terms integral to the Clinical Research Study Group. He said they define clinical research as patient-oriented research in which the patient and the investigator are "both alive and in the same room together." The term "laboratory-oriented research" is used in contrast to basic research. Dr. Carbone said the Study Group is an NIH-wide group representing a variety of disciplines and displayed a slide of the names of Group members.

Dr. Carbone then turned his presentation toward the questions the Group has tried to answer: 1) Do patient-oriented research (POR) grant applications fare less well than laboratory-oriented research applications in the review process? 2) If so, why do the POR

applications fare less well? 3) What should be done about the problem? Dr. Carbone then mentioned two other questions that have arisen: How broad-based is the perception in the academic community that there is a difference in the review outcomes of patient-oriented research versus laboratory-oriented research, and is the perception substantiated by the data?

Some of the ancillary questions the Study Group wished to answer were: 1) Are there differences in review outcomes due to study section composition, i.e., the grant applicant pool, the reviewers, or the review criteria? 2) Are the review outcomes due to a decrease in the number of trained physicians or clinical scientists or are they due to poorly prepared POR applications?

Dr. Carbone said the Group looked at several sets of data to try and answer the questions. They looked at oral and written testimony, comments solicited in a survey conducted by the General Clinical Research Centers Program Director's Association, and data from two grant cycles. He stated that the Group's proceedings and requests for presentations were widely circulated. In response, they received approximately 112 oral or written replies.

Dr. Carbone then described the oral and written responses that were received by the Study Group. He said the responses were from a diverse group of researchers from professional and academic organizations in a variety of disciplines. The majority of respondents defined clinical research as studies on intact humans or patients. Most also agreed that there should be an intent for patient contact or direct patient activities.

Most respondents thought that DRG-reviewed patient-oriented research applications fared less well than RFAs, which are Institute reviewed. Respondents thought that DRG study section members do not understand the importance of clinical problems, that the study section contains too few clinicians, and that the M.D.s in the study section are not doing clinical research. There was also some question as to whether these individuals are competent to review clinical research. About 10 percent thought there were no problems. Many respondents stated that study section members came from laboratory-oriented activities and were trained to look at hypothesis-driven research and do not understand applied or observational research.

Dr. Carbone added that a majority of respondents considered their clinical research training and their applications to be weak. Reasons for this opinion included too little research training, the complex nature of clinical research, the perception that bench research is more crisp and well-defined, and a different faculty environment for bench versus clinical research. When asked if they recommend that their trainees apply for NIH grants, most respondents replied in the affirmative. Many, however, suggest that they apply for RFAs or for subprojects and centers. Twenty percent of respondents said they advise their trainees not to apply to NIH DRG because they believe the chance of success is so low.

Dr. Carbone stated that many respondents believe it is difficult for a young investigator to be funded because patient-oriented research requires multiple investigators, and senior investigators have an easier time getting a group together.

Dr. Carbone next addressed the question of whether there should be a separate clinical investigations study section. Twenty percent of the respondents said there should not be a

separate study section for POR, while 40 percent said there should be. The remaining 40 percent thought that equity for POR could be reached by increasing the number of clinicians or appropriately trained clinicians on the current study sections. Dr. Carbone mentioned that there was a suggestion that NIH provide better training or set aside funds for investigators getting started in clinical investigation.

Dr. Carbone remarked that comments taken from the General Clinical Research Center's Program Directors' Association were similar to the written and oral testimony. They commented that the involved nature of the review process, quality of the grant applications, investigator training, NIH's focus on molecular research, and the fact that young investigators have too much clinical responsibility to devote adequate time to research are all factors in the poor fate of POR applications.

Dr. Ketley then reviewed the data analysis performed by the Group. She stated that the data were collected so they could determine where patient-oriented research is being reviewed and to assess the competitive state of the POR applications. Dr. Ketley said that they completed two surveys of grant applications and one survey of study section members, and performed an analysis of summary statements to attempt to determine the aspects of a clinical research project that are critical for success.

The first survey of grant applications was conducted before the Study Group met and was a more generalized survey of research conducted with humans (or on material of human origin) that had clinical applicability. Dr. Ketley noted that the data were collected by the Scientific Review Administrators (SRAs). The second study was targeted to POR. The surveys were then compared and the results, Dr. Ketley stated, were remarkably similar. The survey data are from applications submitted for the January 1994 council round and the October 1994 council round. In the January and October rounds, the number of applications related to human subjects was 32.8 percent and 32.3 percent, respectively. The data also show, however, that while the number of applications related to human subjects was the same, the proportion related to POR was around 22 percent in both studies. Thus, if one were to look only for the presence of human subjects as the criteria for POR, the results would be inaccurate.

In looking at only those applications with human subjects, Dr. Ketley said that some applications were considered clinical and some were considered nonclinical. While the first survey divided clinical research into five categories and the second survey divided clinical research into three categories, the percentages that were considered primarily patient-oriented were very similar.

In presenting the results of the study, Dr. Ketley stated that the Group wanted to determine a way to present review success, but did not want to use award as the end point. She gave two reasons for this decision. First, they did not want to wait for the awards for the second round under study to be made, and, secondly, award rates take into account Institute priorities. The Group decided to use placement in the top 20th percentiles (even though they are not all funded) as their definition of success. They also used placement in the 50th to 100th percentiles as an indicator of lack of success.

Dr. Ketley noted that clinical research has the smallest number of applications in the top 20th percentiles and the highest "not recommended for further consideration" rate. In looking at the clinical research categories, she remarked that therapeutic intervention has the lowest percentage of applications in the best percentiles. Epidemiological studies, she added, are doing quite well.

In looking at the award rates for the first survey, they were able to verify that clinical research applications had the lowest success rate. The Group concluded that patient-oriented research does fare less well than laboratory-oriented research in DRG study sections. In looking at amended applications, Dr. Ketley stated, the data show that, initially, clinical research does not fare well, but when it is amended, it does almost as well as nonclinical research with human subjects or research with no human subjects. After analyzing the data, they determined that fewer clinical research applications are being amended and resubmitted.

Dr. Ketley reviewed the Group's research on how the degree status of applicants affects the outcome, and stated that they found no difference between Ph.D.s and M.D.s in the top 20th percentile. She noted that there are many Ph.D.s doing patient-oriented research.

The Study Group also reviewed the effects of cost on outcome and determined that cost does not seem to be a confounding factor. They also looked at the study sections. First, they looked at which study sections were reviewing the largest amount of patient-oriented research. Dr. Ketley showed a chart of the top 10 study sections in terms of percentage of POR reviewed, and concluded that POR is doing pretty well in these 10 study sections. The study sections were then grouped by the percentage of their applications that were patient-oriented. The Group looked at the association between patient-oriented research status and the percentile group it is in. The expected percentage of applications scoring in the 20th percentile was calculated, and there appears to be an association between the review success of the POR application and the number of POR applications in the study section—the fewer the applications, the poorer the review success.

Dr. Carbone then reviewed the study "questions and answers." Does POR fare less well than laboratory-oriented research? Yes. Are there differences due to study section composition? Yes. Does the percentage of POR applications in the pool influence the outcome? Yes. Is there a relation between the reviewers and the outcome of POR applications? Dr. Carbone said that there are not enough data to assess this yet. The data also are not definitive on whether training of clinical scientists, complexity of the projects, and duration are issues and whether the POR applications are less well written than laboratory-oriented research applications. The differences between POR and laboratory-oriented research success does not seem to be due to cost, he noted.

Dr. Carbone then reviewed the recommendations. First, grant applications with POR should be reviewed by study sections reviewing a majority of grants in that area. Second, review criteria should be developed by NIH to define good POR and serve as a guideline. Third, there should be an attempt to define the kind of background and experience necessary for individuals reviewing POR applications. Fourth, a tracking mechanism to follow the outcome of these grants should be instituted. Fifth, DRG and NIH should be more proactive in providing clarifying information on the reason for the fate of a grant application. Sixth, a

review of the clinical training mechanism should be undertaken by the Institutes. An intermediary support mechanism might be developed beyond the training grant mechanism.

Dr. Carbone concluded that the reorganization of study sections could take place with little administrative difficulty and could be carried out quite quickly if the NIH agrees to the recommendation.

Questions and Answers

Dr. Calabresi asked why a study section with a 50 percent POR grant pool would improve the current situation and why a clinical study section entirely devoted to reviewing POR was not recommended. Dr. Carbone noted that the findings showed that about one-third of the study sections have grant pools with at least 50 percent POR applications and in those sections the POR applications do reasonably well and that is the basis of their recommendation. Dr. Calabresi reiterated that there is a crisis in clinical research and that something should be done about it.

Dr. Salmon moved that the Board support the implementation of the report by DRG.

Dr. Day asked if there is a correlation between who is a member of the study section and the percentage of POR applications the study section reviews. Dr. Carbone replied that there were not enough data to determine the answer to that question. He added that it is hard to categorize people and that people self-categorizing may not be objective. Dr. Day asked if translational research, which lies between patient-oriented and laboratory-oriented research, was considered. Dr. Carbone answered that they only broke down the research into the two categories. Dr. Day then asked if there was any association between disease category and how an application fared. The response was negative—there was no association by disease category. Dr. Day then suggested that they consider disease-oriented study sections. Dr. Carbone mentioned that their data do not cover clinical trials and RFAs, but general investigator-initiated research applications, and many of the study sections see applications that cross all Institutes.

Dr. Bishop wondered if there is a training or mentoring problem, since amended applications seem to do so well—an indication that the initial applications are poorly prepared. Dr. Carbone responded that he believes the low reapplication rate is attributable to the perception that the POR applications do not do as well.

Dr. Calabresi remarked that it is his understanding that many young M.D.s who do apply for POR grants and are turned down, then go on to an entirely clinical route; however, investigators doing laboratory research do not have the clinical path as an option and therefore amend their applications and resubmit them. Dr. Bishop reiterated his belief that Dr. Calabresi's remark illustrates a mentoring problem, and the senior leadership in clinical research should be sending a different message.

Dr. Broder stated that NCI has used the RFA process to, in effect, try to correct for this problem. He added that there are some disciplines, such as surgery, that will require additional encouragement to stimulate clinical research in those fields and that should be taken into consideration in any changes to the review structure.

Dr. Dickersin suggested that the formation of collaborative groups should be recommended to all clinical researchers. She noted that it is her experience that, often, the problem with POR applications is that the researcher is trying to work alone and is weak in a particular area such as study methodology. She added that comments could be more explicit, i.e., telling the researchers the types of people with whom they should collaborate, and that assistance in the application process prior to submission might also be useful. Dr. Dickersin also asked about the continuation of the Study Group's research and if they plan to review applications in multiple study sections to see what effect that might have.

Dr. Ketley responded to the last of Dr. Dickersin's questions by saying that they have not determined how to mask the applications for review in multiple study sections, so they have not been able to perform that experiment.

Dr. Salmon stated that he believes it would be useful for the criteria of excellence developed for the study sections to be disseminated to the research community. He added that the RFA process can be viewed as a type of mentoring.

Dr. Bishop remarked that the primary responsibility of the Board is to try to make the R01 system more accessible to clinical investigators, thus opening the system up to the broadest research interests. Dr. Carbone commented that the entire training issue needs to be examined, and that an intermediate mechanism between the R29 and R01 should be considered.

Dr. Salmon moved that the National Cancer Advisory Board recommend implementation of the Clinical Research Study Group's report. The motion was seconded and unanimously approved.

XII. ARIZONA CANCER CENTER—DRS. ALAN RABSON AND SYDNEY SALMON

Dr. Rabson begn his introduction by reviewing Dr. Salmon's life history. He noted that Dr. Salmon was born in Staten Island, New York, and moved to Arizona when he was 12 years old. Dr. Salmon attended the University of Arizona and received his bachelor's degree in 1958, and then attended the Washington University Medical School in St. Louis. He spent 2 years as a PHS training fellow while at Washington University, where he published a paper on endocrinology. He then did his internship and residency in medicine at Strong Memorial Hospital. Dr. Salmon was then commissioned in the Public Health Service in 1964 and worked in a cancer research unit in Boston. Dr. Rabson noted that it was at this time that Dr. Salmon developed his interest in myeloma. Dr. Rabson observed that while at the PHS hospital in Boston, Dr. Salmon developed a tie with the immunology group in the Department of Pediatrics at Harvard Medical School and published a number of papers with them. Dr. Salmon then studied with Dr. Hugh Fudenberg in San Francisco before returning to Arizona in 1972 to lay the groundwork for the Arizona Cancer Center (ACC) with a P20 planning grant. In 1976 he was named the first Director of the Cancer Center and in 1978 they were awarded their first core grant as a clinical research center. Dr. Rabson then read some glowing descriptions of Dr. Salmon culled from a number of NCI summary statements.

Dr. Salmon began his presentation by showing a slide marking the location of Arizona within the United States. He stated that Arizona has a population of 4.6 million, of which 1.6 million live in the Phoenix area and 800,000 in the Tucson area. He also noted that there are approximately 200,000 Native Americans who live in Arizona.

Dr. Salmon informed the audience that the Arizona Cancer Center has been one of NCI's designated Comprehensive Cancer Centers since 1990. He mentioned that they began their Basic Research Program and Cancer Prevention and Control Program in 1980. Regarding the earlier discussion on mentoring, Dr. Salmon noted that the former heads of those two programs are now the head of the Cancer Center at the University of California, Irvine and the Intramural Director of the Center for Human Genome Research.

Dr. Salmon stated that the ACC was a Center without walls until 1986, when their cancer center facility was completed. He then showed a slide of the facility, noting that the Center has clinical outpatient facilities, research laboratories, and shared services in the upper two floors, an education and administrative section in the basement, and a biometry section in the middle of the building. Inpatients are hospitalized in the adjacent University Medical Center.

The Center is organized as a matrix, as opposed to some other cancer centers which are freestanding. Dr. Salmon explained that the Center is a Division of the College of Medicine serving the University of Arizona's student population of 35,000. The Center has its own space, budget, and development and communications offices. They have seven funded research programs, with 164 full members from 21 departments and six colleges. They also have 32 associate members, many of whom are located in the community. The Center includes four Divisions: Basic Research (with programs in cell biology, immunobiology, pharmacology, and molecular carcinogenesis), Clinical Research (with programs in cancer diagnosis and cancer treatment), Prevention and Control, and Research, Education, and Training.

Dr. Salmon then enumerated the program projects the ACC runs. Six are from the NCI, he said, and they are in prostate cancer, cytogenetic oncology, medical oncology, nuclear medicine, skin cancer prevention, and colon cancer prevention. The seventh program project is funded through a competitive grant mechanism from the State of Arizona.

Dr. Salmon then described some of the specific research being done by the ACC. He first described some work being done in prostate cancer. The program focuses on carcinogenesis in human prostate cancer and in processes of invasion and metastasis. He noted that research is being done on the role of proteases, particularly metaloprotease and its inhibitors in prostate cancer invasion. Matrilysin, a metaloprotease, is rarely expressed in healthy human tissue; however, it is often expressed in human prostate cancers. To determine whether or not matrilysin plays a role in the invasion process, the gene for matrilysin was placed in a vector and introduced into human prostate cancer cell lines that did not express the protein. The transfected lines showed no change in cell line expression of the inhibitor. In SCID mice transfected with the metaloprotease, 70 percent showed invasion of the prostate cancer, while less than 10 percent of the untransfected mice had invasion and metastases. These studies suggest a possible role for matrilysin in the early process of prostate tumor invasion.

Next, Dr. Salmon reviewed the ACC's research in combinatorial chemistry. He commented that the program was initiated through a program project grant and now is primarily supported by the National Cooperative Drug Discovery Group. They first developed random peptide libraries and applied them to cancer to identify potential inhibitors of protein kinases, ligands for the Her-2 oncogene product, B-cell lymphoma, and cell surface idiotype receptors, among others. Using solid-phase peptide synthesis and a mixing system, each solid-phase bead has a unique peptide sequence. The beads are then probed for a potential ligand using immunochemistry, immunofluorescence, or radioactivity to identify the ligand down to a specific bead. The bead is then physically removed and the sequence of the ligand determined for any given molecular target. This technique has been applied in a number of ways.

Dr. Salmon described the technique as applied to posttranslational modification sites on cyclic ATP-dependent protein kinase, but noted that it has also been used on the *sarc* family tyrosine kinases, protein kinases, and other targets.

The technique, Dr. Salmon said, uses a synthesis of a random peptide bead library, usually 3 to 5 million individual unique peptides with each peptide on an individual unique bead; P32-labeled ATP and protein kinases are added and incubated, and the beads are then washed and immobilized on glass with agar. An autoradiograph is then prepared identifying the labeled beads, which are then removed, diluted, and retested. The beads with the highest labeling are recovered and the specific peptide sequence is determined using automated amino acid sequencing.

Dr. Salmon showed a slide of labeled hepto-peptides for the *sarc* protein tyrosine kinase. A total of 50 strongly positive beads were screened out of 500,000. He then showed a slide comparing the binding affinity of the best known natural ligand to the one detected from the bead library. Dr. Salmon explained that these are the first steps in identifying a ligand. The next step is to get a more potent one and, finally, to convert from the ligand to an inhibitor of the enzyme. The combinatorial library, he summarized, can be applied to a variety of cancer targets and identification of functional ligands binding to cancer targets can add to the understanding of a molecular recognition mechanism and result in a new drug discovery.

Dr. Salmon then discussed the ACC's efforts in researching multidrug resistance (MDR). He stated that they have looked for the expression of multidrug resistance MDR1 p-glycoprotein in hematologic malignancies and worked on the development of inhibitors of MDR for cancer therapy. More recently, he added, they have looked at non-p-glycoprotein forms of MDR.

Cancer cells expressing the p-glycoprotein will pump out the drug through active transport before the drug has a chance to work. Multiple myeloma patients previously untreated or treated with very low doses of natural products infrequently express p-glycoprotein; however, patients treated with a lot of doxorubicin have a high expression of p-glycoprotein. Researchers discovered that a variety of chemosensitizers could inhibit p-glycoprotein expression. These chemosensitizers were tested in clinical trials in myeloma patients who were resistant to doxorubicin and vincristine. Approximately 23 percent were brought back into remission with use of the chemosensitizer. In non-Hodgkins lymphoma, 73 percent of the patients who had relapsed were brought back into remission, including 26

percent complete remissions. Dr. Salmon noted that this finding has been confirmed through NCI's clinical trial in non-Hodgkin's lymphoma using D-verapamil.

Dr. Salmon explained that chemosensitizers have been shown to be effective in gaining remission in leukemia patients as well. In an aside, he remarked that acute leukemia patients who had relapsed showed reduced levels of p-glycoprotein, suggesting that a new resistance mechanism not related to p-glycoprotein takes over. In summarizing the chemosensitizer research, he said his group believes chemosensitizers have some clinical utility and they have several agents in early development that are designed to overcome resistance.

Next, Dr. Salmon described the Prevention and Control Program. He noted that this group performs translational research in skin and colon cancer prevention, nutrition, and chemoprevention. Recently, they performed a large randomized clinical trial using intermediate markers and molecular genetic markers and looking at safety monitoring. He added that retinoids and seleniums have been studied in skin cancer prevention, and fiber, calcium, and prostaglandin inhibitors have been studied for colon cancer prevention.

Dr. Salmon then discussed the accrual and early results from some skin cancer studies. He noted that Arizona has a skin cancer rate approximately four times the national average. The trial compares placebo versus retinol versus vitamin A in treating the premalignant lesion, and actinic keratosis after resection. Of 2,800 subjects, 719 were treated and randomized to the placebo versus vitamin A versus retinol. Placebo versus selenium was tested in 1,700 subjects. Dr. Salmon reported that results from the study show that subjects treated with retinol had a significant reduction in squamous cancer incidence compared with subjects treated with placebo.

Dr. Salmon then described the ACC's colon cancer prevention research. The formation of recurrent adenomatous polyps was used as the intervention evaluation point. Researchers started with early Phase I and Phase II trials with wheat bran fiber in a retirement community. A Phase II study in colorectal cancer patients was performed that looked at colon cell proliferation in patients receiving either wheat bran or placebo. A larger Phase III study was performed in patients with sporadic polyps.

The most recent study, Dr. Salmon explained, is not yet completed and includes 4,407 randomized patients from 700 hospitals enrolled through 27 gastroenterologists. Of the 4,407, 1,406 were eligible and 1,330 were randomized after a period of renin. Eighty patients have completed the study.

Dr. Salmon then presented the conclusions from the various studies. He said that the preliminary conclusion is that skin cancer incidence is reduced with retinol. The results of the selenium trial are still coded, but are nearly ready for final analysis after an audit is performed. The wheat bran colon polyp trial has shown that wheat bran fiber reduces the colon bile acid concentration intraluminally. He added that as a mechanistic follow-up, 1,400 patients have been randomized for a genetic study of polyps. Future plans, he said, include testing the bile acid hypothesis using ursa deoxycholic acid for chemoprevention of colon polyps.

Dr. Salmon concluded his presentation by discussing the ACC's future plans. He said that they are recruiting in the area of molecular biology. They are planning for clinical

research in an era of health care reform primarily by working out contractual arrangements with those health care organizations that will allow research. The ACC also has an active expansion program, and is looking to double their laboratory and clinical research space by adding 54,000 square feet. The project will cost $22.5 million. The ACC has raised $19 million in cash or pledges and received an additional $1.57 million through an NCI construction grant. They are scheduled to break ground for the new space in May 1995. Dr. Salmon then showed an artist's rendering of the new facility.

Questions and Answers

Dr. Broder asked whether the designation as a Comprehensive Cancer Center has had any demonstrable effect on the ACC. Dr. Salmon replied that he does not think it has had an effect on grants, but that it has had an effect on status recognition and donations.

Dr. Bishop asked if the timeframe for developing the ACC is typical for cancer centers in general. Dr. Salmon said that their timeframe is typical.

Dr. Chan asked about the origin of the patients who use the Center. Dr. Salmon replied that approximately 80 percent are from Arizona and the rest are from other parts of the United States, and a very small percentage from overseas. He added that the patients who come from outside of Arizona are mainly interested in treatment for myeloma, lymphoma, and breast cancer.

Dr. Day asked if there has been a change in areas such as patient accrual at the University Hospital due to managed care. Dr. Salmon said that managed care has had an impact on accrual to trials, especially accrual of minorities. He remarked that they are trying to get a law changed regarding indigent health care in Arizona. University Medical Center was not among those contract recipients even though they had a competitive application. This problem produced a marked reduction in accrual of Hispanics. Dr. Salmon said they are experimenting with capitation. He added that they are negotiating for a capitation contract with about 15,000 lines for any kind of cancer treatment.

Dr. Goldson recommended that the issue of the penetration of managed care facilities into research hospitals be addressed at a future Board meeting. Dr. Rimer replied that the topic will be discussed at the May meeting.

Dr. Dickersin asked if there is a fixed number of Comprehensive Cancer Centers and the reply was that there is not. She also asked if not having the Comprehensive Cancer Center designation is detrimental to a center. Dr. Salmon responded that he feels that while having the designation is beneficial and allows for additional public relations efforts, he does not think it is a drawback if a center does not have the designation. Dr. Broder added that he believes the Comprehensive Cancer Center is very important in that it sets criteria which an institution can adopt or choose not to adopt separate from its core grant. It also provides an important internally driven incentive to expand the scope of its activities. Dr. Salmon also agreed with Dr. Broder that the Comprehensive Cancer Center Program is extremely important, especially for bringing cancer prevention and control research into the major cancer centers.

Dr. Day asked if the ACC treats many Medicare patients, since Medicare does not pay for investigational care. Dr. Salmon said that it has not been a problem for them, except in a few cases in which the treatment is highly investigational.

Dr. Sigal asked if the ACC has affiliations with other hospitals within Arizona and outside of Arizona. Dr. Salmon said they have just formed agreements with some hospitals outside of Arizona and are negotiating agreements with some hospitals within Arizona. He added that there is a very active network of community oncologists and others with whom they work.

Dr. Goldson mentioned that forming collaborative links with community hospitals is the best way to compete with the managed care organizations. Dr. Rimer added that they will be looking at ways to thrive under different kinds of health care models.

Dr. Vaitkevicius asked how the ACC matrix system works. Dr. Salmon explained that the ACC is a Division of the College of Medicine. The faculty of the Center are members of a primary department. The Center has control over both financial resources and space management. He added that the University College of Medicine has a Centers of Excellence Program that includes a heart center, an arthritis center, and a cancer center.

XIII. SUBCOMMITTEE REPORTS

Ad Hoc Working Group

Dr. Paul Calabresi reported to the Board on the activities of this working group, which he chairs in conjunction with Dr. Michael Bishop. He informed members that the group has just added a twelfth member, Dr. Karen Antman from Columbia University and President of the American Society of Clinical Oncology (ASCO). He added that a roster of the committee has been made available for those who want to examine it. The group has held two meetings, with the most recent occurring on December 7, 1994. He noted that there is a tremendous amount of information to become familiar with regarding the operations of both the NIH-wide and NCI-specific intramural programs. Dr. Calabresi indicated that working group members have conducted an in-depth review of the premises of the Marks-Cassell intramural report with Drs. Gottesman and Broder. The group has also interviewed both Drs. Broder and Vince DeVita, who was Dr. Broder's predecessor as NCI Director, to discuss their views regarding research priorities for intramural programs. In addition, the working group has begun interviewing other NCI program directors, past and present chairpeople of the Board of Scientific Counselors, and key intramural staff. This December meeting focused on the Frederick Cancer Research and Development Center, and the next session will target clinical and prevention programs, during which Dr. John Gallin, Director of the NIH Clinical Center, Dr. Bruce Chabner, Dr. Peter Greenwald, and other members of the NCI Clinical Intramural Program will speak. Dr. Calabresi announced that these meetings will be kept open to the public whenever possible, and provided the times for the open sessions of the next meeting: a short meeting Tuesday evening, January 23rd, at the Bethesda Hyatt, and Wednesday morning, January 24th, at 8:30 in Building 31 of the NIH campus.

Dr. Calabresi stated that future meetings will explore the cancer-related portions of AIDS programs in terms of planning, oversight, resource allocation, and evaluation. The

advantages and disadvantages of creating distinct intramural programs or combining intramural and extramural missions will also be explored. Dr. Calabresi commented that future meetings, dates, and the agenda for the January meeting are available from Dr. Marvin Kalt. He added that working group members will meet monthly until the next NCAB meeting on May 15, 1995, in order to be able to present a comprehensive and concise view of NCI's intramural programs, which can serve as a foundation for a final document of recommendations that can be submitted to Dr. Harold Varmus.

Dr. Rimer thanked Dr. Calabresi for his presentation and commended the quality of the December presentations. Dr. Day expressed his concern that the Ad Hoc Working Group includes no representatives from cancer control, prevention, or epidemiology, and therefore these areas might not receive a fair priority rating. Dr. Calabresi replied that while this is a good point, the appointments have been generated by Dr. Varmus, and numerous groups have lobbied to gain a representative in the working group. He emphasized the need to keep the group small and the amount of energy expended to update new members, which works against the goal of completing the entire review within 6 months. Dr. Bishop responded as well, by stressing that the working group is primarily concerned with issues of cost-effectiveness and quality control, not establishing program priorities. It is a misconception to think that the working group will make recommendations regarding its submissions. Dr. Dickersin reiterated Dr. Day's concerns and asserted the importance of having an epidemiologist or biostatistician present for at least the meeting on clinical research. Dr. Rimer agreed and suggested that someone from NCAB who works in these fields should attend the next working group meeting on the evening of January 23rd. Dr. Calabresi pointed out that all of the meetings are open to NCAB members, even those that are closed to the public, and that their input is encouraged.

Cancer Centers

Dr. Robert Day reported on the Cancer Centers Subcommittee meeting. He explained that they first addressed the issue of the sliding scale ratio, which may be employed to limit the size of a core grant at each center in proportion to the total amount of NCI-supported research and training at each center. He indicated that committee members decided to wait until Congressional funding allocations are made before making a decision on core grant funding caps. Dr. Day added that Dr. Holmes, who is involved in administering the cancer centers, provided a comprehensive review of measures that have been used to distribute funding equitably among these facilities during a wide range of funding situations. He concluded that committee members are now familiar with the options in terms of distribution mechanisms and will await budgetary action by Congress to see if any need to be implemented.

Dr. Day announced that the Subcommittee also discussed several issues relating to the SENCAP report, including the distribution of cancer centers. He explained that the report included several recommendations in terms of expanding the cancer centers to include geographic areas containing large proportions of underserved population members. One method to achieve better geographical distribution is to use planning grants to extend the Cancer Center Program. The SENCAP report also recommended that an additional $60 million be allocated each year for translational research within the cancer centers. The Subcommittee recommended that a peer review mechanism be established within NCI for the

purpose of reviewing translational research, which could utilize similar mechansims that have been created to augment specific areas of NCI interest in the past.

The Subcommittee also discussed whether cancer centers should focus on providing support for investigators to foster careers in translational research. Several training mechanisms and other recommendations were considered and Dr. Day stated that this discussion will be continued at the next Subcommittee meeting. He reported that in response to a request by Dr. Broder during the December 1994 meeting, the Subcommittee also discussed the P50 SPORE program in comparison with the P30 cancer support funding mechanism. The Subcommittee unanimously resolved that if the number and geographic distribution of P30 cancer centers would be negatively impacted by the funding of SPORES, the SPORE budget should be reduced. Dr. Day concluded by commenting that the Subcommittee will probably meet one more time before the May 15, 1995, NCAB meeting. Dr. Rimer indicated that the next NCAB meeting will include further discussion of the effects of managed care, the SENCAP recommendations, and the review process on cancer centers. A motion was made and seconded to approve the committee minutes.

SENCAP

Dr. Paul Calabresi, reporting for the Subcommittee, stated that on December 13, 1994, Congressional staff members met with Dr. Freeman and himself to discuss the SENCAP report *Cancer at a Crossroads* recommendations. He indicated that his general impression from that meeting was that there would be no funding increases for the National Cancer Program during the next fiscal year; however, Congressional staff expressed their interest in receiving guidance in terms of the relative order of priorities. Dr. Calabresi acknowledged Dr. Freeman's conclusion that the Appropriations Subcommittee had expected a more detailed report on National Cancer Program research priorities, and desires specific input regarding creative mechanisms for effectively distributing funds. Dr. Calabresi informed members that Ms. Dorothy Tisevich suggested that a message to give Congress is how vitally important biomedical research is to accomplishing the goals of the National Cancer Program. In regard to Dr. Sigal's suggestion that a continuing dialogue with Congress be established, Dr. Calabresi noted that Congressional staff members are very receptive to future meetings and one is tentatively scheduled in 6 months.

Dr. Calabresi announced that both he and Dr. Freeman have been invited to speak at several meetings regarding the SENCAP report, *Cancer at a Crossroads*. In addition, the Executive Board of the American Cancer Society (ACS) passed an endorsement of the report and the editor-in-chief of *Cancer* wrote a letter to Dr. Calabresi requesting that the journal be allowed to publish sections of the report. He explained that SENCAP members have agreed that garnering the support of major organizations for the report's recommendations would help emphasize the importance of the NCP to Congress. To this end, SENCAP members were requested to assist in gaining the endorsement of these organizations and to encourage groups to outline their own priorities in terms of the report's recommendations.

Dr. Calabresi reported that SENCAP members also agreed that it is essential to avoid duplicative research among the various organizations conducting activities under the NCP. It was suggested that a group be convened to discuss mechanisms for diversifying the cancer-related research agenda. Dr. Brian Kimes, it was noted, has recommended that an examination

of NCI's use of current resources be undertaken. For cancer centers, Dr. Kimes emphasized the importance of broadening translational research efforts and supporting the development of an infrastructure that is conducive to innovative research ideas, while stabilizing prevention and control research. Dr. Kimes also commented that while, traditionally, recognition is achieved through independent research, much of the work necessary for translational research must be conducted in teams and may get very little recognition under traditional practices.

Dr. Calabresi added that Dr. Friedman stated that it will be necessary to make specific targeted recommendations and suggested that the SENCAP can help the NCI identify program priorities. The Subcommittee members agreed that their role should entail coordinating the implementation of the overarching SENCAP recommendations, four of which were presented in the executive summary, and tracking the progress made toward meeting recommendations chosen for emphasis by the various NCAB Subcommittees. It was also suggested that the NCAB's chairperson reconsider the existence of this Subcommittee at the end of 1995, and that it be dissolved if it is no longer needed. He suggested that this decision be based upon whether the goals of the report have been achieved.

Dr. Calabresi stated that Ms. Cherie Nichols presented an extremely important program that is being designed to provide for planning and pilot testing for an inventory and analysis of all cancer-related research activities across Federal agencies. This would allow better allocation of research money and more coordinated efforts. Final approval of this project is expected to come at the end of January and, if obtained, a contractor will be hired to begin this initiative. Dr. Calabresi commented that it was suggested that both NCAB Federal *exofficio* members and other Federal representatives associated with cancer research would comprise an excellent staff for a working group to coordinate this activity. These individuals may also be able to help the Subcommittee arrange appointments with senior staff in their agencies, perhaps at a cabinet level, as well as to provide advice on ways to communicate with other agencies. Dr. Calabresi emphasized the importance of involving those agencies that are not represented on the NCAB. Dr. Rimer moved to approve the minutes, which were accepted.

Clinical Investigations

Dr. Calabresi informed the Board that this Subcommittee discussed two topics: the funding status for clinical research and P01 grants. The group was originally scheduled to also present an update on the National Surgical Adjuvant Breast and Bowel Project (NSABP); however, since that information was not presented until after the Subcommittee meeting, this was not possible. Dr. Calabresi stated that Ms. Diane Bronzert provided an overview of the funding status for clinical research, which she indicated will primarily focus on programs supported by the Clinical Trials Evaluation Program (CTEP) and will not involve related clinical research areas, such as biologic response modifiers, radiation, and diagnostic imaging. Dr. Calabresi told members that Dr. Freeman pointed out that the expansion of translational research is primarily funded by special set-asides. Ms. Bronzert reported that three clinical research-related programs, which primarily target young investigators, have been initiated, including the R03 small grants program, which is funded at $50,000 per year; the R21 exploratory grants program, which is funded at $100,000 per year with a 2-year limit; and an RFA for clinical cancer therapy research, which received a $1.5 million set-aside. These programs mandate that applicants be at the start of their research careers. Dr. Calabresi

indicated that the Subcommittee decided that this presentation should be made to the entire NCAB at a future meeting, as a brief description would not provide enough detail.

Dr. Calabresi continued by relating the highlights of Dr. Roy Wu's presentation regarding the history and current status of the P01 review and scoring policy. Dr. Wu explained that until 1988, NCI approved applications through three standing parent committees. In 1988, the Institute transferred responsibility for the approval process to ad hoc committees, which require that each application be reviewed onsite and scored individually. For fiscal year 1995, this review policy was altered once again, and the task was assigned to three subcommittees from one standing parent committee. Dr. Calabresi commented that the Subcommittee members decided that this discussion should also be presented in its entirety to the NCAB, as the details of the presentation are extremely important. He reported that Dr. Wu presented scoring statistics for these grants, which indicated that a large proportion of the clinical grants were funded as exceptions, not the standard mechanism. Dr. Calabresi added that Dr. Wu raised several issues regarding funding and review of P01s, which are listed in the Subcommittee report, including: methods for ranking P01s; whether a funding ceiling should be established for P01s; and whether site visits should be terminated, along with possible alternatives to site visits. Dr. Rimer commented that this presentation would be appropriate in combination with the earlier one on the RFA review process.

Dr. Chan indicated that his name was omitted from the roster of the Clinical Investigations Subcommittee meeting. Dr. Rimer asked that the minutes be corrected to include his name. As there were no additional questions, Dr. Rimer called for the minutes to be approved. The motion was made and seconded.

Information and Cancer Control

Ms. Marlene Malek presented the report of this Subcommittee's meeting. She began by explaining that the group is involved in an ongoing project—monitoring the progress made toward the goals of the Healthy People 2000 report. The committee is holding a series of sessions, each of which focuses on a particular goal area. The area discussed at this meeting was tobacco related, and Ms. Malek stated that she would share the highlights of the discussion with the NCAB. She reminded members that the Year 2000 tobacco objective is to reduce smoking prevalence to no more than 15 percent among people age 20 and older by the Year 2000. Various representatives from Governmental and volunteer organizations involved in tobacco control efforts made presentations at the meeting. Ms. Malek informed members that it is clear that this objective will not be met, and that the prevalence of smoking will more likely be approximately 19 percent at the year 2000. She added that none of the other 16 tobacco-related goals will be reached either.

Ms. Malek announced that the largest proportion of smoking cessation has occurred among young African Americans. Overall, youth smoking increased 2 percent, despite the drop in smoking among AfricanAmerican youths; 15 years ago the smoking incidence among these two populations was approximately equal. She reported that most of the speakers emphasized that smoking is a pediatric disease and that tobacco control efforts must target youth.

Ms. Malek informed NCAB members that representatives from the EPA, CDC's Office on Smoking and Health, FDA, NCI, ACS, the Coalition on Smoking OR Health, and California's Department of Health presented their tobacco control programs. She pointed out that California has spent nearly $500 million on tobacco control over the past few years and has experienced a great deal of success in smoking cessation; however, efforts at prevention have not yielded very positive results. Presenters encouraged the Federal Government to assume a more vehement stance against tobacco. Ms. Malek commented that the Subcommittee agreed that research must target public policy issues and development of better clinical strategies for prevention of smoking initiation. She concluded the Subcommittee report by stating that the group determined that it was necessary to gather data on the most effective mechanisms available to reduce smoking prevalence and submit strategies and recommendations to the NCI. Dr. Rimer added that future Subcommittee meetings will produce more concrete recommendations for next steps.

Dr. Dickersin informed the subcommittee members that she believes that the most recent National Health and Nutrition Examination Survey (NHANES), which is conducted by the CDC's National Center for Health Statistics (NCHS), revealed that the incidence of smoking is much higher than was believed. She suggested that the group attain these data or that a representative from the NCHS be invited to present the information.

Dr. Rimer noted that Dr. Michael Eriksen, from CDC's Office of Smoking and Health, reported on behavioral risk factors. Dr. Greenwald added that Dr. Erickson primarily discussed projections for current smoking rates in the year 2000 and highlighted the challenge inherent in the increasing prevalence of smoking among youth. Dr. Rimer asserted that while some progress has been made in decreasing overall smoking prevalence, it is important to recognize that there is still a tremendous amount of progress to be made, which the NCAB must stridently address. Dr. Greenwald pointed out that additional issues are raised by the differences in smoking rates between high school graduates and dropouts. Dr. Rimer asked Dr. Day whether there could be a presentation regarding this topic during the next meeting. Dr. Day indicated that the disparities in smoking prevalence between these two populations was the focus of a comparison community study, and that such a presentation would be possible. Dr. Greenwald indicated that the information could be presented at the next NCAB meeting. He added that the presentation should include a discussion of what the data do not reveal.

Drs. Day, Greenwald, and Broder all commented that efforts need to be focused on developing a pharmacological agent that can act as an effective substitute for nicotine, particularly in view of the tremendously addictive nature of this drug. It was suggested that the National Institute on Drug Abuse (NIDA) might be of help in this effort. Dr. Day remarked that considering the tremendous effort expended to develop new drugs, more research should be devoted to developing an effective substitute for nicotine since tobacco is associated with 30 percent of cancer mortality. Dr. Broder added that its use in cigarette form has also been linked with noncancerous cardiovascular and lung mortalities. It was recommended that cancer control research concepts (i.e., application of a drug addiction model to treat nicotine addiction) be brought to the attention of an appropriate BSC. Dr. Rimer called for a motion to approve the minutes, which was moved and seconded.

Planning and Budget

Dr. Rimer commended Dr. Sigal's tremendous efforts to produce a more readable companion Bypass Budget document. Dr. Sigal told members that the Subcommittee covered an extremely long agenda, and she would therefore provide highlights of the meeting. The committee approved a technician training enhancement program for intramural laboratories, which will provide practical, hands-on training under the direction of senior scientists for up to 20 individuals, at a cost of $20,000 per individual. This decision was based on the recognition that trainees able to perform the latest advanced techniques are essential to the operation of intramural laboratories. Dr. Sigal reported that Dr. Karp discussed the 1997 Bypass Budget, which will include additional topics on the organization of NCI, the design and execution of clinical trials, second malignancies, and surgical oncology. Dr. Sigal informed members that the Subcommittee had an extended discussion regarding an alternative to producing a scholarly scientific document of the breadth and depth of the Bypass Budget each year, and requested that input be solicited from the Board during the New Business session.

Regarding which SENCAP recommendations to emphasize, Dr. Sigal explained that the recommendation to perform a detailed evaluation of the cancer research programs and priorities be deferred until the Blue Ribbon Panel report on the intramural program is received. The Subcommittee agreed to adhere to a balanced portfolio and will develop some strategies for tracking this recommendation. Dr. Sigal indicated that a decision about the $60 million in funding for the cancer centers' translational research was deferred until participants had an opportunity to hear the Cancer Centers Subcommittee report. She related that there was a long discussion regarding distribution of the $180 million increase in the Bypass for RFA funding, which will raise the operational budget by 8 or 9 percent. This will necessitate some major funding shifts, which requires further examination before specific recommendations are made.

Dr. Sigal characterized the report on the overview of the NCP, which will act as a companion piece to the Bypass Budget document, as very good. She commended the work of Ms. Eleanor Nealon and Mr. Paul Van Nevel in developing this document in a short time period. Dr. Sigal asserted that the report provides a concise, yet comprehensive view of where cancer funding has been spent, what accomplishments have been achieved, and what challenges remain. The report will be ready for final distribution in February 1995. She added that the document has received widespread support from all of the groups who have reviewed it. Dr. Broder interjected that the next Director of the NCI will need recommendations for program reductions, not a document written on the assumption that funding increases will be attained. Dr. Sigal replied that the Subcommittee is aware of this perspective, and is particularly challenged by the premise that the SENCAP recommendations were based on a $240 million budget increase.

Dr. Sigal told members that the Subcommittee also discussed its mission. She commented that the Subcommittee, in practice, has completed very little budget-related work and, therefore, will examine strategies for focusing on the budget in a more meaningful way while avoiding micromanagement of the NCI. The Subcommittee will meet during the next 2 or 3 months to develop a more clearly defined role for itself.

Dr. Calabresi commented that it is important to remember that the SENCAP report was not intended to be implemented during the course of 1 year. Instead, it should be viewed as a 10-year guide, during which adjustments can be made based on the relative funding levels of each year. Dr. Rimer called for the minutes to be approved. The motion was made and seconded.

Dr. Rimer distributed a page from the NCAB enabling legislation, which will affect the budget management issue for the National Breast Cancer Action Plan. She asked that members read it over before the New Business session. The Special Priorities Subcommittee was unable to meet, and Ms. Zora Brown asked whether an issue that requires immediate discussion should be brought up at this point or during the New Business portion of the meeting. Dr. Kalt replied that it should be introduced during the New Business discussion.

XIV. CONTINUING AND NEW BUSINESS-SESSION II—DR. BARBARA RIMER

Dr. Rimer opened the Continuing and New Business session by stating that resolutions and continuations of new business from the prior day would be considered first, followed by a discussion of the role of the NCAB. First, however, Dr. Rimer stated that, as Chair, she would like to open discussion on the issue of the NCAB's oversight of the $10 million allocated to the National Breast Cancer Action Plan.

National Breast Cancer Action Plan

Dr. Dickersin asked whether the oversight of funds allocated to the Plan meant oversight of the implementation and staffing of the Plan. Dr. Peter Greenwald responded by first reviewing the statutory authority for NCI oversight. Referring to the Appropriations Committee report, he pointed out that the National Breast Cancer Action Plan is designated as within NCI's responsibility. To the extent that any grant proposals are part of the Plan, they would require the review and approval of the NCAB during the closed session and, presumably, a conceptual discussion during the open session. Dr. Greenwald also expressed his view that the NCAB would want oversight of the process of implementing the Plan, and how it complements other activities at NCI. He continued by reflecting that the Board may also have a role in working with advocacy groups and coordinating the formation of committees to implement this Plan. This precept is supported by Dr. Shalala and Dr. Blumenthal.

In terms of a funding process, Dr. Greenwald recommended that any allocation of the $10 million of funding go through one of the standard competitive processes of NIH that involves peer review. Specifically, he stated that a concept should be developed for funding, that this concept should be reviewed by an appropriate Board of Scientific Counselors, and that the NCAB approve of project funding. In terms of a timeline, Dr. Greenwald indicated that it is probably not realistic to develop and fund a new concept in FY95. However, if a concept were presented at the May 1995 NCAB meeting and approved, an RFA could be developed, advertised, issued, and reviewed, possibly within 9 or 10 months. In the meantime, activities that are already in place relating to the six recommendations of the committee to implement the Plan can be built upon or expanded.

Dr. Dickersin pointed out that implementation of the Plan will go beyond funding research, to health care delivery and education. She asked whether the $10 million will contribute towards management of the Plan and implemented activities. Dr. Rimer stated that her understanding is that the $10 million is to cover all activities related to the Plan. Dr. Greenwald agreed and emphasized that NCI is willing to work with OWH in coordinating activities in order to conserve resources, noting that several NCI staff have already been detailed to Dr. Blumenthal's office.

Dr. Salmon asked whether funds allocated to the Plan could be used to issue contracts separate from NCI. Dr. Greenwald replied that this would probably have to be authorized and done through an interagency transfer. Dr. Salmon stated his opinion that the NCAB should have oversight authority in these situations, particularly to avoid duplication of bureaucracy. Dr. Fingerhut emphasized the sensitivity of this issue in that the Plan has been developed as part of a public-private partnership and is a full interagency effort. Perception will be important in coordinating with other groups, and the NCI should avoid the perception that it is taking over a Plan that has such strong grassroots support. Dr. Rimer acknowledged this as an important point but reiterated that the role of the Board is legislatively defined and it must take final responsibility for expenditure of this money. Dr. Salmon added that public-private partnerships and interagency agreements are within the realm of what NCI does and it has, in fact, played a central coordinating role in this respect for the National Cancer Program. This does not denigrate individual initiatives under the Plan. Dr. Bishop stated that since the NCI has responsibility for the expenditure of these funds, it is imperative to work out a process for exercising quality control.

Ms. Zora Brown pointed out that, as a person serving on the National Breast Cancer Action Plan, she would recommend that they develop and submit guidelines to the Board on how the action plan working groups intend to use allocated funds before requesting approval to spend these funds. This would provide an opportunity to develop parameters in cooperation with the working groups and the Board for effectively utilizing this money.

Dr. Rimer suggested that the Board draft a letter to Dr. Shalala summarizing its perceived responsibility as a Board and offering for a subgroup of the Board to meet with her to discuss and encourage a collaborative relationship. Ms. Brown agreed that a letter to Dr. Shalala, followed by a small group meeting, would be effective. Dr. Broder suggested that Dr. Varmus be invited and strongly encouraged to attend this meeting. As an aside, Dr. Dickersin suggested that Dr. Rimer be a member of the proposed Action Plan steering committee in order to facilitate communication. Dr. Rimer agreed that would be appropriate.

Dr. Bishop made a motion that the Board charge Dr. Rimer, as Chair, with contacting the NIH Director's office and the DHHS Secretary's office about its concern regarding oversight of the $10 million allocated to the National Breast Cancer Action Plan and to establish discussion on this issue. Dr. Calabresi seconded the motion and it was unanimously approved.

Update on *Ex Officio* Member Status

Dr. Kalt reminded Board members that the basis in law for the existence of the National Cancer Institute and the National Cancer Advisory Board are: 1) the Public Health Service Act, which represents a compilation of all legislation pertaining to these bodies; and 2) the National Cancer Act of 1971. The general section of the Public Health Service Act that pertains to advisory councils and boards is Section 406.

Under Section 406, Dr. Kalt pointed out, *ex officio* members of any advisory council are merely those Government employees outside the immediate agency that have a role to play in the overall programs of that Institute. It is specifically designated, for all Institutes, that the *ex officio* members should be the Secretary, the Director of the NIH, the Director of the National Research Institute for which the council is established, the Chief Medical Director of the Department of Veterans' Affairs or the Chief Dental Director, the Assistant Secretary of Defense for Health Affairs or a designee, and "such additional officers or employees of the United States as the Secretary determines necessary for the advisory council to effectively carry out its functions."

Dr. Kalt continued by stating that the National Cancer Act designates *ex officio* members of the National Cancer Advisory Board, being the Secretary, the Director of the Office of Science and Technology Policy (OSTP), the Director of NIH, the Chief Medical Director of the Department of Veterans' Affairs, the Director of the National Institute for Occupational Safety and Health, the Director of the National Institute of Environmental Health Sciences, the Secretary of Labor, the Commissioner of the FDA, the Administrator of the EPA, the Chairman of the Consumer Product Safety Commission, the Assistant Secretary of Defense for Health Affairs, and the Director of the Office of Energy Research at the Department of Energy, and/or the designee of such offices.

Dr. Rimer noted that the AACR is not among this list and Dr. Kalt confirmed this, noting that *ex officio* representatives are legislatively designated as representatives of other Government agencies, not external organizations. Dr. Broder noted that it requires an act of Congress to change the composition of the NCAB.

Dr. Yodaiken suggested that a subcommittee of *ex officio* members be established that could meet on a regular basis as part of regularly scheduled NCAB meetings. He reasoned that this is the only opportunity for other Government agency representatives to discuss what is happening in their particular departments or agencies with respect to the regulation and control of cancer. Dr. Yodaiken continued by stating that the subcommittee could then provide a summary statement to the full Board of its activities and advise Board members of upcoming Federal activities outside the legislative updates. For example, he noted, proposed legislation on passive smoking or tobacco regulation is currently in progress. A resolution passed by the Board on this issue could have been offered at the hearing. There are also upcoming legislative initiatives in which Board members may want to participate.

Dr. Salmon raised a concern that if *ex officio* members are "*ex officio*," to provide for a formal "*officio*" subcommittee may contradict this status. However, he did not oppose meetings of the *ex officio* members on an informal basis and noted that this does not require

authorization from the Board. Dr. Yodaiken emphasized the difficulty of coordinating informal meetings and proposed having a more formal meeting basis for this reason.

Dr. Calabresi acknowledged the valuable functions of the *ex officio* members and noted that the SENCAP report recommended approaching other Government agency representatives that are vital to the success of the National Cancer Program. Dr. Vaitkevicius expressed his opinion that a report from the *ex officio* members of relevant issues outside of NCI would be helpful and that this should be part of the Board's agenda. Dr. Sigal voiced her agreement, emphasizing that there is not enough coordination among other agencies and it would be helpful to create a mechanism for encouraging more dialogue and a report. Dr. Salmon followed up his earlier remarks by clarifying his view that *ex officio* members could schedule a meeting time and location and list it in the Board agenda, so long as it is not conflicting with other subcommittee meetings. He also stated that he would welcome their report. Dr. Vaitkevicius asked that an agenda of the meetings be given to Board members. Dr. Fingerhut reiterated that it is important that *ex officio* members have the opportunity to meet with each other, to report to the Board, and to foster dialogue on common issues.

Dr. Rimer suggested that a formal time period be scheduled during the next several NCAB meetings for *ex officio* members to meet on a trial basis and report back to the Board. Dr. Goldson suggested that the meetings be scheduled on Monday, the day prior to the Board meeting, either from 2:00 to 5:00 p.m. or from 7:00 to 9:00 p.m. This would enable Board members to attend if they desired.

Bypass Budget

Dr. Sigal opened discussion on the possible development of an alternative Bypass Budget document, an idea originally presented by Dr. Karp and considered in the Budget and Planning Subcommittee. She summarized the idea to view the 1996 Bypass Budget as a core document and the 1997 and perhaps 1998 and 1999 Bypass documents as supplements, a "yearly progress report" of sorts. The supplements would include scientific advances, programmatic assumptions, budgetary fiscal information, and an abbreviated executive summary of the 1996 Bypass Budget. Dr. Sigal noted that if the Board were to approve this concept, key representatives of Congressional staff should be notified to avoid any surprise. She stated her opinion that this alternative concept might be more meaningful in that it would address scientific advances and issues in a timely manner without reinvention each year.

Dr. Broder responded that, legally, the Bypass Budget is within the province of the NCI Director, not the Board. The Board can provide advice; however, it cannot bind the Director. Dr. Broder noted that when his successor is named, he or she should be given as much flexibility as possible with regard to this issue. Dr. Salmon supported Dr. Broder's position, particularly since the Bypass Budget is one of the few statutory authorities that provides a special role to the Director of the NCI. He recommended that this discussion be placed on hold until a successor Director is appointed and then allow that person to develop a process for review of the Bypass Budget.

Dr. Calabresi clarified that as an observer at the Planning and Budget Subcommittee meeting at which this issue was discussed, it was his understanding that the issue was meant to be addressed by the Board in its advisory capacity—in other words, for the Board to provide

the Director with its advice, which the Director could accept or reject. Dr. Sigal remarked that this is correct. She noted that the Planning and Budget Subcommittee minutes over the past 5 or 6 years reflect a recurring discussion over the readability of the Bypass Budget. Dr. Sigal asked for advice from the Board on how to proceed since this issue is consistently brought to the attention of this Subcommittee. Dr. Rimer expressed the consensus of the Board that this issue be tabled until a new NCI Director is appointed, at which time it may be appropriate to discuss the Bypass Budget and offer recommendations.

Dr. Salmon, as an aside, noted that it would be helpful for the Planning and Budget Subcommittee to play a more major role in reviewing NCI's operational budget and determining if it is being used in a balanced fashion. Dr. Broder agreed this would be constructive. Dr. Sigal said that she would be pleased to do that and that, clearly, the function of the Subcommittee needs to be reexamined. Dr. Rimer stated that this leads in nicely to the next item of discussion, which is the role of the NCAB.

Role of the NCAB

Dr. Rimer began by remarking that some new members are not sure what the purpose of the Board is in practical terms, aside from its legislative mandate. She stated that the role of the Board is defined in part by its relationship to the NCI Director. She reflected that when she began as Chair, a large number of people told her not to expect too much or try to do too much, but that she and all of the Board members she has spoken to want to contribute something meaningful as part of their role on this Board. She asked for comments from Board members on their perceptions of the role of the Board.

Dr. Sigal expressed her view that while the Board's statutory authority is over research grants, its role as an advisory board can be made more meaningful. She noted that while presentations are informative, they are only informational and do not provide a basis for giving advice. To provide advice it is necessary to be more involved in a process.

Dr. Salmon agreed that providing advice is an important function that is identified in the media, distributed nationwide to cancer centers and health professionals in the cancer field, and recognized by Congressional committees. As such, the Board needs to maintain its ability to advise, whether on budget issues, research initiatives, new and emerging areas, or the balance between basic, translational, and clinical research. Dr. Salmon commented that the past year has had a balance between presentations and advisory issues.

Dr. Broder recommended that a group of Board members attend other council meetings, i.e., National Heart, Lung and Blood Institute, to observe their operations and proceedings. There may be differences and common areas from which to learn. Dr. Broder also reminded the Board of the power of its influence, noting that there are only occasional, dramatic examples where its advice is not followed. Some of the NCI's most successful programs, i.e., the Black Leadership Initiative, arose based on the recommendations of the Board. When concern was expressed about program project grants, discussions were held and policies developed. He reflected that it may be difficult to view the Board's growth at a given point in time, but that if it is measured over time, there are fundamental changes. Dr. Broder noted that presentations are often scheduled at the request of Board members. He concluded by stating that the Executive Committee makes a special effort to integrate and adopt what the

Board has advised, and that the Board should not overlook its enormous capacity to influence events.

There were no additional comments and Dr. Rimer stated that this will be a continuing discussion and that the Board will continue to adjust its expectations and roles to fit the time and its membership.

Minority Recruitment into Clinical Trials

Dr. Kalt brought up for final action the concept of a regional conference on minorities and NCI clinical trials. Ms. Brown commented that this was to have been discussed in the Subcommittee on Special Priorities; however, that meeting was cancelled. She stated that the objective was to establish a working partnership between minority community organizations, cancer centers, Community Clinical Oncology Groups (CCOGs), and university hospitals to accrue more minorities to clinical trials. Five awards were anticipated at an estimated cost of $125,000.

Ms. Brown continued by reflecting that first having an NCI-sponsored and -hosted conference, before holding regional conferences, may provide better direction in planning methods for increasing minority accrual in clinical trials. For example, she has worked with many communities and knows a lot about why minorities do not enroll in clinical trials. However, this dialogue needs to be brought to the National Cancer Institute in order to formulate a broader plan for implementing regional conferences that will have a true impact. Dr. Rimer concurred with this suggestion.

Dr. Dickersin commented that recruiting for clinical trials seems difficult regardless of race; for example, she said it is her understanding that only 1 to 2 percent of women with breast cancer enter clinical trials. She recommended having a conference or series of conferences on general recruitment to clinical trials, before focusing on one particular group.

Dr. Kalt presented an alternative model of encouraging individual sites that actually perform clinical research and need to accrue underrepresented populations to submit conference grants and begin generating ideas on this issue. This would provide "raw data" that could then be addressed on a national level at a summit type of conference. Ms. Brown stated that she feels this is "putting the cart before the horse" and that any major effort should emanate from the NCI and be minority specific.

Dr. Correa agreed with Ms. Brown that deficiency of recruitment among minorities should be given priority. He suggested combining the two ideas and holding a first regional conference in Washington, DC, possibly cosponsored by Howard University. Participants from other regions could attend and perhaps lead the next round of conferences. Ms. Brown suggested, for example, the International Black Leadership Initiative. Dr. Rimer suggested that a conference could be held in conjunction with an NCAB meeting in the form of a symposium following the Board meeting. Dr. Broder noted that this has been done in the past; a symposium on rehabilitation was held following an NCAB meeting.

Dr. Vaitkevicius expressed his opinion that having a prototype conference on a national level would be helpful in organizing local meetings. However, he cautioned against

postponing an RFA. Dr. Salmon indicated that he does not recommend postponing an RFA, but that this discussion indicates that follow-up is needed on this issue.

Dr. Calabresi indicated that he has discussed this issue with Dr. Freeman, who described to him a meeting of the President's Cancer Panel on cultural differences and backgrounds of different minority groups. Dr. Freeman felt that it was extremely important to recruit these groups to diagnosis and into clinical trials and prevention programs. Dr. Calabresi suggested that, perhaps, a synopsis of the PCP meeting could be held for members of the Board.

Dr. Chan strongly supported Ms. Brown's idea and noted that this discussion has been ongoing for at least 2 years. Dr. Rimer stated that closure needs to be brought to this issue and asked Ms. Brown for her comments. Ms. Brown made a motion supporting Dr. Correa's suggestion that the first conference be held in Washington, DC, followed by other regional conferences. Dr. Goldson seconded this motion and commented that it is important to use the resources that are available to work with communities. For example, have a national summit and coalesce the knowledge from Harlem, Howard, and other problem areas, and try to create a group that can disseminate that information around the country. Providing $25,000 to one group and $25,000 to another is not going to have a large impact. A process needs to be developed on a broad scale for using this information. Ms. Brown's motion was unanimously approved by the Board. Dr. Rimer recommended that the Special Priorities Subcommittee be involved in this effort.

Dr. Kalt briefly reviewed the guidelines for grant awards, referring Board members to a statement in the business section of their notebooks. He noted that it is just for year to year and that it is normal to review it at this time. The statement, he noted, simply refers to the ability of the Institute to make certain funding actions relating to adjustments in budgets between Board meetings. He asked if there were any questions, and made a motion to the Board to concur with this statement. Dr. Rimer moved to concur and this motion was seconded and unanimously approved by the Board.

Search Committee for NCI Director

As the final item of new business, Dr. Day introduced a resolution on behalf of Dr. Salmon to resolve that at least two members of the Board be included in any search committee process for the selection of the nomination of a successor to Dr. Broder. The resolution should be directed to the President. The resolution was seconded by Dr. Calabresi. A vote was taken with all Board members in favor except Dr. Bishop, who abstained. Dr. Rimer noted that she has already communicated this to Dr. Varmus and Secretary Shalala and will now transmit this request to President Clinton.

XV. NSABP UPDATE—DRS. BRUCE CHABNER AND LESLIE FORD

Dr. Chabner began this presentation by informing members that the NSABP has elected Dr. Norman Wolmark as its new chairperson. He explained that Dr. Wolmark will not submit a formal application for confirmation to the NCI until negotiations with the University of Pittsburgh regarding administration of the grant and allocation of funding between the general headquarters and biostatistics operation headquarters are completed. Dr. Chabner

commended the newly developed auditing procedures for the NSABP clinical trials, which were absent 9 months earlier. He indicated that reports are being submitted within the 6-week period requested by the NCI, and audits are being conducted onsite in 30 to 40 percent of the cases, which was not occurring before. In addition, a contractor has been hired to conduct confirmatory audits to evaluate the accuracy of each institution's auditing process. Dr. Chabner supported NSABP's impressive effort to diminish the backlog of cases requiring auditing. The group has scheduled 60 audits to occur during the next 2 months.

Dr. Chabner reported that NSABP currently has three clinical trials open, including the B-23 trial, B-26 trial, and a rectal cancer trial. The B-23 trial involves an investigation of the efficacy of adjuvant therapy consisting of intensive adriamycin and cytoxan versus conventional CMF chemotherapy. He characterized accrual of participants since the trial reopened in June 1994 as slow. Seventy-four new participants joined the trial from June to December, and an additional 10 individuals were recruited in December. An average accrual rate of 10 to 12 individuals per month is slower than the study designers had hoped and would require an additional 100 months for the team to recruit the targeted 2,100 participants. Dr. Chabner indicated that it would not be practical to extend the recruitment period this long. The NSABP group has been working on the issues that are impeding accrual and, once the new chairperson assumes control of NSABP, it is hoped that this rate will greatly increase.

Dr. Chabner characterized the B-26 trial as important. This trial compares the response rates associated with 3-hour infusion of taxol and the conventional 24-hour infusion. While the brief infusion has become more widely used, there is some preclinical evidence to suggest that the longer dosage period may be more effective. Since taxol acts by inhibiting mitosis, it seems logical that more cells would be affected if an individual were exposed to the agent for a longer period of time. Accrual for this trial has also been slow, with a total of only 38 participants, 10 of whom joined in this past month. Dr. Chabner added that they hope to reach 460 participants.

Dr. Chabner informed members that the third trial, the rectal cancer trial, is comparing the effects of perioperative 5FU/radiation therapy versus postoperative delivery. Again, the progress made toward recruiting participants has been slow. Dr. Chabner indicated that while the trials are open, the group is primarily focusing on restructuring its management and, therefore, recruitment and initiation of the trial are not a priority at this time

Dr. Chabner discussed three trials that NSABP is currently preparing to reopen. The B-21 trial focuses on the comparative effects of radiation versus tamoxifen therapy after lumpectomy among individuals with small tumors. The trial will probably reopen as an intergroup study, which may increase the accrual rates. Currently, there are 700 participants in the trial; a significantly higher accrual is necessary to confer meaningful results. Dr. Chabner informed the Board that an intergroup trial examining the results of postoperative 5FU/levamisole and radiation versus a perioperative 5FU regimen among individuals with colon cancer is also reopened. The third trial involves a monoclonal antibody pilot study among colon cancer-diagnosed individuals. Dr. Chabner expressed his doubt concerning the ability of NSABP to increase their accrual rates until their new leadership is installed and headquarters become functional.

Dr. Chabner moved to a discussion of the issues the NSABP will encounter in the next few months. The first involves the official recognition of the new chairperson, Dr. Wolmark, which will probably not occur until plans for restructuring the grant management are finalized and negotiations regarding other issues are completed. Existing grants will be disaggregated and allocated to two distinct grants for biostatistics headquarters and general operations headquarters; however, close coordination between the two headquarters will be established. Dr. Chabner told members that intense deliberations are occurring and that a draft document has been prepared that outlines this plan. Once it is signed by Drs. Wolmark and Herberman, it will immediately take effect. Dr. Chabner remarked that the NSABP also needs to create a new scientific agenda to be able to recompete. He explained that the protocols that have been presented thus far originated in the previous era or are intergroup studies and, therefore, do not constitute a new agenda. Dr. Chabner asserted that the group must also define the role of Dr. Fisher within the new NSABP. He continued by stating that contrary to newspaper reports, NCI has been in contact with Dr. Fisher and encouraged his return to the group as a scientific contributor. At this point, it is uncertain whether he will return.

Dr. Chabner presented a timeline for recompetition of the grants. An RFA should be ready for consideration by January 15, 1995, and published by March 25th. The anticipated date to receive applications is August 25th, and peer review will probably occur between September and December. The NCAB should have these applications to review by February 26, 1996, allowing an award to be made by spring 1996. Dr. Chabner indicated that this timeline is primarily dependent upon the ability of the chairperson-elect and the grantee, the University of Pittsburgh, to forge a working relationship. Dr. Chabner emphasized the importance of NSABP and the University having a plan designed before February 1, 1995, at which time noncompetitive renewal of the grant must occur. If this plan is not ready, funding for the grant may be withheld.

Dr. Chabner announced that Dr. Leslie Ford would provide members with an update regarding the Breast Cancer Prevention Trial (BCPT). Dr. Ford credited the efforts of the staff at the University of Pittsburgh, who worked to revise the protocol and consent forms and hold workshops and meetings to redirect efforts with the reopening of this trial. She explained that, to date, 77,000 risk assessments have been processed, and 45,000 women have been determined to be eligible. Eleven thousand participants have been randomized to receive protocol treatments and an additional 600 are in the "pipeline"—they have received all of their eligibility exams. Approximately 1,000 of these women were waiting for randomization, after receiving mammography, when accrual ceased. Their mammographies will need to be repeated, as they must be conducted within 6 months of randomization to be valid, and non-hysterectomized women must receive endometrial biopsies.

Dr. Ford continued with a discussion of the informed consent documents. When the study was reopened it was agreed that the informed consent document of every center participating in the trial would be reviewed and approved. Until approval was given, no recruitment could begin. Of the 299 centers participating in this trial, the consent forms of 212 have been reviewed during the last 2 1/2 months. Dr. Ford commented that the short time period it has taken these centers to reformat and receive internal approval of the form from their Institutional Review Boards (IRBs) is a testimony to the enthusiasm these centers are exhibiting. Of these 212, 180 have been approved as containing adequate information. The 32 that have not been approved are primarily cases in which the IRBs modified the standard

consent form. These changes must be justified before approval can be granted. In sum, 120 sites have been reopened after receiving approval of their informed consent document and audit process. Dr. Ford reported that randomization has begun for these women, and that six or seven women have been randomized to date.

Since the trial was reopened in September, 2,700 risk assessments have been processed, 14 percent of which have involved minority women. When the study first began, this percentage was approximately 2 to 5 percent, increasing to 8 percent following efforts to target these populations. Dr. Ford related that the bone density study has been opened at a small group of centers. This investigation will entail conducting bone densitometry to examine the effects of tamoxifen versus placebo on the normal aging process. In December 1994, a meeting of the Participant Advisory Board, composed of approximately 15 women participating in the study, was held. Some of these women have reached endpoints in the study. Dr. Ford described the participants as multicultural, multiethnic, and geographically dispersed. She expressed her satisfaction with the commitment and knowledge regarding the research question and the importance of the trial that was displayed by the women who compose the advisory board.

Dr. Ford announced that two projects have been initiated to increase minority participation in the BCPT. Working through Ms. Zora Brown and Mr. Les Butler from the Breast Cancer Resource Committee, the cities of Philadelphia and Chicago will be targeted to develop strategies to involve minority women in clinical trials by collaborating with community and medical leaders. These two cities were chosen for their large minority population and high proportion of minority data managers and program coordinators. The other initiative entails working with Dr. Antronette Yancey from University of California at Los Angeles, who is affiliated with the national bone marrow donor registry. Dr. Yancey will contact bone marrow registry participants to solicit their participation in the trial. Dr. Ford added that an informational video has been created to explain the reconsenting process and the new endometrial biopsy requirements to women already participating in the BCPT. The tapes have been distributed to all sites and have been well received; requests for additional tapes are being received.

Questions and Answers

Dr. Day asked whether Dr. Ford has information regarding the dropout rate experienced by the trial. Dr. Ford replied that approximately 20 percent of the initial 11,000 participants have stopped receiving study medication. Some of these cessations are a result of the participants reaching study endpoints, while others have chosen to discontinue the protocol therapy. The second group are considered "dropouts," and efforts are made to recover them. Often, women believe their symptoms are related to the protocol and will stop receiving their treatment for a time period. Some of these women will reinstate. All women, except those who withdraw consent, are followed in the study. Dr. Ford emphasized that some 9,000 women are still conforming to the protocol. This figure is closely watched by the data monitoring committee. Dr. Ford commented that there is no need to increase the sample size at this time. The monitoring committee will reconvene soon and reconsider this issue.

Dr. Rimer thanked Dr. Chabner for his efforts on behalf of the NSABP and characterized his departure as a loss to the NCI.

XVI. ANNUAL RFA REPORT—DR. MARVIN KALT

Dr. Kalt presented an overview of NCI's RFA mechanisms and asked for feedback on the types of information on which NCAB members would like to be apprised. He explained that this overview is a standard procedure that is primarily for the benefit of the newest members of the NCAB. Dr. Kalt explained that reporting procedures tend to follow the wishes of previous members, until new members communicate their requests for information.

There are three types of solicitations NCI utilizes to attract research applications. The first is the RFA, which consists of a formal announcement to the research community that the NCI is interested in receiving applications regarding a specific topic by a particular date. The notice also presents a potential budget that has been designated for the research. Dr. Kalt emphasized that with an RFA there is a commitment to fund projects up to a set dollar limit, on the provision that a sufficient number of meritorious applications are received. Applications are reviewed for merit by peer review committees appointed by the Division of Extramural Activities.

Another method of solicitation is the program announcement (PA), which is also a published announcement requesting that applications be submitted regarding a particular topic. However, the PA has no budgetary commitment and generally implies a long-term interest in a particular field, and ongoing application submissions. Cooperative agreements may not normally be funded through a PA. Dr. Kalt announced that a third mechanism was recently established, called a program announcement with first round set-aside. This type of solicitation includes a specific funding level for the first round of applications, but indicates that while subsequent rounds are expected, no allocations have been set aside for them. Dr. Kalt commented that this option will generally be employed in concert with single investigator-initiated research project grants, R01 and R29 (FIRST awards). The Division of Research Grants will be the most likely site of review for future rounds of these applications.

Dr. Kalt described common reasons for announcing an RFA. The request may be in response to a "window of scientific opportunity," an opportunity that becomes apparent through conversations with researchers in the field, workshops sponsored by Divisional program staff, meetings with Boards of Scientific Counselors, new clinical findings, drug discoveries, and scientific publications. By keeping abreast of current literature, program gaps often become apparent. RFAs may also be used to stimulate an underrepresented area of research or pool of investigators (i.e., prostate cancer). Public health emergencies, such as AIDS, are another impetus for RFAs. In addition, Congress will mandate research regarding a particular field, often through authorization or appropriation bills. Dr. Kalt reiterated that RFAs are used to arrange most cooperative agreements, particularly when there are requirements regarding the nature of the research or monitoring procedures. These requirements can be included in the terms of the award. Finally, RFAs are often utilized to attain rapid development of a new research structure, such as the SPORE grants.

Dr. Kalt presented the process of RFA development. First, a need is identified and the concept is outlined in a single-page statement. Dr. Kalt emphasized that an RFA is the last alternative of choice, as the NCI would prefer to utilize private-sector and investigator-initiated research. However, if no other alternative to stimulate a particular area can be developed, then

issuing an RFA will generally attract sufficient interest in the designated field. He remarked that more RFA concepts are developed than could possibly be funded and, therefore, each one is prioritized and then approved both internally within a Division and by the NCI Executive Committee. Once an RFA concept has been approved by the Executive Committee, it is submitted to Divisional Boards of Scientific Counselors (or, occasionally, to another specifically designated review group) for approval. If approval is granted, then it passes through various stages of review at NIH, during which other Institutes are contacted to determine whether they have an interest in conducting the research. Once the terms, conditions, and type of mechanism are approved, the RFA is announced in the *NIH Guide to Grants and Contracts* and direct mailings are issued. For highly complex RFAs, or in instances in which there is not an established community within which the announcement is appropriate, published briefings are convened. The notices for these briefings are also published in the *NIH Guide*. The same process is utilized to approve PAs. RFAs also include a date by which applications must be received. Dr. Kalt emphasized that there are no exceptions to these deadlines; otherwise, issues of bias might arise.

Upon receipt of all relevant applications, Dr. Kalt continued, the review process begins, primarily among review committees within the Division of Extramural Activities. Peer review is always employed during this process, which can become quite difficult when extensive submissions occur. To avoid conflicts of interest, peer review groups are generally established after it is known who has submitted applications. Following the peer review process, the applications are brought to the NCAB in combination with all other grant applications. Dr. Kalt explained that NCAB members are provided with an inventory of the rank ordering of the applications for each RFA. Before any awards can be designated, NCAB members must concur with the review. A funding plan is developed based generally upon rank order; however, awards may sometimes be based on geographic distribution or population composition. The final funding plan is then developed and submitted to the NCI Executive Committee for approval. Final determinations of the NCI Executive Committee are sent to the Grants Administration Branch and program directors, who issue the awards.

Dr. Kalt explained that, sometimes, mail ballots are utilized for NCAB members to review RFAs. This generally occurs when an RFA must be funded before September 30th and, therefore, the standard approval during the September/October meeting is not temporally possible. Circumstances might include scientific emergencies and unexpected Congressional language necessitating immediate action. Dr. Kalt pointed out that in these instances an award will have to be issued before the next Board meeting. The other instance in which mail ballots are used is when there is a statutory requirement (e.g., AIDS) that there be a 6-month award cycle, as opposed to the standard 9-month period. Dr. Kalt assured members that DEA attempts to provide the Board with every opportunity to have in-person discussions of applications; however, inevitably, there are mail ballots for RFA review each year.

Dr. Kalt recognized that the greatest benefit of the review process is that it produces a rank ordering of applicants at a fixed point in time, making it easier to determine which applications merit funding in a global context. Dr. Kalt stressed that awards are not entirely based upon rank ordering and that NCAB members' input is extremely important. He informed members that some applications that do not receive funding are recycled for up to three consecutive Board rounds, and may gain approval if increased funding becomes

available. Applicants are also welcome to revise and resubmit applications through the standard grant review process.

Dr. Kalt then moved to a discussion of proportional expenditures on RFAs. He reported that in 1993, $39 million was allocated to RFAs, which was approximately 19 percent of the total appropriation for competing RPG awards. In 1994 significantly fewer funds were designated for RFAs—$35 million, which was only 16 percent of the funds designated for competing RPG awards. While budget allocations for 1995 have not yet been made, the allocation for RFAs will likely be between these two figures.

Dr. Kalt presented the 1994 RFA allocations by Division. Dr. Rabson's Division (DCBDC) utilized this mechanism the least, with only three RFAs issued in 1994, and 18 awards, at a total cost of $4 million. Most of these awards were for training and career development associated with the cancer centers, not the tumor cell biology program. The Division of Cancer Etiology issued four RFAs and funded 34 awards in response to those applications, for a total of $5.7 million. The Division of Cancer Therapy issued eight RFAs and funded 62 awards at a total of $12 million. Dr. Kalt reiterated that the concepts for these RFAs are generated not only in response to research opportunities, but to program gaps. He pointed out that there was also an increase in the funding of cancer control efforts by Congressional mandate. He added that DEA issued the Minority Enhancement Awards in response to one RFA; these awards were funded at a total of $1.7 million. In sum, there were 25 RFAs issued in fiscal year 1994.

Dr. Kalt provided NCAB members with a summary of the RFAs published in the *NIH Guide* during 1994. He indicated that many of these applications were either recently brought before the Board, or will be presented at the May 1995 NCAB meeting, when 15 RFAs will be considered. RFAs for the Division of Cancer Biology, Diagnosis and Centers cover a range of high-interest areas, including breast and prostate cancers, palliative and hospice care, and planning grants. The Division of Cancer Treatment has issued three RFAs that will be considered at the next Board meeting covering the Cooperative Drug Discovery and Natural Products Groups, investigator-initiated grants for clinical cancer therapy research, and new therapeutic approaches for breast cancer. Dr. Broder interjected that many of these RFAs are written very broadly so that they function as clinical research project study sections and impose few limits on potential applicants. Dr. Kalt continued by summarizing the Division of Cancer Etiology's RFA topics, which include prostate, *helicobacter*, AIDS and nutrition, basic biology research, and a joint RFA with the Division of Cancer Prevention and Control (DCPC). The DCPC RFAs reflect the increase in funding that was mandated for cancer prevention and control efforts. Dr. Kalt pointed out that there is a well-known absence of R01 submissions in both the prevention and control and cancer therapy areas. High-priority areas for DCPC include breast cancer prevention, nutrition as it relates to cancer prevention, and Community Clinical Oncology Program recompetition, which is organized as a cooperative agreement. He reiterated that some of these RFAs were reviewed already and others will be introduced in May.

Dr. Kalt discussed some of the benefits of the RFA process, including the ability to target funds to areas of the greatest need. In addition, RFAs are always certain to generate applications that, if the proposals are meritorious, will address the identified needs. The use of a single review process provides a rank ordering that leaves no doubt about variations in

procedures between different study sections. Dr. Kalt pointed out that RFAs also have the potential to attract new researchers to particularly complex issues. In response to criticism that the NCI entices investigators by "throwing money into a field," Dr. Kalt noted that this is a potentially positive method. For example, for breast and prostate cancers, molecular biologis and basic scientists were motivated to work with clinicians to produce translational technology through RFAs. In addition, RFAs can be used to stimulate interest in areas that no one has begun to work in and often promote coordination and communication among awardees, particularly those joined under cooperative agreements. Dr. Kalt asserted that RFAs also advance training and career development.

Dr. Kalt shared several criticisms of RFAs. First, they are only issued at one point in time, precluding participation of applicants who do not reply in a timely manner. He pointed out, however, that the RFA stimulates interest in a particular area even if some applicants miss a deadline, and that those who are unsuccessful will often revise and resubmit their applications under an unsolicited investigator-initiated mechanism. Another criticism of RFAs is that many individuals assert that they divert funds from peer competition in the RPG pool. Dr. Kalt indicated that while this is true, there is not a large increase in funding for second and third awards. He added that RFAs contribute to an expansion of the research base. Dr. Kalt reminded Board members that RFAs also were created for areas in which investigators could not obtain approval through the study sections of DRG. He cited prostate cancer as a classic example of this.

Questions and Answers

Dr. Bishop asked how often the BSC rejects a concept for an RFA. Dr. Kalt responded that while it happens, it is more likely that a concept will be modified or a set-aside altered. Dr. Rimer called for comments on this point from Division leaders. Dr. Greenwald indicated that at the last concept review of the DCPC BSC of six or seven concepts, two were tabled. He explained that before a concept is considered by the full BSC, subcommittees that are associated with program areas conduct in-depth reviews of that concept. Therefore, once the concept reaches the entire Board, there is a fairly high approval rate. Dr. Broder pointed out that many RFAs are issued because the BSC requests them. Dr. Rice supported Dr. Broder's statement by explaining that in the Division of Cancer Etiology, many concepts are generated and refined within BSC workshops and are then presented to the BSC. Dr. Chabner reported that in his program area, the tremendous emphasis on breast and prostate cancer, as well as clinical research, has led them to utilize PAs to stimulate other areas. They are more cautious about approving concepts.

Dr. Bishop queried who is responsible for designating the funding level for an award. Dr. Kalt replied that the NCI Executive Committee establishes this figure based on the recommendation of the program director. Dr. Broder added that the NCI Director has the final authority for establishing these levels.

Dr. Rimer asked Dr. Broder if he had any comments about RFAs. Dr. Broder characterized his attitude toward RFAs as "ambivalent." While well-informed individuals often generate the concepts and RFAs often address areas that would otherwise be ignored, their use still raises issues. Pancreatic cancer is a good example of an area in which RFAs are useful. The RFA's ability to establish a "level playing field" is vital to ensuring that

investigators who target cancers that seem intractable are not discriminated against. In addition, sometimes RFAs, due to their inherent set-asides, are the only mechanism by which a Congressionally designated funding level for a particular program area can be achieved. Dr. Broder reiterated his ambivalent attitude toward this mechanism and recommended that NCAB members monitor the process closely to ensure that it does not assume too large a proportion of appropriated funding. Dr. Rimer thanked Dr. Broder for his comments.

XVII. ADJOURNMENT—DR. BARBARA RIMER

In closing, Dr. Rimer thanked the Board members and NCI staff for their participation and emphasized that Dr. Broder and Dr. Chabner will be missed and thanked them for all their work on the NCP. There being no further business, Dr. Rimer adjourned the 93rd National Cancer Advisory Board meeting at 12:49 p.m.

May 9, 1995
Date

Barbara Rimer
Dr. Barbara Rimer, Chairperson

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