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

Summary of Meeting
May 31 and June 1, 1994

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

Department of Health and Human Services
Public Health Service
National Institutes of Health
National Cancer Institute
National Cancer Advisory Board
Summary of Meeting[1]
May 31 and June 1, 1994

The National Cancer Advisory Board (NCAB) convened for its 90th regular meeting at 8:00 a.m., May 31, 1994, in Building 31, C Wing, 6th Floor, Conference Room 10, National Institutes of Health (NIH).

NCAB Members

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

President's Cancer Panel

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

Alternate Ex Officio NCAB Members

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

Members, Executive Committee, National Cancer Institute, NIH

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

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

Liaison Representatives

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

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

Dr. Calabresi called to order the 90th meeting of the National Cancer Advisory Board (NCAB). He congratulated Dr. Marvin Kalt on his appointment as Director of the Division of Extramural Activities (DEA) and Executive Secretary of the NCAB.

Dr. Calabresi introduced several guests representing medical, research, and professional organizations. He welcomed members of the public and informed them that they could express their views on issues discussed during the meeting by writing to the NCAB Executive Secretary within 10 days of the meeting. Dr. Calabresi called for approval of all proposed meeting dates for 1994, 1995, and 1996. The meeting scheduled for September 1994 was changed to October 3-5, 1994, to accommodate new NCAB appointees. Dr. Calabresi noted that there will be a mail ballot in early September for applications being considered for award in fiscal year 1994. The meeting date for September 5-6, 1995, was also changed because of a conflict with the end-of-year fiscal review and prior commitments of some NCAB members. The Board unanimously approved all proposed dates.

Dr. Calabresi called for approval of the minutes of the previous meeting, which were unanimously approved without change. He emphasized the critical importance of attendance by all Board members at all segments of the meeting.

Dr. Calabresi announced that the Subcommittee on Cancer Centers would not meet as scheduled. He reminded Board members that the closed session portion of the meeting would begin promptly at 3:00, after the subcommittee meetings, and that a quorum would be required. Some subcommittees, he noted, would also meet after the closed session.
Dr. Calabresi then introduced Dr. Harold Freeman to report on the President's Cancer Panel.

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

Dr. Freeman began his report by acknowledging attendees of the Workshop on Avoidable Causes of Cancer held on April 7 and 8, 1994, and expressing his thanks to Drs. Fraumeni, Davis, Zahm, Sondik, Taylor, and Hoover. Dr. Freeman mentioned that many of his remarks would be paraphrased from their comments at the Workshop.

Dr. Freeman said he initiated the Workshop by asking 48 invited experts to discuss the current status of knowledge about cancer and what will be needed to expand this knowledge in the future. The concept on which the meeting was based, as Dr. Freeman said had been verbalized by Dr. Muir, was that serious discussion about avoidable causes of cancer must incorporate two general requirements—consideration of the size of the burden and assessment of the results of interventions.

Dr. Freeman stated that a reexamination of the measurement tools currently in use to assess cancer risk must occur and that scientists must constantly seek to improve upon them. He said that Dr. Broder challenged those present at the meeting to consider poverty as a potential carcinogen and as an interacting factor with ethnicity and genetic inheritance in examining the causes of cancer.

Although Workshop members agreed that tobacco is an avoidable cause of cancer, they could not address "the political will to intervene," which Dr. Freeman said is the key concept

in avoiding tobacco-related cancer risk. An increase in tobacco avoidance behavior, Dr. Freeman continued, has resulted from tobacco tax increases and an advertising ban. Pressure from public opinion on lawmakers may be the final step in making tobacco-related cancers truly avoidable.

Health effects from alcohol consumption can be both beneficial and deleterious, Dr. Freeman stated, and further review of alcohol studies is needed. The interplay of alcohol and tobacco also needs to be reviewed, as has been implied in breast cancer research.

Dr. Freeman then discussed the role of diet in cancer risk. He stated that it is well known that diet influences cancer risk, as evidenced by recent studies of dietary interventions in China. Workshop participants reviewed cancer research in the context of the influences of dietary content of red meat, fruit, vegetables, folates, calcium, and other elements, and discussed the interaction of diet and hereditary factors on cancer risk, including the possible influence of metabolism on the duration of exposure and dose of potential carcinogens. Residual chemicals found in food may also pose a risk for cancer; however, no well-established means of dietary intervention have been identified to circumvent this potential risk.

Dr. Freeman then mentioned the consensus of the Workshop that upon development of a sound cancer intervention, the intervention must be successfully transferred into practice and evaluated for effectiveness. Case-control studies involving diet, he noted, seem to lack an evaluation component, and improved methods for measuring all aspects of diet are needed.

Another area for investigation, Dr. Freeman continued, is type of diet in relation to human development. He posed the question of whether key nutrients might influence cancer susceptibility during certain stages of development, and noted that the answer to this question is as yet unknown. He also suggested that if migrant populations were examined to determine the effect of dietary changes on cancer risk, then perhaps those same populations should be examined prior to their migration and subsequent dietary assimilation.

Dr. Freeman indicated the participants' consensus that clean air and water could prevent some measure of cancer of the lung, bladder, and rectum, but indicated that regulatory implications related to specific pollutants are unclear.

Workshop participants agreed, Dr. Freeman continued, that hormones and medications during pregnancy should be avoided, but that it is unclear how the public should be advised regarding estrogen replacement therapy, oral contraceptives, and endometrial, ovarian, cervical, and uterine cancer risk. He stated that further research into the age-dependent dose phenomenon would be helpful, and that research into the dose-response phenomenon also applies to antineoplastic drugs and immunosuppressants, where alternatives to medications may not be possible.

In a discussion of occupational risk, Dr. Freeman continued, participants discussed the complexity of the single agent in the scientific experiment versus the mixture of carcinogens observed in real-life situations. Workshop participants agreed that while many highly suggestive studies have been conducted, they have tended to be scientifically useless and have resulted in a distortion of the problems in small industries. Dr. Freeman indicated that agricultural exposures were examined in the same context, i.e., the quality of scientific evidence.

The workgroup found that 2 percent of cancer deaths are attributed to ionizing radiation, and that public fear may be a greater issue than the real risk involved. While studies of sun exposure and electromagnetic fields were discussed, Dr. Freeman continued, it was

concluded that definitive studies of the type and duration of exposure have yet to be undertaken.

The relatively new field of infectious agents as avoidable cancer risk factors was also discussed. Dr. Freeman stated that while infectious agents are implicated in the causation of liver, cervical, intestinal, and perhaps other malignancies, the impact of using a vaccine as a preventive tool may not be seen for at least another 25 years.

Dr. Freeman then discussed genetic susceptibility to cancer, stating that while one cannot avoid one's genes, the risk of hereditary cancers may be reduced by employing other avoidance techniques. He noted that while it is not possible to mend damaged genes, it may be possible to compensate for them. Concern was also raised during this section of the Workshop as to who should have access to the information about genetically mediated susceptibility and how individuals with the suspect genes should be counseled.

Dr. Freeman mentioned that Dr. Samet suggested during the Workshop that the problem of language is ubiquitous to many scientific endeavors. For example, in discussing avoidable causes of cancer, experts who share common research purposes frequently present information that confounds the terms "exposure," "agent," and "medium of exposure." As an example, Dr. Freeman said that an individual can be exposed to an agent such as radon through various media which are determined by factors such as race, ethnicity, education, gender, and income. These largely behavioral or sociological factors determine where we work, what we eat, and how we respond to lifestyle exposures. These factors also determine the opportunities or the media through which exposures to certain agents, such as tobacco smoke, can occur. The response to such exposures, Dr. Freeman concluded, may impact on the dose of each agent.

Dr. Samet had also pointed out that the public often confounds the terms "attributable" and "avoidable." Dr. Freeman summarized Dr. Samet's illustration in that "attributable" is defined as that proportion of disease that is theoretically removable had a given exposure never existed, while the term "avoidable" represents the reduction of the relative risk of exposure to a given agent under optimal conditions and defines a reasonable level of prevention that can be achieved. Dr. Freeman indicated that these terms help to define a preventive strategy that recognizes the population as a whole, but also recognizes exposed subpopulations within the whole in an effort to examine these groups in terms of their individual relative risks. Dr. Freeman added that as the field of genetic research continues to expand, there should be an effort to identify more subpopulations for which relative risks and prevention strategies can be developed. To achieve this goal, new tools for exposure assessment, new approaches for studying complex mixtures of specific agents acting within various media, and improved surveillance techniques are needed. Dr. Freeman stated that trained scientists who speak a universal language and can integrate epidemiology, biostatistics, and population needs in an effective and sensitive manner are needed to carry this work forward.

Dr. Freeman continued by paraphrasing a discussion by Dr. Miller, who stated that if the goals of Dr. Samet are achieved, the scientific community will be in a position to conduct research on intervention and, thus, be bound to conduct public health interventions and to monitor the effects of the interventions in order to use that knowledge to improve basic understanding of causation. Dr. Freeman stated that it will be necessary for the scientific, legislative, and public policy communities to come together to achieve prevention as facilitated by research and intervention. He noted that Dr. Alfred Haynes pointed out during the meeting that special populations to which these concepts may be applied include women, ethnic minorities, and the poor. Dr. Haynes stressed that the role of culture in the development of behavioral patterns governing diet, smoking, and other behaviors should be considered as well.

Dr. Freeman noted that Dr. Haynes also questioned the sometimes contradictory pleas for additional funds for research and statements that sufficient knowledge exists to truly impact on cancer in many areas. In Dr. Haynes' words, an investment in behavioral research should be considered and may result in expanded application of current knowledge and a better return of the investment. According to Dr. Haynes, behavior alone does not explain certain differences in lung cancer risk between African American and White men, and between American White and native Japanese men; understanding these differences will require additional basic research.

Dr. Haynes also emphasized an important guiding principle for human subject research, that of respect for persons. In Dr. Haynes' discussion, Dr. Freeman stated, he emphasized the need to develop interventions whose goals are not derived solely by consensus and trial, but also by consumer availability and recognition that the truly informed consumer can make reasonable decisions. Dr. Freeman stated that the variables of gender and ethnicity are not to be avoided and must always be considered. He added that in the future, a balance must be reached between the potential for exquisite science applied to genetically defined subpopulations and the development of practical intervention strategies in diverse populations.

Dr. Freeman concluded by summarizing Workshop recommendations and highlighting the importance of seven specific issues: the essential role of behavioral research in identifying cancer-causing agents and developing successful interventions; the role of the traditional dose-response model in intervention; the compelling call for integration and collaboration across scientific disciplines; the crucial need to reexamine traditional experimental methods and devise more methods of observation and quantifiable approaches to cancer causation; the key role monitoring plays to determine the outcome of both epidemiological research and prevention/intervention, and the need to integrate the large databases that are currently available; the need to establish clear guidelines for access and use of the explosion of genetic information which is forthcoming; and the need to nurture a new breed of scientists who can speak a universal language that can bridge the communication gap between epidemiology, molecular biology, genetics, statistics, and community intervention to achieve effective prevention.

Dr. Freeman said that at the conclusion of the 2-day Workshop, it was apparent that while much is known about avoidable causes of cancer, much remains that is unknown and an extensive agenda remains for the future. Dr. Freeman stressed the responsibility of the President's Cancer Panel to communicate their findings to the President of the United States, as well as the Panel's joint responsibility as scientists and citizens to respond to the questions that have been posed.

Dr. Freeman then thanked the audience and offered to answer any questions.
Dr. Calabresi ascertained that there were no questions from the audience.

Dr. Calabresi then made note of the fact that while Drs. Bruce Chabner, Richard Adamson, Peter Greenwald, and Alan Rabson were not sitting around the table but, rather, in the first row due to a change in the size of the chairs, they nonetheless were participating fully in the meeting.

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

Dr. Broder began his remarks by noting that speakers during the meeting would include Dr. Harold Varmus, recently appointed NIH Director, and Dr. Karen Antman, President of the American Society for Clinical Oncology (ASCO). He added that topics discussed during the meeting would include the National Surgical Adjuvant Breast and Bowel Project (NSABP) and the tamoxifen breast cancer prevention trial.

Dr. Broder related that on March 13th, he attended a memorial service in Madison, Wisconsin, for Board member Dr. Howard Temin. He described the occasion as a simple and moving ceremony that demonstrated Dr. Temin's great love for the research agenda of the National Cancer Institute. Mrs. Rayla Temin, Dr. Broder added, expressed her gratitude for the kind thoughts expressed by the cancer research community and the members of the NCAB.

Dr. Broder also observed the death in May 1994 of Dr. James Shannon, NIH Director from 1955 to 1968. Dr. Shannon, he explained, oversaw the development of the Intramural Research Program and made long-term support for investigator-initiated research an understandable concept for the Congress and the public at large. Dr. Shannon did much, Dr. Broder stated, to make the biomedical research community in America the envy of the world.

Turning to staff changes within the Office of the Director, Dr. Broder announced the appointment of Dr. Jerry Rice, Chief of the Laboratory of Comparative Carcinogenesis, as Associate Director of the Frederick Cancer Research and Development Center and the assignment of Dr. Lucy Anderson as Acting Laboratory Chief.

Within the Division of Cancer Etiology (DCE), Dr. Broder announced with regret the plans of Dr. Richard Adamson, DCE Director, to retire at the end of the current fiscal year and recognized Dr. Adamson's contributions in service and leadership. Dr. Broder also reported that Drs. Michael Sporn and Anita Roberts recently delivered the G. Burroughs Mider lecture at NIH on their research on TGF-beta.

Within the Division of Cancer Prevention and Control (DCPC), Dr. Broder announced the appointment of Dr. Leslie Ford, Chief of the Community Oncology and Rehabilitation Branch, to serve as Acting Division Deputy Director while Dr. Edward Sondik serves as Acting Deputy Director for the Institute.

Within the Division of Cancer Treatment (DCT), Dr. Broder announced that Dr. Charles Myers, Chief of the Clinical Pharmacology Branch, retired in May to become the Director of the Cancer Center at the University of Virginia in Charlottesville.

Within the Division of Extramural Activities, Dr. Broder noted that Dr. Marvin Kalt became Director in March and that Dr. Robert Browning, Chief of the Grants Review Branch, had been named as Acting Deputy Division Director.

Within the Division of Cancer Biology, Diagnosis, and Centers (DCBDC), Dr. Broder reported the presentation of a 1994 Arthur S. Flemming Award to Dr. Elise Kohn, Chief of the Laboratory of Pathology, Transfection, and Prevention. He explained that Dr. Kohn is being recognized for her work leading to the first human clinical trial for signal transduction therapy.

As a final staff-related observation, Dr. Broder expressed sincere condolences from the NCI and NCAB to Dr. Bruce Chabner on the recent loss of his mother.

Dr. Broder explained that the meeting would include a report from the Subcommittee to Evaluate the National Cancer Program. He expressed gratitude to Dr. Calabresi, the Subcommittee chair, as well as to Ms. Cherie Nichols, Planning, Evaluation, and Analysis Branch Chief, and her staff for their work on this important undertaking.

Since the last NCAB meeting, Dr. Broder reported, NCI and American Cancer Society (ACS) staff worked together to achieve as much unity as possible on various issues related to mammography. Dr. Sondik, he said, would provide a report on progress that has been made in reaching a consensus on these issues during the afternoon subcommittee meetings. Dr. Broder added that representatives of the ACS had reviewed a draft of the document to be discussed by Dr. Sondik and had been quoted as commenting "we are not far apart."

To provide background for the scheduled discussion of the NSABP trials, Dr. Broder reviewed several issues related to the Institute's clinical trials process. He observed that basic research, cancer centers, and clinical trials represent the three "foundation stones" supporting the National Cancer Program in the areas of prevention and treatment. A substantial portion of the clinical trials, he stated, are now conducted through cooperative groups and Community Clinical Oncology Programs (CCOPs). Dr. Broder stated that these mechanisms provide an indispensable capacity to conduct large-scale testing of new ideas for radically improving therapy for cancer patients. In addition, he suggested, participation in NCI-sponsored clinical trials improves the likelihood that patients will receive state-of-the-art care in their own communities, regardless of which particular study arm they are assigned to enter. While the primary purpose of clinical trials is to generate new scientific knowledge, Dr. Broder continued, they also often lead to new drug applications, changes in drug labeling, and revisions to the policies of third-party payers.

Dr. Broder used two slides to present an overview of funding for clinical trials in recent years. From fiscal year 1991 through the proposed fiscal year 1995 budget, he said, support for clinical trials has increased by 57 percent, while the NCI budget has grown by 28 percent. While professional needs still exist in this area as well as in other areas of the Institute's research program, Dr. Broder stressed that a substantial commitment has been made to support clinical trials in prevention, diagnosis, and treatment.

Dr. Broder acknowledged the work of two pioneers who contributed to the founding of the cooperative groups while serving as NCI employees. Dr. Gordon Zubrad saw the need for multi-institutional clinical trials during the 1950's, Dr. Broder related, and helped create administrative support for the forerunners of today's cooperative groups. In effect, Dr. Broder stated, Dr. Zubrad was at one time chairman of the Eastern Cooperative Oncology Group (ECOG). Dr. Neil Frye, Dr. Broder continued, was leader of the ALGB, the precursor to the CALGB. In addition to his other accomplishments at NCI, Dr. Frye chaired three cooperative groups—the ALGB, the Southwest Oncology Group (SWOG), and, finally, the CALGB.

Dr. Broder noted that cooperative groups are tightly woven throughout the fabric of the NCI, and emphasized that the Institute will continue to identify and disseminate the extremely important strengths of the clinical trials program. He stressed, however, that the Institute should identify any problems with the program and take clear steps to correct them. Although the essence of the clinical trials process is the grantee's primary responsibility and accountability for the performance of the grant, the NCI has responsibilities as well, which, Dr. Broder continued, would be reviewed by Dr. Chabner in his discussion of the NSABP. The NCI is cautiously optimistic, Dr. Broder stated, that certain NSABP studies will resume in the near future, at least for sites with excellent audit records and those that are NCI-designated cancer centers or CCOPs.

Dr. Broder then reviewed several recent meetings. During the joint meeting held by NCI and the American Cancer Society on April 20–21, 1994, in Atlanta, he said topics included breast cancer clinical trials, other evaluation methodologies, new technologies, and evaluation of screening for persons at high risk and special populations, such as minorities. Dr. Broder added that preliminary reports from the chairs of the discussion groups are currently being developed. On May 19, 1994, Dr. Broder reported, NCI staff participated in a briefing for the Assistant Secretary for Health on cancer prevention and control projects relevant to the Healthy People 2000 goals. As Dr. Freeman reported earlier, Dr. Broder added, the President's Cancer Panel held a meeting on avoidable cancers, discussing tobacco use, diet, electromagnetic fields, and occupational exposures.

Dr. Broder announced that in response to a specific Congressional mandate, the NCI has launched the Long Island Breast Cancer Study under the leadership of Dr. Iris Obrams, the extramural program Branch Chief for Epidemiology and Biostatistics in the Division of Cancer Etiology; Dr. Obrams will be assisted by Ms. Clarissa Whittenberg, who Dr. Broder said has been helpful on issues related to interactions with consumers.

Dr. Broder explained that for some issues identified by Congress, such as aircraft emissions, the NCI will be charting new ground and developing new methods for measuring individual exposures. A core group of scientific advisors has been gathered to assist with the study design, and the Institute will work with consumer groups to ensure their participation in the research and will draw upon the expertise of other Federal, State, and local agencies; regional and local power utilities; and NCI-supported cancer centers. A meeting has already been held with New York area cancer centers, Dr. Broder noted, and these centers have sent a letter to the Institute signaling their intent to collaborate in the study. Several Requests for Applications (RFAs) have been released related to this study, which is designed to develop knowledge on environmental causation on Long Island and to explore practical interventions for at-risk women that may be applicable to the country at large.

Dr. Broder provided an update on the Women's Health Initiative, a 15-year, $600 million, randomly controlled clinical trial to study breast cancer, colorectal cancer, heart disease, osteoporosis, and other issues. The study is coordinated by the Office of the Director, NIH; Dr. Broder noted that the new Director, Dr. Harold Varmus, has endorsed the study, which was launched before he took office. The trial will involve approximately 65,000 women in studies of the effects of a low-fat diet in preventing breast cancer and heart disease, the potential benefits and risks of hormone replacement therapy to prevent heart disease and osteoporotic fractures, and the effects of calcium and vitamin D supplements in preventing osteoporotic fractures and colorectal cancer. Dr. Broder announced the establishment of a toll-free number, 1-800-54-WOMEN, to provide information on the Women's Health Initiative.

IV. LEGISLATIVE UPDATE—MS. DOROTHY TISEVICH

Ms. Dorothy Tisevich, legislative liaison for the Institute, presented a brief overview of Congressional activities that had occurred in the months since the last meeting.

Ms. Tisevich said that screening mammography, particularly as it relates to health care reform, continues to be a topic of major interest, provoking three hearings on the subject since January. The first was held on January 26th, before Representative Henry Waxman (D-CA), chairman of the House Subcommittee on Health and the Environment; the second, on March 8th, before Representative Edolphus Towns (D-NY), chairman of the House Subcommittee on Human Resources and Intergovernmental Relations; and the third, on March 9th, before Senator Barbara Mikulski (D-MD), chairwoman of the Senate Aging Subcommittee.

Ms. Tisevich related that in all three hearings, members expressed an interest in NCI's process and concerns about the polarization of the scientific community with respect to the change in NCI's statement regarding mammography screening in women under age 50. To address questions regarding risks and benefits of mammography, research on other screening technologies, and potential improvements to current mammography technology, Drs. Edward Sondik and Karen Johnson from the Division of Cancer Prevention and Control have participated in several briefings for Congressional members and staff. Furthermore, Dr. Johnson and Dr. Susan Blumenthal from the Women's Health Office at the Public Health Service (PHS) are presently conducting additional briefings.

Ms. Tisevich explained that many Congressional members and staff perceive strong support in both the scientific community and the public for continuing to provide screening mammography for women under age 50. She said that many members view mammography as an entrée into the health care system, particularly for minority and underserved women. She described the frustration of many members with the lack of consensus on the issue, especially among the scientific community, and mentioned the strong support for including a mammography benefit for women ages 40 to 49 in the health care reform package. Given the fact that NCI's current statement does not recommend routine screening for this age group, Ms. Tisevich said that several members of the House have signed a resolution calling for a randomized clinical trial to obtain a definitive answer about the benefits of screening for this age group.

Ms. Tisevich also mentioned Senator William Cohen's (R-ME) resolution regarding screening mammography, which would provide for screening mammography when appropriate, and calls for more research by NCI to determine the role of screening mammography in women ages 40 to 49, research to improve imaging techniques, and more research on new and improved methods of early detection. The Senate resolution also encourages the PHS to arrive at a consensus with other organizations on the studies needed to determine the benefits and appropriateness of screening in women ages 40 to 49.

Ms. Tisevich brought up the hearing held on April 13th before Representative John Dingell (D-MI) to address the Office of Research Integrity's (ORI's) finding of fraud at a member institution of the National Surgical Adjuvant Breast and Bowel Project. She said there was considerable discussion at that hearing regarding the Breast Cancer Prevention Trial (BCPT) with tamoxifen and the reconsenting process for women participating in that trial. These same topics were discussed at a hearing held on May 11th before the Senate Cancer Coalition and will be addressed at two upcoming hearings: June 9th before the Senate Appropriations Subcommittee on Labor, HHS, and Education chaired by Senator Tom Harkin (D-IA); and June 15th before Representative Dingell. (A copy of Dr. Broder's testimony from the April 13th hearing was distributed along with the legislative update.)

Ms. Tisevich related that Mr. Donald Shopland, from the Division of Cancer Prevention and Control, testified before the House Subcommittee on Commerce, Consumer Protection, and Competitiveness, chaired by Representative Cardiss Collins (D-IL), regarding potential changes in toxicity of fire-safe cigarettes. She explained that under the Fire-Safe Cigarette Act of 1990, the Consumer Products Safety Commission has responsibility for exploring the feasibility of developing a fire-safe cigarette. Mr. Shopland serves as the HHS representative to the technical advisory group to this commission. Ms. Tisevich mentioned that this initiative has been a special interest of Representative Joseph Moakley (D-MA).

Ms. Tisevich described other briefings for Congressional staff that have been held recently, including one regarding the Agricultural Health Study, which is funded by NCI, the National Institute of Environmental Health Sciences (NIEHS), and the Environmental Protection Agency (EPA). She mentioned the concerns raised by staff about Hispanic

representation in this study, and the interest expressed in the possibility of biological sample collection that may yield valuable information regarding exposure to pesticides and health outcomes.

Ms. Tisevich said that NCI staff also have briefed Senator Patrick Leahy (D-VT) and Representative Bernard Sanders (I-VT), regarding the Congressionally mandated study of elevated breast cancer rates in the Northeast and mid-Atlantic States. She referred to the six grants NCI has funded under an RFA issued last fiscal year to study the factors that may be contributing to elevated breast cancer rates, and the strong environmental component to these projects. Ms. Tisevich noted that the Northeast/Mid-Atlantic Study is being coordinated with the Long Island Breast Cancer Study Project, which is also Congressionally mandated, to encourage collaboration and avoid duplication.

As promised at the last meeting, Ms. Tisevich provided some information regarding pending health care reform legislation. She pointed out that the 20 health care reform bills with relevance to NIH are listed in the legislative update package, with a brief description about each one. Ms. Tisevich explained that there are five Congressional committees with primary jurisdiction for health care reform, of which only one, the Senate Committee on Labor and Human Resources, was close to its target date of Memorial Day for reporting its bill. The other four committees, which include Senate Finance, House Education and Labor, House Ways and Means, and House Energy and Commerce, were set to continue or begin mark-up after the Memorial Day recess.

Ms. Tisevich listed features of some bills that would affect NIH, including: emphasis on prevention research, coverage of investigational therapies, and additional funding for health research through a set-aside of health care premiums or income tax check-off for NIH funding. She identified the administration's proposal for health care reform as the Health Security Act, S. 1757, which was introduced by Senator George Mitchell (D-ME) in the Senate, and its companion bill, H.R. 3600, introduced by Representative Richard Gephardt (D-MO) in the House. To conclude, she stated that her office could provide further information or answer questions about the proposals summarized in the package.

Questions and Answers

Dr. Sigal asked about Congressman Waxman's role on environmental tobacco smoke (ETS) and the Occupational Safety and Health Administration's (OSHA's) regulations on ETS, and whether NCI will give supporting testimony or take a formal position on the issue. Ms. Tisevich answered that the NCI has not been involved at this point, but that she can obtain information on the subject. She proceeded to explain the way in which the NCI would comment on a bill by formulating a position and sending it through channels for the Department to take a position. Dr. Sigal suggested that the NCI should take a strong position against smoking. Ms. Tisevich responded that the Department's general position that smoking is regarded as a health hazard is widely known, but that she can attempt to verify whether they have taken a formal position on the issue. Dr. Calabresi reminded Dr. Sigal that the NCAB passed a very strong resolution on the subject and asked if she had more to add. Dr. Sigal said she had only supporting testimony and felt it was a very important application. Dr. Adamson mentioned that Dr. Bill Blot of the Biostatistics Branch has been their liaison to the EPA on ETS, and that they supported the EPA's testimony at a recent Senate hearing that ETS is a known human carcinogen.

Dr. Chan asked for the definition of a fire-safe cigarette. Ms. Tisevich explained the idea was to develop a cigarette that, if it came into contact with furniture or other materials, would have a lower likelihood of starting a fire. The trade-off of this feature, however, would be added components that might increase toxicity or health complications.

Dr. Salmon suggested that Dr. Sigal draft a resolution from the Board in relation to the Waxman bill if she believed it would be useful.

V. REMARKS BY THE PRESIDENT, AMERICAN SOCIETY OF CLINICAL ONCOLOGY—DR. KAREN H. ANTMAN

Dr. Calabresi reminded everyone of the recently adopted tradition of inviting the president of the American Association for Cancer Research (AACR) to speak before the Board, and of previous speakers Dr. Harold Moses and Dr. Margaret Kripke. He announced the extension of this tradition with an invitation to the president of the American Society of Clinical Oncology, the other clinical cancer society, to speak before the Board. He introduced Dr. Karen Antman, professor of medicine and Chief of the Division of Medical Oncology at Columbia University, as well as the current president of ASCO. He added that Dr. Antman had worked for the Subcommittee to Evaluate the National Cancer Program (SENCAP), on which she assumed a major role in the translational research effort and was one of the chief authors of that chapter.

Dr. Antman thanked the Board for the opportunity to speak on behalf of ASCO, and began her slide presentation by stating ASCO's primary mission: science and education. Initially, she explained, ASCO leadership worked primarily on planning and implementing a joint annual scientific meeting with the AACR. With the recent separation of the two meetings, ASCO has integrated reporting of more basic research and educational programs into its organizational structure. These additions include new committees or subcommittees on clinical pharmacology, immunology, biomarkers, and cancer biology, as well as eight new scientists on the education committee, so that one-third of the committee will be made up of translational or basic scientists.

She described the current number of productive interactions between the laboratory and clinical investigators addressing medical problems as astounding. To illustrate, she referred to the CALBG trial of erb B-2 expression in dose-response where, for women with high erb B-2 expression, there was a significant difference with dose, whereas for women with low erb B-2 expression, there was no significant difference with higher doses, suggesting the ability to select patients who would benefit from more aggressive treatment and avoid the use of toxic treatment in those who would not. Dr. Antman said that, currently, journals are replete with translational research, citing three articles in *Lancet* and the *New England Journal of Medicine*.

Dr. Antman said that a decade ago the ASCO began taking advocacy positions, not only supporting the importance of clinical research, but also taking positions on medical policy, such as coverage for screening mammograms. She discussed the clinical research community's continuing concerns regarding the level of NCI support for clinical research activity, grant funding, grant review, and the present impact of managed care.

Regarding grant funding, Dr. Antman pointed out that while perhaps only 5 percent of cancer patients participate in clinical trials, the cooperative groups and major institutions coordinating large randomized trials currently cap the number of trials that can accrue patients based on the institutional and statistical center budgets. She expressed relief that the budgets of the cooperative groups have been rising recently in real dollars, but concern that these budgets maintain a cap on the number of patients that can have the opportunity to participate in trials.

Dr. Antman alluded to Wyngarden's statement two decades ago that clinical investigators were an "endangered species," and reported that the Institute of Medicine's (IOM's) 1988 report noted that few young investigators were available to replace those leaving the field. She said that ASCO is encouraged by the new grant mechanisms intended for young clinical investigators, and aims to improve grant-writing quality with an annual grant workshop held during its annual meeting. She urged the Board to carefully monitor the implementation of new grant programs to ensure that clinical research, not just preclinical efforts, involving human samples are supported. She observed that P01 grants traditionally and more recently Specialized Programs of Research Excellence (SPORE) grants have been effective mechanisms to ensure collaboration among the spectrum of investigators interested in the disease and that such grants need continued support.

Dr. Antman indicated that peer review of clinical research is perceived as problematic, since clinical research relies on larger numbers to quantitate the impact of any intervention. She pointed out that close control of all variables, as in laboratory research, is impossible in human studies, so Dr. Richard Peto has advocated the use of large, simple trials.

According to Dr. Antman, the design and statistical analysis of disease endpoints require the use of rigorous and precise principles that are clearly different from the principles used in laboratory research and must be understood by the reviewer of clinical grants.

She informed the Board that ASCO supports the NCAB in its recommendation that the Division of Research Grants establish a clinical cancer research study section and offered to coordinate ASCO's efforts with those of the NCAB to work with Dr. Varmus' committee in reviewing the matter.

Dr. Antman said that one of the most important things to emerge from the health care reform debate is the general recognition of the importance of clinical research, particularly for life-threatening diseases such as cancer. She informed the Board that plans introduced by President Bill Clinton, Congressman Jim Cooper (D-TN), and Senator John Chafee (R-RI) all include provisions requiring coverage of patient care costs incurred in high-quality, peer-reviewed clinical trials. She expressed ASCO's hope to work closely with the NCI and the NCAB to obtain the necessary refinements in the legislative language when the plans are reviewed by Congressional committees.

Dr. Antman noted that market forces are prompting changes in health care, even without legislation in place. Until passage of one of the pending bills, she stated, there will be managed care in the absence of a legislative mandate to cover the cost of care for patients in clinical research.

Dr. Antman discussed public perceptions of clinical research. She said that the ASCO Board of Directors strongly supports the principles and practice of rigorous and honest clinical trials research. She expressed the ASCO Board's concern over recent events leading to the current suspicion of clinical trials, and the Board's belief in the sincerity, integrity, and scientific rigor with which most individuals, institutions, and organizations conduct clinical trials. Quality control and auditing procedures have been mandated and proven effective by many cooperative groups, according to Dr. Antman. She said that ASCO believes that revision of existing policies must be based on careful and thoughtful dialogue among the clinical trials leadership in ASCO, in cancer centers and cooperative groups, and within the NCI.

Dr. Antman said she considers health care reform the foremost challenge confronting the National Cancer Program because of its potential to improve cancer treatment by ensuring the President's goals of universal coverage and a defined set of benefits, as well as eliminate

the exclusion of patients with pre-existing conditions; however, she warned about the need to ensure that cost containment does not endanger the cancer program by inappropriately limiting access to specialists, cancer centers, or clinical trials. Dr. Antman announced that proposed reductions in Medicare payments for direct and indirect medical expenses will create shortfalls for the academic centers, including regional cancer centers, unless other sources of payment for academic health centers are made available.

Within the next decade, Dr. Antman stated, the NIH estimates that cancer will surpass heart disease as the major cause of mortality. Dr. Antman discussed the need for changes in undergraduate and graduate medical school curricula if primary care providers are to adequately treat patients with cancer. Some major medical schools do not currently provide training in cancer treatment. To address this problem, she informed the Board of ASCO's efforts to design an optimal second-year medical school curriculum that integrates surgical, medical, pediatric, radiation, and basic oncology. She said that ASCO is also devising curricula for medical residents who may act as gatekeepers in the managed care system.

According to Dr. Antman, regulatory restrictions on the number of specialty training slots allocated to medicine and surgery will shrink the pool from which medical, surgical, and radiation oncology fellows are recruited, with the number of slots for medical oncology fellows estimated to drop about 44 percent. A reduction in training slots would substantially reduce the number of physicians training for cancer careers in academic medicine, making NIH training awards to enhance opportunities for careers in academic medicine critical.

Dr. Antman said that ASCO also supports efforts to enhance research funding available to the NIH, having recently endorsed proposals by Senator Tom Harkin (D-IA) and Senator Mark Hatfield (R-OR) to set aside a percentage of insurance premiums for augmenting NIH funding. She also expressed ASCO's willingness to work closely with the NIH, NCI, and the NCAB in formulating and implementing policies that have an impact on cancer research and patient care, emphasizing the importance of cooperation between the extramural research community—including academic and community centers, cooperative groups, and each of the various professional societies—and the intramural community to advance cancer research for the ultimate benefit of patients with cancer.

Questions and Answers

Dr. Calabresi thanked Dr. Antman and mentioned that she had chaired the program committee for AACR, which is an example of the liaison between AACR and ASCO and the AACR program in translational research. Dr. Antman added that she believes collaboration rather than competition between the professional societies is essential to address current problems.

Dr. Salmon emphasized that the most serious threat to clinical cancer research at present is managed care created by market forces, because it prevents patients from seeking care at cancer centers or participating in cooperative group trials, even though the treatment offered there may be the best available using only standard agents. While this is not true of all managed care groups, he said, the increasing emphasis on cost-effectiveness is progressively excluding treatment through clinical trials. Dr. Salmon noted the spread of this phenomenon from west to east, and expressed concern that without legislation, it may lead to the demise of clinical cancer research. Additionally, it decreases the desirability of a career in academic medicine for a clinician.

Dr. Broder agreed with Dr. Salmon, expressing concern that certain cancer centers or analogous institutions accept very difficult cases, effectively alleviating the burden on other groups. Accepting these challenging cases makes such groups appear less competitive in

comparison with those who do not take this responsibility. Dr. Broder said that those institutions that accept difficult cases should be acknowledged for relieving other organizations of this burden.

Ms. Visco agreed with Dr. Antman that changes in processes involved with clinical trials should be discussed, not imposed, but suggested that patients are also participants in the dialogue with the cooperative groups and the NCI. Dr. Antman replied that ASCO would support such a proposition as evidenced by the consumers on some committees.

Dr. Stovall asked whether ASCO supported the Harkin-Hatfield trust fund, particularly the part of the legislation dealing with premium caps. She mentioned that some patient groups would prefer no caps on premiums, because the dollars available for patient care would not be in such jeopardy. The effect would be to skim money "off the top" that would otherwise be used for reimbursement in areas such as clinical trials. Dr. Antman answered that ASCO wants several corrections in the legislative language of the Harkin-Hatfield Amendment and believes they can be accomplished with the assistance of other organizations. One desired change is in the language regarding premium caps, for the reason Dr. Stovall suggested. Another change ASCO seeks is in the Clinton bill, which presently allows insurance companies to choose whether to cover the costs of clinical trials at their discretion. If insurance companies believe their only responsibility is to pay the 1 percent tax and are not required to cover patient care costs, Dr. Antman suggested this solution could create more difficulty than currently exists.

Dr. Newton mentioned the importance of cancer registries for the conduct of research on cancer etiology and asked about ASCO's efforts in this area and attention to professional education among its members to improve cancer registries in the United States. Dr. Antman explained that that issue is being discussed by the Cancer Prevention and Control Committee.

Dr. Calabresi thanked Dr. Antman for her presentation, and asked Dr. Becker to speak about Dr. Randolph Lee Clark, who recently passed away.

In Memory of Dr. Randolph Lee Clark

Dr. Becker announced the death of Dr. R. Lee Clark, founder of the University of Texas M. D. Anderson Cancer Center. He said that Dr. Clark was the driving force in M. D. Anderson's first 35 years of growth and accomplishment. Dr. Becker described Dr. Clark as a brilliant surgeon and innovator who recognized, during the first stages of the M.D. Anderson Center, the need to establish the basic science foundation, which was created simultaneously.

Dr. Clark was also a founder and driving force in the establishment of the National Cancer Act, and was one of the earliest to recognize the need for international cooperation and collaboration in cancer research. He also served as national president of the American Cancer Society.

Those who knew Dr. Clark, Dr. Becker said, would describe him as charismatic, and John Connelly once complimented him by saying, "Thank God he never ran for governor." Dr. Becker described the unceasing admiration of Dr. Clark's friends and the way he remained active despite a severe stroke several years prior to his death. Dr. Becker mourned Dr. Clark's passing as a great loss to M. D. Anderson, to the State of Texas, and to the establishment of cancer in general.

VI. AWARDS/NEW BUSINESS: SESSION I—DR. PAUL CALABRESI

Dr. Calabresi asked for new resolutions or items and explained that these items would be considered and discussed before taking final action during the second new business session held on the following day.

Dr. Calabresi introduced the first item of new business—the chairpersonship of the subcommittees. Because new NCAB member appointments have not been made, Dr. Calabresi asked several current members who are scheduled to rotate off the Board in March to remain until September, when new appointments are anticipated. In preparation for the new appointments, Dr. Calabresi asked several members to assume the chairpersonship for those committees in which members will be rotating off.

Dr. Calabresi reviewed these changes in chairpersons and consolidation of committees. He announced that he will continue to chair the Subcommittee on Activities and Agenda. The AIDS Subcommittee will remain inactive due to the death of Dr. Howard Temin, but Dr. Calabresi said that appointment of a new member with expertise in the viral/antiviral area is anticipated. He informed the Board that the Subcommittee on Cancer Centers will be chaired by Dr. Robert Day, president of the cancer center in Seattle at the University of Washington.

Dr. Calabresi announced that he would also remain the chair of the Clinical Investigations Task Force, which would be terminated after presenting a final report on the following day. Dr. Calabresi explained that the Subcommittee on Clinical Investigation is being divided into two task forces—one on translational research and the other on clinical trials, the importance of which Dr. Broder emphasized in his report. In order to obtain external input, Dr. Calabresi invited Dr. Ross McIntyre, chairman of both the Council of Chairs of Clinical Trials Groups and CALBG, as well as Dr. Chuck Colton from SWOG, Dr. Doug Tormey from ECOG, Dr. Jim Cox from RTOG, Dr. Karen Murphy from the Pediatric Oncology Group (POG), and Dr. Ron Heberman, a representative from NSABP, to attend that day's meeting. He announced the intention of the Board to work with these chairpersons and NCI staff to amend the clinical trials program.

Dr. Calabresi added that these chairpersons are enthusiastic about the cooperative effort among the external scientific and clinical trials community, NCI staff, and NCAB regarding the foremost clinical trials program in the world. He reminded the Board of Dr. Broder's caution about the importance of maintaining momentum on this project to avoid losing support of and funding from Congress.

According to Dr. Calabresi, Dr. Becker will continue to serve as chairman of the Subcommittee on Environmental Carcinogenesis, and Ms. Malek will remain chairwoman of the Subcommittee on Information and Cancer Control. He announced a change in the chairpersonship of the Subcommittee on Planning and Budget from Dr. Bettinghaus to Dr. Sigal, and in the Subcommittee on Special Actions from Dr. Wells to Dr. Salmon.

Dr. Calabresi reminded the Board of the creation of the Subcommittee on Special Priorities, a combination of the Subcommittees on Aging, Minorities, and Women's Affairs. Dr. Calabresi asked Dr. Wilson to chair this Subcommittee because of Ms. Mayer's prior commitments. The three arms of this Subcommittee are: Aging and Cancer, cochaired by Ms. Mayer; Minorities, cochaired by Ms. Brown; and Women's Affairs, cochaired by Ms. Johnson.

Questions and Answers

Ms. Marge Foti inquired whether Dr. Calabresi had considered creating a subcommittee on basic research. Dr. Calabresi expressed interest in her idea and agreed to consider her suggestion.

Dr. Wells asked if a separate subcommittee on translational research exists. Dr. Calabresi responded that the Subcommittee on Clinical Investigations had not yet created that subcommittee, but would discuss the issue at its meeting that day.

Dr. Bettinghaus reminded Dr. Calabresi of the resolution drafted by Drs. Bettinghaus and Becker honoring Dr. Temin and his service to the NCAB. He asked for the Board's comments or suggestions so that the resolution could be adopted at the next meeting. Dr. Calabresi suggested that the resolution be "in memory of" Dr. Temin instead of "in honor of" him. Dr. Bettinghaus agreed with the suggestion and read the proposed resolution.

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

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

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

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

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

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

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

"Whereas, with passion and brilliance, he delineated the crucial role of investigator-initiated basic research as the major force in advancing scientific knowledge, and the strength of his service was typified by the fact that he attended his final meetings of the National Cancer Advisory Board via speakerphone when he found himself unable to attend in person;

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

Dr. Calabresi thanked Drs. Bettinghaus and Becker and asked for a motion to adopt the resolution. The motion was seconded and the Board unanimously voted in favor of the motion. Dr. Calabresi announced that the motion has been adopted and that Mrs. Temin will be invited to the September NCAB meeting for presentation of the resolution.

Ms. Visco asked to return to the subcommittee discussion, and inquired about what precipitates the formation of a new subcommittee, the functions of subcommittees, and how determination is made that a new subcommittee is necessary. Dr. Calabresi responded that subcommittees are created when there is a special need in an area that requires attention. He added that careful consideration is given to avoid the past problem of creating too many subcommittees given the limited amount of meeting time. Dr. Calabresi stated that subcommittees are important for conducting analysis and infrastructure work when the large size of a full Board meeting frustrates the ability to transact major items of business or define details. Referring to Ms. Foti's earlier suggestion of a subcommittee on basic research, he said that a major function of the Board is to deal with that area, but that the potential need for a special subcommittee relating particularly to the unique problems of basic research will be carefully considered. Ms. Visco stressed the need to restrict development of new subcommittees to those that meet certain criteria. Dr. Calabresi stated that an effort is being made to stem the proliferation of subcommittees by joining those subcommittees whose functions can legitimately be combined.

Dr. Calabresi proceeded to lead the Board in formally celebrating Mrs. Barbara Bynum's retirement from Government after 36 years of Federal service, the last 11 of which have been as Director of the Division of Extramural Activities and Executive Secretary of the National Cancer Advisory Board. On behalf of the Board, he expressed happiness that Mrs. Bynum and her husband have a new opportunity to enjoy the rewards of their many years of service to the Government, but a sense of loss in losing Mrs. Bynum as a guide and advisor. As a token of her contribution to the NIH and the NCAB, Dr. Calabresi invited Ms. Bynum to come to the podium for a presentation. He read aloud the framed resolution:

"Whereas, Mrs. Bynum, as part of her 36 years of government service, was Director of the Division of Extramural Activities, NCI, since 1981; and

"Whereas, Mrs. Bynum was not only the Executive Secretary of the National Cancer Advisory Board (NCAB), but its conscience, historian and managing force behind the NCAB; and

"Whereas, Mrs. Bynum, in those positions, was responsible for the scientific review and surveillance of extramural research; and

"Whereas, Mrs. Bynum played a visionary role in the NCI's efforts to encourage minority participation in a range of cancer research activities; and

"Whereas, Mrs. Bynum did all of these things, and more, with grace, humor, intellect, caring and vision;

"Therefore, be it resolved that the National Cancer Advisory Board recognizes and honors Mrs. Bynum's exemplary contributions in furthering the National Cancer Program. May 1994."

Dr. Calabresi asked Mrs. Bynum to say a few words. She thanked him and everyone else in the room, expressing appreciation for the cards, letters, calls, and gifts given to her on her retirement. She said good-bye and wished the Board continued success at the NIH.

VII. REMARKS BY THE DIRECTOR, NATIONAL INSTITUTES OF HEALTH—DR. HAROLD E. VARMUS

Dr. Varmus reported that he has been visiting the advisory councils of all of the NIH Institutes, Centers, and Divisions, both to ensure them that they have access to his office and to solicit their counsel. He expressed interest, particularly, in receiving advice on how to improve performance with a diminishing budget. Dr. Varmus noted that in his budget request for fiscal year 1995, the President has asked for a $517 million increase for the NIH, an increase of 4.7 percent. He described this as a moral victory, noting that Secretary Shalala has worked very hard to obtain a budget request greater than the rate of inflation during a time when Congress is dictating zero growth. The budget hearings went well, Dr. Varmus reported, but appropriations are unlikely to match the full amount requested; estimates of the portion of the requested increase that will be funded range from 15 to 60 percent. At any rate, he continued, NIH is unlikely to meet the rate of inflation, creating a demoralizing situation within which to try to exploit today's scientific opportunities.

For fiscal year 1996, Dr. Varmus stated, NIH is taking a more aggressive approach to shaping the budget. Part of the process, he said, has included asking Institute Directors to indicate their spending preferences, in order to control costs while increasing efforts in new and exciting areas. Dr. Varmus acknowledged that he has received more enthusiastic responses to his request for ideas on the need for additional funding than to his request for suggestions on trimming the budget. He announced that a 2-day retreat for Institute Directors and other staff will be held in August to discuss various scientific and administrative prospects throughout NIH.

Dr. Varmus expressed particular interest in ideas that would allow individual Institutes to receive increased funding, justified by documented evidence of scientific promise, and to serve as a focal point for initiatives in those areas that would extend across many Institutes. He said he anticipates seeing the NCI reach out to other Institutes with which a common vision is shared in areas such as aging and environmental science.

Dr. Varmus voiced plans to keep abreast of scientific opinion by employing what he referred to as ombudsmen to the scientific community. Dr. Varmus noted that this issue relates to a number of domains, including peer review, NIH management, and strategic planning for the scientific future of the agency and development of budgets based on scientific changes. Dr. Howard Schockman, a physical enzymologist and entomologist from the University of California at Berkeley, is the first ombudsman hired; he has been traveling to many campuses and bringing information back to the Director's office. Dr. Varmus stated that someone from the clinical sciences arena is being sought to play a similar role. He added that the advisory councils should play a role as well, and urged NCAB members to suggest areas that require attention through Dr. Broder or NCI's Division Directors.

Because of decreasing budgets, Dr. Varmus explained, it is necessary to find ways to accomplish more with fewer resources. Two arenas in which this goal is being pursued, he said, involve reevaluation of the intramural program and examination of the peer review process. In response to a request from the House Appropriations Committee, Dr. Varmus stated, a panel of extramural scientists and clinicians recently delivered to his office a report on the status of the intramural program. The report has prompted a healthy debate among intramural scientists, Dr. Varmus noted, and will be presented within days to the NIH Director's advisory committee at its semiannual meeting.

The report contains a number of important suggestions, Dr. Varmus continued, concerning the recruitment, training, evaluation, and tenuring of scientists. It suggests the establishment of a central tenure committee composed of intramural scientists and clinicians. Dr. Varmus stated that these suggestions provide the impetus to pursue ideas that he and Dr. Michael Gottesman, Acting Director of Intramural Research, have already discussed to make the intramural program more effective. He added that Dr. Gottesman has instituted new procedures for tenuring intramural scientists that have been well received on the NIH campus.

Dr. Varmus acknowledged that the report does not give adequate credit to Institute Directors or advisory committees such as the NCAB, and he stated that this does not reflect the thinking of the NIH hierarchy. He expressed disagreement with his advisory group's suggestion that Boards of Scientific Counselors (BSCs) be involved in decisions on distribution of funds between intramural and extramural programs. He expressed hope that the NCAB will, in due course, provide advice on allocations for intramural research. Dr. Varmus noted that the current overall NIH allocation for intramural research is 11.3 percent of the total budget, while the NCI spends nearly twice that amount on its intramural program. He asked NCAB members to consider the issue and discuss the appropriateness of this proportion of funding for intramural research with Dr. Broder and the Institute's Division Directors. Dr. Varmus added that while the retirement of Dr. Adamson is a sad departure, it is also an opportunity to rethink the structure of the intramural program.

Dr. Varmus observed that budgetary constraints have made the peer review of grant applications extremely difficult, adding that study sections are dispirited by the fact that as few as 10 to 15 percent of applications received by certain Institutes can be funded. He said that he has met with Dr. Wendy Baldwin, Deputy Director for Extramural Research, and Dr. Jerry Green, head of the Division of Research Grants, to explore new ways to improve the review process, save money, and improve the scientific evaluation of applications. The most dramatic new approach that has been adopted, he said, is a procedure called triage, which has been used by some Institutes for several years as a way to focus discussion on those applications that are truly competitive. This process, which has already been used by four study sections and will be tested by another 12 study sections in the upcoming review, allows the reviewers themselves, rather than NIH staff, to identify the 40 to 50 percent of applications that are unlikely to be competitive. If no one contests the exclusion of these applications, Dr. Varmus explained, grants administration staff can quickly inform applicants that they will not be successful. The study section is then faced with reviewing a much smaller number of applications, allowing more time for discussion. While this process is not a substitute for more money, which would allow a higher success rate, Dr. Varmus described it as the best that can be done under the circumstances.

Another interesting approach to improving the peer review process, Dr. Varmus stated, is something called the "just in time" procedure, which involves postponing most of the large amount of paperwork associated with the processing of grant applications until an application is identified as one that is clearly fundable. Dr. Varmus noted that 70 to 80 percent of grant applications do not reach this point. He stated that the "just in time" procedure could save

several hundred million dollars a year. Attempts are also being made to improve the handling of paperwork through electronic mail.

Efforts are also being made, Dr. Varmus added, to ensure a continuing supply of highly qualified persons to serve on study sections. He said that many beneficiaries of NIH research support, if identified by grants administration staff as desirable candidates, will receive a letter from the NIH Director congratulating them for their good fortune in receiving NIH funding and stressing the moral responsibility to serve on an advisory council at some time in their careers.

Concerning the NSABP, Dr. Varmus applauded the swift action taken by Dr. Broder and his staff in dealing with a situation that is volatile and difficult, resulting not only in a serious setback for clinical research, but also in a challenge that will prove useful in the long run. He observed that this has not been the only difficulty encountered by NIH recently, referring to the deaths of five patients who were being treated with FIAU, an experimental nucleoside drug for hepatitis B infection. That episode, he stated, is also being reviewed by an outside group that will report to the Director's advisory committee at its upcoming meeting. These and other events, Dr. Varmus observed, have led to a minor crisis of confidence in the clinical research community.

These are not likely to be the last such episodes, Dr. Varmus continued, considering the fact that clinical research in community settings is being expanded. He said it is not certain that all of the doctors becoming involved in clinical research have been trained in the auditing procedures required for patient accrual, and many are concerned about whether training in clinical science has been adequately carried out in medical schools and at postgraduate levels. Dr. Varmus reported that NIH is considering the establishment of a high-level commission to look at broad issues such as the definition of clinical research, the adequacy of clinical research funding and training, and the effects of inclusion guidelines and health care policy changes on clinical research. Ideas are being gathered from Institute Directors, advisory councils, and other NIH staff on the creation of such a commission to restore confidence in clinical research programs.

Questions and Answers

Dr. Becker suggested that utilizing the input of those who have served as peer reviewers in the past would be useful in redesigning the peer review process. Dr. Varmus replied that this is being done. On July 14th, he noted, a full-day meeting is planned that will include both NCI staff and extramural representatives, many of whom have written letters expressing their ideas concerning the peer review process. He added that one of his former colleagues suggested the possibility of using the "chunk grants" approach, which involves predetermined grant sizes at various funding levels. This idea, Dr. Varmus acknowledged, might help eliminate "haggling" over budgets.

Dr. Varmus also expressed interest in learning more about how researchers are funded, not by examining award rates or resubmissions, but by asking institutions how many people are doing research and where their funding comes from. He said that when he has asked department chairmen how many people are doing research, the answer has usually been about 80 percent, and that sources of funding vary widely.

Dr. Freeman asked if Dr. Varmus had given thought to the continuity between scientific discoveries and their dissemination to the public. Dr. Varmus replied that in response to concerns expressed by the House Appropriations Committee, NIH has assembled a full accounting of its efforts in this area. He stated that NIH spends close to $200 million per year on the dissemination of research findings and recommendations concerning clinical care.

The NCI, he added, is among the Institutes that are most active in this respect, but all Public Health Service components are expected to play a role in these activities. While much remains to be done, Dr. Varmus observed, NIH is open to suggestions from advisory groups on solving problems in this area.

Dr. Freeman stated that oversight and guidance are needed to provide continuity from research funding to basic research, translational research, and applied research to assist individuals at the community level. He noted that many people still do not have access to advances in health-related research due to lack of education, income, or insurance. Dr. Varmus stated that several offices have responsibility for information dissemination, including those focusing on minority health, women's health, and prevention, as well as offices within individual Institutes.

Dr. Freeman acknowledged that information dissemination is one part of the issue, but argued that the larger question is whether there is coordination of efforts to ensure that discoveries actually benefit the American people—a question that incorporates issues concerning access to care and health care reform. Dr. Varmus agreed that this is a large question, suggesting that the issues it encompasses are brought together at the Departmental level—since the Department of Health and Human Services has the broad responsibility for health-related matters—and, ultimately, at the Presidential level. He emphasized, however, that the NIH does not see its mission as purely to develop breakthroughs in basic biomedical science. He concluded that those concerned about this issue should be encouraged by the Clinton administration's commitment to health care reform.

VIII. UPDATE ON THE PLAN FOR NSABP RECOMPETITION—DR. JANET OSUCH

Background—Dr. Bruce Chabner

Dr. Calabresi introduced Dr. Bruce Chabner of NCI and Dr. Janet Osuch of Michigan State University to provide an update on plans for the NSABP recompetition.

Dr. Chabner provided a background of events concerning the NSABP and corrective actions either taken or planned for the future. In June 1990, NSABP staff discovered that two operative reports had conflicting information on the same patient, and NSABP leadership was notified of this discrepancy. Instead of immediately informing NCI, they waited for the results of a regular, scheduled audit in September 1990. The audit confirmed discrepant data in a number of cases, and a repeat audit conducted in January 1991 uncovered additional inconsistent cases. The NSABP reported its findings to the NCI in February 1991. The NCI notified the Office of Scientific Integrity (OSI) and the Food and Drug Administration (FDA) and an investigation was immediately begun. Early in the investigation it was clear that fabrication had taken place, primarily in data related to eligibility for trials. The investigator, Dr. Roger Poisson, admitted in May 1991 that he had changed dates and, in some cases, had fabricated estrogen receptor data to enter patients into clinical trials. A thorough review of the 1,500 cases entered by Dr. Poisson revealed that 99 had been affected by fraud—in some cases, more than one instance per patient—and 115 data items had been changed.

The statistical and scientific leadership of NSABP decided to reanalyze the trials. Although NCI did not ascertain that the other 1,400 patients had been affected by fraud, staff resolved to expunge all data from St. Luc's Hospital. NSABP staff presented a verbal report to NCI in July 1991, stating that the mastectomy versus lumpectomy trial (a key trial) results had

not changed after exclusion of the St. Luc's data. In March 1992, a more extensive oral presentation of the reanalysis was made to NIH and NCI staff. NCI and the Office of Research Integrity (ORI) recommended publication of the reanalysis when the investigation was completed. ORI completed the investigation in April 1993. In January 1993, NCI sent a letter to NSABP informing them that the investigation was nearing completion, that they should prepare to publish as soon as the investigation was officially complete, and that ORI would present information about the investigation. NCI instructed NSABP to conduct a detailed reanalysis immediately, remove any St. Luc's data from ongoing studies, and notify collaborators working with St. Luc's data. In April 1993, ORI published the first report in its newsletter; a brief report was published in the *Federal Register* in June 1993.

Despite numerous requests, NSABP did not submit a reanalysis to the NCI until February 1994 in the form of reanalyzed B-06, B-13, and B-14 trials. NCI asked for external review of the reanalyzed data from these three trials. Dr. Chabner emphasized that the NCI felt it was important to present this data publicly, although reanalyses of the trials in 1992 and 1994 did not show a change in the outcomes of any of these trials. The *Chicago Tribune* published an article in March 1994 that questioned the findings of the B-06 trial, which showed equivalence for mastectomy and lumpectomy. There were several requests for reanalysis and republication of findings; however, Dr. Chabner related, the NCI did not compel the NSABP to follow through with the request until later by including it in their terms of award. He stated that the reanalysis, unfortunately, did not occur until the issue had become public record.

Following publication of the newspaper article, NCI conducted an extended visit to NSABP to examine their operations, particularly site visit and auditing procedures. Since NCI was aware that there were delays in report submission, they were concerned that there could have been other overlooked or untold episodes of fraud.

Dr. Chabner reviewed several problematic areas. The NSABP had not established a Data Safety and Monitoring Board, as they had been asked to do repeatedly since December 1992. NSABP staff unilaterally suspended all treatment trials audits in April 1993, primarily because their chief auditor had retired and they were overburdened with responsibilities for the P01 trial, without notifying NCI. Also, despite requests, the NSABP had not provided NCI with a schedule of 1993 audits, and, in March 1994, NCI found a second case of suspected fraud in NSABP files. NSABP conducted a site visit at St. Mary's Hospital in September 1993, which had been reported and filed. NSABP leadership was aware of the visit and the suspected fabrication and had even discussed it with the investigator, but had not informed NCI until late March 1994. There were several other reporting problems, particularly in two institutions in New Orleans that had had unsatisfactory audits. NSABP had delayed almost a year in reporting these problems to NCI. Also, audit reports disclosing serious problems in cases filed at South Nassau and at Memorial Hospital in Los Angeles were not called to NCI's attention nor, in some cases, to the investigator's. NSABP audits of 38 prevention sites in 1992 and 1993 revealed several problems, mainly in data accumulation. NCI audits determined that the raw data existed but were not found in the NSABP site visit process; thus, their reports contained missing information (e.g., 40 percent of physical examinations missing, 15 percent of mammography procedures not reported on the charts). Because of the second case of fraud at St. Mary's Hospital, confirmed by a site visit to Montreal, NCI asked the University of Pittsburgh to name a new principal investigator for the grant in late March 1994 and restructure the grants.

Dr. Chabner listed some additional problems encountered with NSABP, including failure to publish the results of the B-06 trial and to notify the NSABP membership of fraud at St. Luc's Hospital. The fraud had been mentioned briefly at an executive committee meeting without identification of the institution or mention of the scope of the fraud. NSABP

membership was not aware of this problem in March 1994. NSABP failed to expunge data from their files and continued to publish papers from 1991 to 1994 using these data. Statistical arguments were made *post facto* to justify the use of these data in publications; however, St. Luc's failed to follow instructions to expunge the data from its files. There was also a failure to reanalyze and submit for publication all previously published papers containing St. Luc's data.

Dr. Chabner then described NCI's deficiencies in handling this issue, and indicated that NCI failed to compel publication of reanalysis and compliance in auditing and reporting. He remarked that NCI trusted the cooperative groups and treated them as independent grantees and scientists, expecting certain standards. NCI was aware of differences in the NSABP's auditing system and requested that the group model their procedures after other groups; they refused. Dr. Chabner stated that the NCI recognized that there was a lack of standardized procedures to guide their response to fraud. Previous problems in the cooperative group had occurred in the early 1980's and led to the institution of auditing procedures. Notification of journals and the public, recovery of funds, removal of all fraudulent data from protocol files, and reanalysis of trials had not been worked out in detail until the present problem arose. Other episodes of fraud had involved fewer patients and had not involved data significant enough to require reanalysis and republication of papers.

NCI placed NSABP on probation on March 30, 1994. Dr. Chabner praised the NSABP interim leadership, Drs. Ron Herberman and Skip Trump, for their cooperation and organizational skills. Drs. Herberman and Trump have facilitated plans for site visit monitoring and changes in auditing procedures. They have improved audit procedures for verifying data and protocol compliance and will be on-site to collect data. Outside individuals will participate in each site visit. NSABP has accepted standard procedures for reporting problem audits within 24 hours and submitting all audit reports within 6 weeks. They have agreed to provide NCI with monthly audit schedules, arranged schedules for the next few months, and agreed to complete the backlog of audits that have accumulated since April 1993. They have also established an independent Data Safety and Monitoring Board. An oversight committee, including two consumer advocates knowledgeable about clinical trials, has been appointed to advise the group and achieve compliance similar to other cooperative groups.

NCI is also requiring NSABP to reanalyze and report all trials containing data from St. Luc's Hospital and to submit these manuscripts to NCI for approval prior to a release from probation. The NSABP has submitted one paper describing the B-06, B-13, and B-14 trials to the *New England Journal of Medicine*; it is being held for publication pending completion of auditing. The Project has submitted to NCI plans for submitting reanalysis of all other trials containing St. Luc's data to other journals. Because of the urgency of releasing the B-06 reanalysis to the public, NCI has hired a contractor to conduct the analysis. NCI holds the data tapes from those trials, which are available online through computer networks.

NCI has revised the terms of award for all groups. It has established auditing timelines and guidelines; verbal reports on findings must be submitted to NCI within 24 hours and written reports must be submitted within 6 weeks. Groups must notify the Cancer Therapy Evaluation Program (CTEP) of serious data irregularities within 24 hours. Dr. Chabner presented a slide detailing revised terms of award that include actions required to correct the literature and reanalyze trials in cases of scientific misconduct. The procedures, he said, are similar to those followed in the NSABP circumstance.

Dr. Chabner reported that NSABP leadership failed to notify trial participants and participating investigators about significant toxicities related to tamoxifen. Thus, proposed revised terms of award will include notification of all involved parties, including NCI, FDA,

and the sponsoring drug company (if there is one), of any adverse drug reaction. This term will be the responsibility of all participating investigators.

Dr. Chabner explained that the NCI created a Clinical Trials Monitoring Branch, headed by Dr. Michaele Christian, to address auditing problems. He complimented Dr. Christian for centralizing NCI activities in auditing that were formerly performed by a small group of individuals within another Branch. Dr. Chabner added that contract support must be developed for the new Branch, and that they are experiencing the obvious current difficulties in staffing, but recognized their success in bringing the procedures to reality.

The outstanding issue for NSABP, Dr. Chabner related, is choosing new leadership and recompeting the grant, for which there is a procedure in the NSABP constitution. NSABP had considered revising that constitutional procedure to broaden the scope of work for a new chairperson and transfer responsibility to a broadened executive committee. Dr. Chabner noted that if the NSABP decides to revise the constitution, they must bring a proposal to their June meeting; election could take place in the fall. Under the existing constitution, the current executive committee would nominate a new chairperson and the membership would elect that individual.

In light of several fundamental problems, Dr. Chabner stated, NCI feels that the group should recompete for its funding. NCI plans for recompetition to begin in January or February of 1995, with a grant to be issued in spring or summer 1995, and awarded in fall or winter 1995—January 1996 at the latest. It is important for the group to choose a new leader, since scientific leadership is necessary for recompetition of funding (e.g., response to funding, etc.). It is possible, Dr. Chabner explained, to shift the operations and statistical offices to another center, if the new leadership is from another institution. There is precedent for the grant following the new leadership to a new institution, and NCI will provide advice and support for transition, if necessary. Dr. Chabner emphasized that NCI does not want to make the selection of new leadership, but that it is essential for the long-term viability of this group to elect new leadership in the near future.

Resumption of patient accrual to clinical trials in NSABP is another important issue, Dr. Chabner pointed out, which NCI plans to start within the next 7 to 10 days. He expressed his confidence in an effective auditing and site visit process that has resulted from NSABP's corrected plan. NCI plans to monitor activities on-site in Pittsburgh through resumption of clinical trials and auditing.

There was an interruption in Dr. Chabner's presentation to accommodate the schedule of Dr. Harold Varmus, Director of the National Institutes of Health. After Dr. Varmus' presentation, Dr. Chabner resumed his discussion of the NSABP.

Dr. Chabner discussed two other issues that arose from the NSABP situation—validation of the B-06 study and effect on the way clinical trials are viewed. The B-06 study was a landmark study which other randomized trials have confirmed to be the first and largest of the trials to show an equivalence of mastectomy and lumpectomy. NCI has carefully audited the major contributing centers to this trial. The Poisson data was a major component of the B-06 study, contributing 350 of the 2,100 patients on the trial. Finding all of the data for this study, which began 17 years ago, has required repeat audits in several sites. When all of the data are collected, NCI plans to: ask an impartial expert committee to advise on its analysis and indicate which portions are useful; convene a conference in late summer to discuss the trial, its reanalysis, and other trials; and update all other trials in the same field. The impartial committee will help to validate NSABP's results and to offer the best scientific opinion on this subject to women who are concerned about the validity of lumpectomy as an alternative to mastectomy.

The NSABP episode affected the way the community views clinical trials and drew attention to weaknesses in the cooperative group system. Dr. Chabner listed some of these deficiencies. The groups should have a common approach to auditing (i.e., common standards for pass and fail) and stringent credentialing criteria for investigators. Most groups, he said, require a probationary period before an investigator may join; NCI hopes to formalize this process with common criteria. Dr. Chabner indicated that membership should be reimbursed for more than accrual; quality research, participation in clinical trials design, and preparation of papers should also be recognized and rewarded.

NCI has negotiated with cooperative groups to provide access to data for landmark studies and in cases of fraud. Dr. Chabner reiterated that NCI has revised the terms of award for all groups to ensure access to data; therefore, it will be easier and faster to perform the necessary functions to reassure the public about a trial in which scientific misconduct has occurred. Dr. Chabner related that the NCI wants the same access to or archive of data for landmark studies that affect clinical practice, at least after publication of the studies. There were some initial misunderstandings, but the group now agrees that access to the data is a reasonable request. Dr. Chabner stated that NCI representatives would meet with the group chairman several days after the NCAB meeting.

Dr. Chabner emphasized the importance of a cooperative relationship between the groups and NCI. He explained that cooperative interaction between NSABP and NCI did not occur on issues related to auditing and republication of the trials; he noted that this has not been true for other groups. Dr. Chabner recognized that, at the peak of this episode, the NCI did not always consult the groups adequately in decision making, although he has collaborated closely with the chairperson of the Board of Scientific Counselors for DCT, Dr. Clara Bloomfield. Dr. Chabner acknowledged that attaining consensus and agreement on issues related to this incident has not always been a smooth process, but stressed that the NCI does not intend to act in a "dictatorial fashion." NCI believes strongly, he stated, in preserving the freedom of investigators to conduct their research and make their own decisions. However, Dr. Chabner concluded, the NCI must protect the public investment; the implications of these trials for public health are great.

Dr. Chabner then introduced Dr. Janet Osuch.

Presentation—Dr. Janet Osuch

"I am standing here before you as a surgical oncologist, as a physician whose practice is limited to diseases of the breast, as an active clinical trials investigator, as a woman. I have been an active member of the NSABP for 7 years, and I am a member of its Surgery Committee. I am also a physician passionate about the clinical trials process and, as such, I have entered dozens of patients onto NSABP protocols.

"As an active NSABP investigator, I receive much needed professional identification from the organization. Bernie Fisher was one of my mentors. I called myself one of his disciples. He had the capacity, as Director of the NSABP, to enlist a feeling of passionate involvement and loyalty. He made the meetings of the membership scientifically sound, incredibly intellectually challenging, and his passion for the advancement of knowledge in the breast cancer arena was contagious beyond description. He forced all of us beyond time-honored assumptions and toward challenging new goals. For this, he deserves and has my respect and admiration. I harbor intense loyalty to him.

"However, I have a role beyond that of an NSABP member. I have chosen a career which carries responsibilities as a doctor for the women who choose to entrust their lives to

me. My primary obligation is to the women who seek my help. As a physician, I have a duty to preserve two important values: the trust of my patients and the integrity of science.

"The feelings of personal betrayal that I felt over the lack of public disclosure of the scientific misconduct of Dr. Roger Poisson on the part of the NSABP, the NCI, and the Office of Research Integrity, continue to plague me. To have learned of the issue from the *Chicago Tribune* rather than from Dr. Fisher only serves to deepen the sense of betrayal.

"What was the purpose of keeping the issue invisible? Could the NSABP membership, and the scientific world in general, not have learned from the resulting public discourse? Was it so hard to make a statement that fraud in science is unacceptable? Is it not the responsibility of the principal investigator of a grant to disclose scientific fraud to the members of an organization? Is it not that person's responsibility to the journals which have published the papers containing fraudulent data to submit a reanalysis in a timely manner? Is it not the responsibility of the National Cancer Institute to protect the public health, to preserve the integrity of science, and to provide leadership in times of crisis? I ask these questions because it seems as if some of us have lost perspective about the responsibilities of people in science.

"What has happened in the NSABP is wrong. The membership has been betrayed. The women who have participated in the clinical trials have been betrayed, and the ethical standards of science have been betrayed. The integrity of the NSABP has been compromised. The academic culture at the University of Pittsburgh that allowed the lack of disclosure, the lack of timely publication of data, and the lack of communication to the NSABP membership, needs to be questioned.

"Some of my colleagues see my position as harsh. Bernie Fisher is, after all, one of the greatest and most recognized breast cancer researchers in this country. However, Bernie Fisher had responsibilities which he did not meet. He failed to respect the members of the NSABP and the scientific community enough to be accountable to us. The organization has lost its integrity in the eyes of the public, and among many physicians in our community with whom I must interact on a daily basis. When integrity is lost, nothing of consequence remains. All of us have a need to believe that there are certain leaders among our society who will do the right thing and take a position of strength in times of crisis. The events of the past 2 months have destroyed the confidence of the public in the clinical trials process.

"As one articulate woman who had chosen breast preservation for treatment said, 'If you can't trust the researchers, who can you trust?' Do we have a satisfactory answer for her? In the process of reopening any NSABP trial, do we have a plan that will enlist a sense of trust in our patients? It is very important to point out that no one from the NSABP has done what needs to be done for the women of this country. No one has admitted any wrongdoing. No one from the University of Pittsburgh has apologized to the women and doctors who have made the research of the NSABP possible. This is very difficult for me to understand.

"The NCI has apologized. The apology was made public in every newspaper, radio, and television program that covered the recent Dingell hearings. This underlined for me the importance of public acknowledgment of wrongdoing, the importance of an apology, and the establishment of a plan to keep similar events from reoccurring. This is the minimum that is expected by the public.

"On April 19th, six women surgeons wrote to Congress expressing our belief that the NSABP had been intellectually honest in reporting the side effects of tamoxifen to the NSABP membership. It appears that that understanding was incorrect. The *Cancer Letter* dated April 29th reports in a lead article of knowledge on the part of NSABP leadership that four patients in protocol B-14, which is the tamoxifen treatment trial, had died of uterine cancer prior to the

opening of the breast cancer prevention trial. The NSABP membership was not informed of these deaths. The written informed consent that we provided to our patients specifically stated that no deaths from uterine cancer were reported, and that uterine cancers that have occurred have been at an early stage and are thought to be curable. The article goes on to report that the NSABP's biostatistics director had written Dr. Fisher a letter expressing her serious legal, ethical, and moral concerns over not requiring annual gynecologic exams on women enrolled in the breast cancer prevention trial, given this information. The facts on this article have, at least in part, been verified in conversations with my colleagues.

"I would like to make it as clear as possible that I have no interest in defending what I consider to be indefensible behavior on the part of the NSABP leadership. There is no justification for this kind of behavior on the part of a nationally funded clinical trials group. To express disappointment would be a gross understatement. I tend to be a very forgiving person. None of us are perfect. We all make mistakes. When we falter, as we always do, basic human decency compels us to admit that we are wrong and to apologize. It is impossible to forgive a person, or an institution, that fails to admit any wrongdoing.

"Under these circumstances, there is a profound breach of trust. Under these circumstances, the integrity of the party or parties in question is compromised irreparably. These are the circumstances in which we in the NSABP are mired. Unless we take action, we will lose our organization. And, along with that, we will lose the only cooperative group in which surgeons actively participate. It should be our priority to have the NSABP trials reopen at the earliest possible date. However, the current climate at the University of Pittsburgh is more committed to silence than accountability.

"What the NSABP needs are leaders committed to communication, accountability, intellectual honesty, and integrity. Our primary responsibility is to our patients, past and future, who have been or will be diagnosed with breast cancer. As we sort out our priorities to resolve the issues of the fiasco that have been raised, let us remember that our primary duty is to them, and to the ethical conduct of the clinical trials process."

Questions and Answers

Dr. Salmon commented on Dr. Chabner's statement that many cooperative groups reimburse on a case basis. Dr. Salmon explained that this is true for a few groups, and in other groups is a minor way of supplementing grants or involving investigators who could not participate otherwise. Largely, he continued, multidisciplinary cooperative groups have research grants that examine investigators' overall scientific contributions. Dr. Salmon pointed out that the NSABP is not the only group in which surgeons participate in clinical trials research, as Dr. Osuch commented, since several large multispecialty groups have surgeons who actively participate in the design and conduct of clinical trials. He added that the Southwest Oncology Group and Eastern Cooperative Oncology Group also have surgeon committees and are involved in the design of trials. Dr. Salmon suggested that the ORI, the International Cancer Advisory Board, and their members be informed about an occurrence of scientific misconduct in a timely manner, so that NCI staff also do not learn about these occurrences in the newspapers. He cautioned that the NCI not become so involved in the auditing process that its focus shifts from science to regulatory matters.

Ms. Visco asked Dr. Chabner to explain in detail the process of recompetition and asked whether the group will continue to accrue patients. Since the group is on probation, Dr. Chabner explained, it must submit a plan for reorganizing several elements of operation to begin accrual. The group has a broad, yet detailed, plan for establishing a credible auditing process that could serve as an interim plan while it resumes accrual. The group has established a plan for submitting the reanalysis of various trials for publication, which is another critical

element. In the long run, Dr. Chabner stated, the group must identify new leadership either according to the current constitution—requiring the executive committee to nominate a candidate or candidates and the membership to confirm the candidate(s)—or a revised constitution, which would expand the executive committee to include more new members in the nomination process and election of a new chairperson. Drs. Herberman and Trump will continue to provide leadership in the interim. Per the NCI stipulations, the NSABP identified an executive officer to oversee day-to-day details of operations and report problems while the group is on probation. As a result, the volume of mail between the NCI and NSABP has increased significantly.

Ms. Visco asked if the NCI is examining possible adverse effects of the recompetition on the women who are in the trial. Dr. Chabner responded that they had given it thought; one of the stipulations of the recompetition is that competitors must assume responsibility for the current trial. He discussed various scenarios: an alternative leadership could propose itself to take over NSABP; or another cooperative group or newly organized group could commit itself to assume responsibility for these trials. If a group had a better scientific agenda and leadership, it could compete with NSABP. Dr. Chabner related that it is possible but unlikely that a newly organized group could successfully compete for the trial. More than 10,000 women, he noted, have been recruited to the prevention trial. Considering the problems associated with the current group, Dr. Chabner indicated that it would be reasonable for the site of the NSABP to move to the institution of the new leader.

Regarding Dr. Osuch's reference to the *Cancer Letter* article, Ms. Visco asked if she understood correctly that the NSABP leadership was unaware of the deaths that had occurred prior to the beginning of the prevention trial. Dr. Osuch explained that the membership was unaware and the leadership was aware. Dr. Chabner contended that this statement was incorrect, and the first death was reported after the trial began. Dr. Osuch maintained that the first report came out in 1991 (it took some time to learn the person's cause of death), and there were other reports in early 1992.

Dr. Ford reported that deaths did occur before the trial began. Many of the deaths were not reported for 6 to 8 months after they had occurred. All known deaths were reported to NSABP membership in October 1993. Dr. Ford explained that some of the deaths that were reported before the prevention trial opened (listed in the *Cancer Letter*) were not caused by endometrial cancer, but occurred in women with an early diagnosis of endometrial cancer. She added that the prevention trial has required prestudy and annual gynecologic examinations and immediate follow-up of any abnormal gynecological symptoms from its inception. The letter referred to in the *Cancer Letter* concerned changing requirements for ongoing treatment with tamoxifen. Dr. Osuch commented that she entered patients into trials and recorded in her files that gynecologic examinations were recommended, not required, for the prevention trial. Dr. Ford indicated that some of the issues are in the province of ORI and the Office of Protection From Research Risk (OPRR).

Dr. Becker emphasized the importance of the Board being notified of NCI plans. He suggested that patients in the trial experienced more harm than the actual clinical trials process because cooperative members, the scientific community, and the Board learned about events after the fact. Dr. Becker referred to plans to develop a procedure ensuring that participants "know how" to conduct clinical trials (i.e., the credentialing process). He expressed misgivings about "training" these professionals, and requested that the Board receive detailed information about such plans for a training program in advance of their implementation. In reference to documents on ethics that were circulated, Dr. Becker commented that the incidents that occurred in NSABP were extreme examples that were not part of a hospital-wide effort in those clinical trials. Dr. Becker stated that the NCAB should have the written and revised terms of award for cooperative trial participants to preclude overreaction. He

cautioned against immediately notifying the public about NSABP events and suggested that strict criteria for communication are established. Dr. Calabresi stated that the chairs of the clinical trials, NCI staff, and the NCAB will have an opportunity to review the revised terms of award.

Dr. Chabner explained that the credentialing process involves a probationary period and submission of a curriculum vitae denoting clinical research and fellowship experience. The resumé is not an absolute requirement if the participant performs according to the standards of the group during the probationary period. Dr. Chabner stated that this process is necessary because programs do not always provide formal training in clinical research. Also, the NCAB urges the NCI to involve community physicians; the NSABP was one of the charter groups that attempted such involvement. Dr. Chabner related that there is a need to involve community physicians, while maintaining high standards; thus, it is necessary to have physicians prove their ability to conduct trials.

Dr. Becker stressed that the trial must have certain standards, because it is not adequate to agree that a physician can process "a few participating patients." He inquired about the trial standards; Dr. Chabner suggested that this topic be discussed in the afternoon.

Dr. Becker then asked about criteria for immediate notification, which, Dr. Chabner explained, applies to suspected scientific misconduct or fraud, or gross failure of an institution being site-visited. Dr. Broder explained that it is not necessary for qualified members of a group to notify NCI of a suspicion of misconduct or fraud, until that suspicion is fostered. Dr. Calabresi related that, as a result of Dr. Salmon's suggestion at a previous meeting, these matters will be discussed during the closed session of the NCAB meetings. Dr. Becker reminded Dr. Chabner to distribute the written revised terms of award to Board members as soon as possible after they are finalized.

Dr. Bettinghaus suggested that the NCI strongly consider asking the NSABP and other cooperative groups to have their policy advisory committees report directly to NCI, rather than to the group membership. Dr. Chabner stated that an NCI representative attends every meeting of the Data Safety and Monitoring Board. Dr. Bettinghaus contended that it might be more efficient if such committees operated outside of the group itself. The NCI, Dr. Chabner commented, wants to preserve the independence, integrity, and self-confidence of the groups and instill a sense of responsibility for conduct within the groups. He added that there must (non-negotiably according to NIH) be a Data Safety and Monitoring Board for Phase III studies to address randomization issues, and a consensus that that board can act independently for the protection of subjects in the study and the public at large. Dr. Bettinghaus speculated that this requirement would help solve problems associated with data availability.

Dr. Broder related that the NCI wants to know about Data Safety and Monitoring Board decisions, at the time of those decisions. An investigator, he said, should inform the Board if he or she takes an unscheduled look at the data, so that everyone is informed. Dr. Broder emphasized the importance of the independence of the Data Safety and Monitoring Boards. He noted that it is not necessary for every study to have a Data Safety and Monitoring Board, but such boards are required for most Phase III studies with randomization among treatment or prevention arms.

Dr. Lawrence expressed a feeling of reassurance that there will not be excessive interference between the investigator groups and NCI. He said he favors including the cooperative group leaders in deciding the revised terms of award and is supportive of resuming the NSABP trial as soon as possible. He commented that the NCAB should have been informed about this incident and the resulting process of rectification earlier. Dr. Lawrence

related that the loss of public confidence that resulted from this episode is a problem that must be addressed.

Dr. Chabner enumerated the various forms of communication that have taken place during the past several months, including meetings with the Board of Scientific Counselors and prominent members of the clinical trials community, and a meeting of all group chairpersons and cancer center directors at the American Society of Clinical Oncology. Dr. Lawrence acknowledged this communication, but conveyed his feeling that Government leadership is making decisions in the field instead of investigators. Dr. Calabresi emphasized the importance of coalescing scientists and group leaders; he stated that the Clinical Investigations Task Force will meet regularly with NCI staff, NCAB members, and chairs of the major groups to set new guidelines for clinical trials and restore public confidence.

Reflecting on Dr. Osuch's comments, Dr. Broder explained that the cooperative group has primary responsibility for a trial and the ethics related to it. He suggested attributing responsibility for these issues instead of classifying them as "Government" or "non-Government." It is important, Dr. Broder continued, for the NSABP to admit that it has problems. He added that the NCI is "in a rehabilitative mode" and wants to allow the groups the first opportunity to correct a problem, but the Institute's failure to act when this does not happen would cause damage to the groups and the institutions. The groups cannot only assume ownership for the "good things," such as published papers, but also the difficult issues.

Dr. Osuch commented that only two people in the NSABP knew about the fraud; the executive committee was informed briefly, but were told they could not discuss the matter. Someone must take responsibility, she added, for the research being conducted with the taxpayers' money, and all groups must be accountable to one another.

Dr. Calabresi noted that he has been insistent that the NSABP clinical trials, particularly the tamoxifen prevention trial, resume and is pleased that the trials will reopen within 7 to 10 days. Dr. Broder specified that accrual will resume *at certain sites* that have excellent records, or are part of cancer centers or CCOPs.

Dr. Sigal remarked that it is a high priority to reestablish confidence in clinical trials. She cautioned against "overcorrection" (creating a bureaucracy of auditors and managers) and not addressing the source of the problem. Dr. Sigal expressed concern that funding for accrual to the trials will be diverted to investigation of this problem.

Dr. Salmon responded to Ms. Visco's question about how to reassure the women in the trial. He cited several examples in which contracts were recompeted and awarded in the research community, such as the Frederick Cancer Research and Development Center, his cooperative group, and the Southwest Oncology Group. Dr. Salmon expressed his belief that it is possible to recompete the NSABP, identify new leadership, and allow other cooperative groups to assume some of its trials. The primary difference between the NSABP and other trial groups, he noted, was NSABP's auditing procedures. The trials conducted by the NSABP have undergone rigorous peer review; the trial designs and validity of the scientific questions are important. Recompetition of trials has not placed patients at risk in the past. Dr. Salmon concluded that although it is important to reassure patients in the trial, research can be an orderly process; renewal and replacement occurs in clinical research, as in other fields.

Ms. Visco reiterated that the impact of recompetition on women should be examined and made part of the process of determining whether to recompete and the recompetition itself.

Concerning meta-analyses conducted by NCI, Dr. Broder pointed out that the NCI has a strong database that suggests that breast-sparing surgery is valid and that women should not be concerned that their lives are at risk because they have chosen a breast-sparing procedure. He noted that Dr. Sondik will discuss this issue, and the NCI will publish and disseminate the information widely, as well as hold workshops communicating these findings. Dr. Broder reported that several parties, including the *New England Journal of Medicine*, have asked NCI to redo the audits and have made it a condition for republishing papers. Thus, NCI will try to reaudit a substantial portion of the B-06 records and other trials, as appropriate. NCI is also investigating other mechanisms for disseminating results; for example, anyone can obtain the reanalysis of B-06, B-13, and B-14 on Internet.

Dr. Calabresi suggested that NCI should emphasize to the public that clinical trials can be flawed; however, because they have a built-in safeguard, reliable data can result from flawed data or discrepancies in data. He then thanked Drs. Osuch and Chabner for their presentations and the Board for an excellent discussion. At that time, the open session of the first day of the meeting was adjourned.

IX. CLOSED SESSION

A portion of the first day of the meeting was closed to the public because it was devoted to a meeting of the Special Actions Subcommittee. A total of 1,834 applications were received, requesting support in the amount of $308,326,601. Of those, 1,544 were recommended as being eligible for funding at a total cost of $243,544,423.

X. OMB CIRCULAR A21—MR. GEOFFREY E. GRANT

Dr. Kalt recalled that at the last Board meeting, some of the members had expressed an interest in the Office of Management and Budget (OMB) Circular A21, which is the major document concerning indirect cost rates, and that a question arose regarding allowable indirect cost rates, especially with respect to personnel such as secretaries and nurses. He proceeded to introduce Mr. Geoffrey Grant, the chief grants policy officer of the National Institutes of Health.

Mr. Grant began by explaining that this issue arose because OMB Circular A21, which addresses the allowability of costs and their allocation between direct and indirect costs, was revised last year. It will go into effect for academic institutions and nonprofit organizations at the beginning of their fiscal year—in most cases, next July—but this will depend in part on when their indirect cost rate negotiations take place.

Mr. Grant explained that within the circular is a passage discussing departmental administration. This passage states that the cost of secretaries and clerical help shall normally be treated as indirect costs, but that direct charging of these costs may be appropriate when a major project explicitly budgets for administrative or clerical services and the individuals involved can be specifically identified with the project or activity. Mr. Grant related that this passage has created some confusion in the scientific community about the exact effects of the change. As a result, the issue is still being discussed within the academic community and Federal agencies to try to clarify the definition in a reasonable and equitable manner. Mr. Grant then distributed a single-page handout explaining how to discern whether

individuals, such as secretaries or clerical staff, can be specifically identified with a project or activity.

Mr. Grant provided some background information on this issue, explaining that auditors were concerned that the NIH was being charged twice for staff who appeared both in the departmental administration as indirect costs, and in the direct cost budgets of research grants. In an effort to define a line, the NIH determined that if clerical support is typically related to departmental administration and exerts less than 15 percent of its effort toward a given project, it should be identified as an indirect cost. Conversely, if an individual can clearly be associated with the activity of a project (i.e., ascribe more than 15 to 25 percent of his or her effort to project administration), such costs can be legitimately identified as direct costs.

Mr. Grant recognized that this definition leaves some discretion to the staff, but indicated that the continuum of effort offers guidance. He illustrated with examples of specific activities. Nominal effort of 0 to 15 percent should be treated as indirect costs, although it may be associated with typing of manuscripts or the preparation of applications. As activity becomes more substantial and obviously associated with the project, such as data collection, patient scheduling, or clear project administration, costs may be treated as direct. If the Federal agencies and OMB staff agree to this definition, Mr. Grant said, it will be published in the *Federal Register* and the *NIH Guide for Grants and Contracts* and provided to staff to establish uniform guidelines for direct/indirect cost determinations.

Questions and Answers

Dr. May asked whether nurses are considered in this category. Mr. Grant replied that they are not, because they are typically associated with project activities.

Dr. Salmon expressed concern that a single statement on this issue could severely impair some research centers because institutions vary in their policies for indirect costs; some provide no support for departmental administration. Mr. Grant explained that the NIH is sensitive to this problem, but that the more difficult point relates to the issue of nominal effort associated with the regular research project. Dr. Salmon stated that he was including the research project as a center.

Dr. Wells remarked that this issue created an enormous amount of confusion in the academic community in May 1994 and that Mr. Grant's statement needs to be articulated and publicized. He then asked for an estimated timeframe for a decision on the final guidelines. Mr. Grant said he expects an agreement on definition in June 1994. He mentioned that representatives of colleges and universities, along with OMB and the Office of Science, Technology, and Policy, had discussed the issue the previous week, and that Ms. Alice Rivlin, Deputy Director of OMB, will make the final decision. Once finalized, the definition can be published and disseminated through the *NIH Guide* and the *Federal Register*. Dr. Bettinghaus agreed with Dr. Wells on the need for speedy clarification and resolution of this issue.

Dr. Chan inquired whether it is necessary to subtract 15 percent from the contract if there are no line items permitted as clerical or secretarial work. Mr. Grant responded in the negative, adding that approval in the contract constitutes approval to cover those expenses.

UPDATE: OMB issued the expected guidelines without the reference to the percentages. There will be an announcement in a September volume of the *NIH Guide for Grants and Contracts*.

XI. BREAST CANCER PREVENTION TRIAL/TAMOXIFEN UPDATE— DR. LESLIE G. FORD

Dr. Peter Greenwald stated that the Breast Cancer Prevention Trial with tamoxifen is the "flagship study in cancer prevention," not only because of its own important objective, but because it strengthens the field of clinical trials in prevention. He explained that the trial is part of the Community Clinical Oncology Program, conducted through the NSABP and directed by Dr. Leslie Ford of NCI and her colleagues. Dr. Greenwald then introduced Dr. Ford to present an update on progress in the trial, which was discussed by the DCPC Board of Scientific Counselors on May 5, 1994.

Dr. Ford began by stating that the BCPT has been controversial since its inception. She outlined her presentation describing the history of the trial, current status of the study, new information about tamoxifen, revised risk-benefit calculations, and recommendations from the DCPC BSC and Data Safety and Monitoring Committee about continued conduct of the study.

Dr. Ford discussed the major causes of mortality in women, starting at age 35, based on 1980 mortality data from Dr. Elizabeth Barrett-Connor. The major cause of death in women as they age, she said, is still cardiovascular disease, while mortality rates for endometrial cancer are low and remain low throughout women's lifetimes.

The BCPT was originally designed to recruit 16,000 women at increased risk for breast cancer, with risk being determined by age, family history, and personal history. Women are randomized in this double-blind, placebo-controlled clinical trial to receive either tamoxifen or a placebo for 5 years. The major study endpoints are invasive breast cancer incidence and mortality, cardiovascular mortality, and bone fractures. Dr. Ford pointed out that a unique feature of the study is that quality-of-life data are routinely collected both at study entry and throughout the study. It is important, she commented, to examine the balance between changes in quality of life and symptoms and, perhaps, disease prevention. Companion studies looking at endometrial changes, bone and mineral metabolism, and genetics are also part of the trial's design. Dr. Ford added that the National Heart, Lung, and Blood Institute and the National Institute of Arthritis and Musculoskeletal and Skin Diseases have contributed funds to the BCPT for the study of cardiovascular disease and bone mineral density.

Dr. Ford explained that tamoxifen was considered a likely candidate to prevent breast cancer because the drug had shown marked decreases in contralateral breast cancers in adjuvant tamoxifen clinical trials over the years. Tamoxifen was considered to be well tolerated, with few side effects, and showed evidence of potential benefits from lipid lowering and bone mass stabilization that appeared to be similar to hormone replacement therapy. Potential risks from endometrial cancer and thrombotic events were known at the outset of the study and were factored into the study design and risk/benefit calculations. For these reasons, Dr. Ford related, the decision was made to conduct a study of women at increased risk of breast cancer in the clinical research setting.

Dr. Ford presented slides showing data on contralateral breast cancers and uterine cancers in clinical trials of adjuvant tamoxifen. Although the NSABP B-14 study was an important source of information about the decrease in contralateral breast cancers, at least six or seven other studies also showed between a 30 and 50 percent (30 percent, overall) decrease in contralateral breast cancers at the time the BCPT began. Dr. Ford commented that the recognized increase in endometrial cancers associated with tamoxifen was factored into the trial's original design. She noted that the risk for uterine cancer appeared to double with

tamoxifen even without the data from the Stockholm study where both the dose (40 milligrams) and incidence of uterine cancer were higher.

Tamoxifen, Dr. Ford stated, is probably one of the best documented and most widely studied drugs available. The Peto meta-analysis includes 41,000 woman-years of data on tamoxifen versus controls or placebos; the NSABP B-14 study, 8,000 woman-years of information; and the ICI, which is now the Zeneca Registry, about 4.5 million woman-years of information. The prevention study, Dr. Ford added, is being conducted under an Investigational New Drug (IND) application with the Food and Drug Administration.

Regarding recruitment to the study, increased risk was defined as a composite of risk factors that were determined from a model developed by Dr. Mitch Gail and others at NCI based on Breast Cancer Detection Demonstration Project (BCDDP) data. Risk factors taken into account for eligibility include: age at menarche; number of first-degree relatives with breast cancer; pregnancy history; age at first live birth; number of biopsies for benign breast disease; and demonstration of atypical ductal hyperplasia. A woman is eligible for the trial if her next 5 years of risk are equivalent to that of the average 60-year-old woman. The incidence of breast cancer among 60-year-old women is 350 to 400 per 100,000.

Women are asked to complete a risk assessment to be used in determining eligibility by risk. Prominent ineligibility criteria include use of estrogen or progesterone (such as in hormone replacement therapy or oral birth control pills); eligibility depends upon discontinued use for at least 3 months. Other ineligibility criteria include any prior malignancy, history of deep vein thrombosis, current coumadin use, pregnancy or desire for pregnancy, history of macular degeneration, and life expectancy of less than 10 years.

Dr. Ford explained that there was significant discussion concerning the fact that younger women are not at high enough risk. She then discussed examples of risk profiles, explaining that a 35-year-old woman would be eligible for the trial if she had had at least two biopsies, one or more first-degree relatives with breast cancer, and a history of benign breast disease. A woman would not be eligible if she had only two first-degree relatives with breast cancer and was 35 years of age. Women with a diagnosis of lobular carcinoma *in situ* (LCIS) are eligible at any age. Dr. Ford related that it has been estimated that 3 of 1,000 35-year-old women will meet these eligibility criteria. Age, she continued, is a strong risk factor; as a woman's age increases, the number of other risk factors needed for eligibility decreases (e.g., to be eligible for the trial, a 45-year-old woman could have one or more first-degree relatives with breast cancer *or* a history of benign breast disease with at least two biopsies). It has been estimated that approximately 7 percent of women aged 45 will be eligible.

Dr. Ford presented slides depicting lifetime risk for developing breast cancer according to age. The statistics and sample size calculations, she explained, were based on risk within the next 5 years, which is a minimum of 1.7 percent for all ages. Based on a risk profile of an average 35-year-old woman (at which age a minimum lifetime risk of 40 percent is required for eligibility), the lifetime risk for an average woman at age 40 (whose minimum eligible risk requirement drops to 23 to 24 percent) would be approximately 10 percent, based on her additional 5 years over the age of 35 without developing breast cancer and no other risk factors. In contrast, a woman at age 40 with two biopsies with atypical hyperplasia and one relative with breast cancer would have a lifetime risk of more than 40 percent. A woman aged 50 (minimum risk for eligibility of about 12 percent) with two biopsies, one of which showed atypical hyperplasia, would have a lifetime risk of about 20 percent.

NCI began processing risk assessments for the BCPT in April 1992, and accrual and randomization began in June 1992. Dr. Ford reported that the NSABP had processed 66,000 risk assessments by the end of March 1994; 41,000 of these women who volunteered to

complete risk assessments were determined to be eligible based on their breast cancer risk. Approximately 11,300 of 11,800 women who underwent full eligibility assessment (which includes risk assessment, physical examinations, and testing against ineligibility criteria) were eligible for the study. At the end of March 1994, 10,883 women had been randomized into the study to receive tamoxifen or a placebo for 5 years.

Dr. Ford related that the issue of minority recruitment, which was initially discussed after Dr. Bernard Fisher's update on the trial at the September 1992 NCAB meeting, has continued to be a problem. It will be difficult, she remarked, to achieve 10 percent minority recruitment, since one-quarter of the total accrual occurred within the first 3 months of the trial; in September 1992, approximately 4.5 to 5 percent of risk assessments were from women of color. Following the September 1992 Board meeting, a special minority recruitment committee was formed, and presentations at the NSABP group meetings and prevention workshops were instituted in January 1993. A program was also established to pay for the tests and procedures necessary for under- or uninsured women. Through the Office of Research on Women's Health, it was possible to provide extra funding for special recruitment techniques in underserved and minority populations. As a result of these activities, the number of risk assessments from women of color increased to 14 percent; however, though some of these efforts to attract minority women have been effective, accrual has peaked and fallen. If randomizations are examined according to race and time, only 2 percent of the population was composed of women of color early in the trial, while by mid-1993, 4 percent were minority women. Dr. Ford stated that efforts to increase minority recruitment are continuing—for example, through a Public Service Announcement made by singer Nancy Wilson that has been distributed over the last few months.

Dr. Ford related that almost 5 percent (500) of the participants are women who have been diagnosed with lobular carcinoma *in situ* . The BCPT, she stated, is the only known randomized trial looking at the treatment of lobular carcinoma *in situ*. Women with this diagnosis are at high risk for developing breast cancer, and almost 50 percent of those with LCIS who have been assessed have agreed to be randomized, while 25 percent of eligible women without this diagnosis have agreed to be randomized.

Dr. Ford reported that 39 percent of the 10,800 NSABP/BCPT participants are under age 50, 30 percent are between ages 50 and 60, and 30 percent are over age 60. The women who have chosen to enter the study have approximately twice the minimum risk that was initially defined for study participation, regardless of whether average risk, relative risk, or absolute risk is being measured. Dr. Ford stated that women between the ages of 35 and 39 have an average relative risk of about 10 (relative to a woman with no risk factors). Only 10 women in the study, all over 60 years of age, have a relative risk of one. The majority of women have a relative risk between 3 and 10. Dr. Ford noted that as the relative risk increases, the percent of women agreeing to be randomized also increases. About 30 to 40 percent of women with a relative risk of 10 or more have agreed to be randomized.

One of the most important variables contributing to risk, Dr. Ford continued, is the number of first-degree relatives with breast cancer. Eighty percent of women that have been randomized into the study have at least one such relative with breast cancer. About 60 percent of women over age 60 have at least one first-degree relative, while between 80 and 85 percent of younger women in the study have at least one first-degree relative because of this variable's importance in determining risk in this age group. Dr. Ford explained that at every age there is a substantial increase in the original calculation of a 1.7 percent probability of developing breast cancer over 5 years of follow-up. There is a 2.6 percent 5-year probability for women ages 35 to 39, while the overall probability of developing breast cancer among participants is 3.5 percent.

Dr. Ford next discussed risk of developing endometrial cancer and death from endometrial cancer. She presented data from a manuscript recently published in the *Journal of the National Cancer Institute* regarding endometrial cancer among 25 patients in the NSABP B-14 treatment trial. She emphasized that the mortality figures do not represent deaths from the prevention trial and are from 25 cases composed of two women in the placebo group, 15 in the group randomized to receive tamoxifen, and eight in a group registered to receive tamoxifen. Dr. Ford pointed out that the two women who developed endometrial cancer in the placebo group had been exposed to tamoxifen at the time of recurrence or new disease. One woman who developed endometrial cancer and was randomized to tamoxifen never took the drug; thus, 24 of the 25 women were exposed to tamoxifen at some time during the course of their therapy. The average age of the women at study entry was over 60 years.

Dr. Ford stated that about 20 to 22 percent of the women had taken tamoxifen for less than 1 year prior to their diagnosis of endometrial cancer. The majority of the women had had at least 2 years of tamoxifen therapy. About one-third of the women had had previous hormone therapy, either estrogen or progestin prior to their diagnosis of breast cancer and their subsequent development of endometrial cancer. Dr. Ford noted that the role of prior hormone therapy in the development of endometrial cancer is under investigation. Two-thirds of the women developed endometrial cancer while they were actively on tamoxifen, and one-third had either never taken tamoxifen or had discontinued its use. While five deaths due to endometrial cancer were reported among these women, one of them had never taken tamoxifen and, thus, there were four deaths related to tamoxifen therapy. This information, Dr. Ford indicated, was presented to the Data Safety and Monitoring Committee and discussed with the FDA.

Dr. Ford then reviewed BCPT risk-benefit considerations. The benefits, she noted, have either remained the same or become stronger since initial development of the protocol. More data have supported the potential for tamoxifen to decrease invasive breast cancer, which is a study endpoint. The NCI and NSABP are conducting annual mammograms and clinical breast examinations and planning a genetic substudy in which both white cells from all participants and tissue from individuals who have biopsies or develop invasive breast cancer will be stored to conduct more detailed studies in the hope of finding biomarkers or precursor lesions. Cardiovascular events are also a study endpoint, and lipids and EKGs have been monitored in women over age 55. There has been an increasing number of reports on the ability of tamoxifen to stabilize bone metabolism. Bone fractures are also a study endpoint, and a substudy of detailed bone density measurements is being conducted in a subset of the women. Psychosocial impact is also being monitored with detailed quality-of-life assessments.

Toxicities associated with the BCPT include the risk of endometrial cancer as explained in the protocol's informed consent. Annual gynecological examinations are both a prestudy and continuing requirement, and a gynecological substudy looking at detailed endometrial changes has been planned. Dr. Ford reported that she and her colleagues are conducting a case-control study of Surveillance, Epidemiology, and End Results (SEER) data to examine women with breast cancer who have subsequently developed endometrial cancer and obtain a detailed history of both tamoxifen and other hormone exposure. Recently, she reported, a requirement for annual biopsy or endometrial sampling was added to the study to more carefully follow endometrial changes in the entire population. The substudy will look at newer techniques for determining endometrial changes (e.g., use of ultrasound to determine which women need biopsies). Because of the report of mortality from endometrial cancer, the study's informed consent was changed in January 1994 and letters were sent to all participants in the study detailing new information on endometrial cancers and updates on packaging labels. No new information is available on thromboembolic events. This risk was included in the informed consent, and exclusion criteria about thromboembolic events are included in the

protocol. A cross-sectional study is in progress in NSABP B-14 to investigate ocular changes among women who were on placebo, those who took tamoxifen for 5 years and then discontinued its use, and those who took tamoxifen for 5 years and continued. An update on ocular changes was included in the informed consent, and exclusion criteria about macular degeneration were added to the protocol. Liver function tests have also been monitored during the course of the study.

Dr. Ford then presented a slide on BCPT risk-benefit analysis. She explained that it is important to conduct a carefully controlled study because there is considerable disagreement about the potential risks and benefits of tamoxifen use to prevent breast cancer. Dr. Ford outlined data presented in the chart on the slide, including beneficial effects of breast cancer reduction and coronary heart disease; total decrease in these events; detrimental effects of endometrial cancer, liver cancers (if they occur), and pulmonary emboli; projection of the total number of detrimental events; and net benefit. The analysis is based on assumptions of no increase or a twofold increase in liver cancer, and either no increase, twofold increase, or fivefold increase in pulmonary embolic deaths. Dr. Ford pointed out that much more information exists at the present time (e.g., on endometrial cancer and thromboembolic events) than when treatment trials originally began in the early 1980's, and noted that these increases have been accounted for. Dr. Ford explained that the other assumptions in the table were based on the actual 10,800 women first accrued to the study, not a theoretical population. The breast cancer reduction in this model is based on a 30 percent decrease, while endometrial cancers are based on a threefold increase over SEER data. Dr. Ford indicated that current information from all worldwide trials is showing a two- to threefold increase. The data regarding liver cancer are also based on SEER data and the pulmonary embolism deaths on U.S. mortality figures. This analysis is based on 3 years of accrual; original risk-benefit calculations were based on 2 years of accrual. Dr. Ford noted that many hormone replacement studies consider a 40 percent decrease in coronary heart disease events; this model, however, accounts for a conservative 20 percent decrease. In this model, for every assumption, a net benefit is calculated for tamoxifen over placebo. Dr. Ford emphasized, however, that risks such as endometrial cancer that are associated with tamoxifen must be considered seriously and relayed to women.

Dr. Ford described some highlights in the development and implementation of this study. Treatment trials with tamoxifen as an adjuvant began in the early 1980's based on data pointing to a decrease in contralateral breast cancer. Concepts were first solicited for the Breast Cancer Prevention Trial in June 1990 and presented to the DCPC BSC, the Division of Cancer Treatment BSC, and the NCAB. Applications were received in October 1990 and peer reviewed in January 1991. NSABP was selected to conduct the study, and a draft protocol was sent to the FDA. The first investigator's meeting was held in January 1992, and the first protocols were sent to participating sites for Institutional Review Board (IRB) review. Dr. Ford clarified that participating sites were peer reviewed by an NSABP/BCPT steering committee. Approximately 120 nucleus centers with a total of 280 subcenters are participating in the study. A press briefing was held in April 1992, and the study began processing risk assessments and randomizing subjects in June 1992.

A briefing on the BCPT was held for the Congressional Caucus on Women's Issues in August 1992 and a progress report was presented at the September 1992 NCAB meeting. As a result of hearings on the trial in October 1992 by a Congressional oversight committee (chaired by Ted Weiss prior to his death and then Donald Payne), there were revisions to Office of Protection From Research Risk policies. The revisions concerned informed consent documents in multi-institutional trials and restricted the ability of local IRBs to change those documents. Additional endometrial cancers were reported from July to November 1993. The first report to NCI of death due to endometrial cancer in the NSABP B-14 trial occurred in November 1993. NCI began notifying investigators about these deaths and informed consent

revisions in December 1993. Zeneca released a letter to physicians (i.e., "Dear Doctor" letter) regarding changes in tamoxifen prescription in April 1994, and the NSABP sent a letter to all BCPT participants (i.e., "Dear Participant" letter) and patients in treatment trials about new tamoxifen information. Representatives of the NSABP and Dr. Ford gave a presentation to the DCPC BSC in May 1994. Also in May 1994, Drs. Ford and Chabner attended the Senate Cancer Coalition hearings, chaired by Senators Dianne Feinstein (D-CA) and Connie Mack (R-FL), to discuss the BCPT and the NSABP. Dr. Ford added that meetings of the steering committee and Data Safety and Monitoring Committee, both in existence since the beginning of the trial, also occurred during this time.

Dr. Ford concluded her presentation by citing the DCPC BSC's recommendations, based on unanimous recommendations of the Endpoint Review Safety Monitoring and Advisory Committee (ERSMAC) chaired by Dr. Ted Colton of Boston University. ERSMAC is an independent committee that reviews both blinded and unblinded data from the prevention trial, as well as new information about tamoxifen, in recommending continuation of the trials. The Committee last met on May 4, 1994, and recommended that participants in the BCPT be informed about age-specific risk for developing endometrial cancer and cardiovascular disease in addition to the age-specific risk for developing breast cancer. The Committee also recommended additional monitoring by endometrial aspiration/sampling. Assuming that these recommendations are followed, the Committee recommended no changes in the present eligibility criteria and that the trial be reopened as soon as possible.

Questions and Answers

Dr. Correa asked Dr. Ford to explain the histology of the 25 endometrial cancer cases, based on experience with estrogen-induced endometrial carcinogenesis. Dr. Ford reported that a study on endometrial cancers revealed that women at the Yale Cancer Center taking 40 milligrams of tamoxifen had more aggressive tumors than average. These women, she continued, were not in any kind of placebo-controlled environment. Dr. Ford added that subsequent reports from Memorial Sloan-Kettering did not confirm this finding and found tumors to be similar to those in other women with endometrial cancers. Among these 25 cases, there were two papillary serous (low-grade) carcinomas usually not associated with estrogen-induced endometrial cancers. Dr. Ford explained that this is why the Data Safety and Monitoring Committee recommended that all participants have access to endometrial sampling. She agreed with Dr. Correa's statement that the type of tumor affects what kind of screening or early detection program is needed in the trial.

Dr. Greenwald estimated that there are more than 35 studies on estrogen replacement therapy and that the relative risk for endometrial cancer varies in the literature, which supports the conduct of a controlled clinical trial. Unfortunately, he added, a controlled clinical trial for estrogen replacement was not initially undertaken and is only now being conducted. He expressed his belief that endometrial cancer risk related to tamoxifen is approximately the same or slightly less than that associated with estrogen replacement therapy.

Dr. Calabresi asked whether tamoxifen caused existent tumors to proliferate or if it actually generated the tumors. Dr. Ford explained that it is difficult to discern tamoxifen's role without a more detailed assessment. Dr. Greenwald added that these data come from the B-14 trial. Since 8 of the 25 women diagnosed with endometrial cancer have had prior estrogen replacement therapy, Dr. Greenwald suggested that an additive or a synergistic effect of tamoxifen is possible. Dr. Ford mentioned that there were no cases in the placebo group; based on SEER rates, one would expect seven cases. Thus, she indicated, there is probably a differential ascertainment. She added that tamoxifen can cause irregular bleeding, which spurs investigations. Dr. Ford related that these 25 cases were detected after unblinding of study medication which occurred when the first 5 years of the trial were completed. Reports of an

increase in endometrial cancer suggest that there was greater surveillance among women who received tamoxifen early in the trial.

Dr. Bragg asked if the histology of cancers in tamoxifen patients differs from that of random breast cancers. Dr. Ford answered that they do not differ. Dr. Nayfield agreed that the histologies of breast cancers do not seem to differ. The proportion of estrogen receptor (ER)-negative cancers, Dr. Nayfield continued, is greater because the total number of cancers that develop is less. Follow-up of women after treatment for contralateral breast cancer has shown that there is no difference in survival between patients with ER-positive or -negative cancers. Also, there is no difference in lobular versus ductal histologies.

In answer to Dr. Bragg's second question, Dr. Ford answered that annual mammograms were conducted in patients under age 50, as well as patients older than 50, as an early detection technique in this clinical trial of women at increased risk of developing breast cancer.

Dr. Salmon stated that the most important factor for randomization is the 5-year risk of breast cancer. He asked if the proportion of women under age 50 is greater than had been projected in the design stage. Dr. Ford explained that the original statistics and design were based on three theoretical populations: 1) a younger population; 2) a middle-aged population; and 3) an older population. The actual population, she related, "mimics the middle population almost exactly." Dr. Salmon suggested increasing accrual of participants over age 50, if the average age is younger than projected. He commented that it is known that tamoxifen increases circulating estrogen levels in younger women, and asked if the decrease in breast cancers was observed in women under age 50. Dr. Ford answered that there was a greater decrease in breast cancer among women under age 50 than in women over 50 in the B-14 trial. A small study from Dr. Craig Jordan, she continued, found an increase in circulating estrogens in a very small number of women. Trial staff have discussed duplication of this investigation in premenopausal women entering the study. She reiterated that statistics and sample size calculations were based on a 1.7 percent probability of developing breast cancer within the next 5 years; the actual risk is averaging between 3 and 4 percent over the next 5 years. Staff are examining issues of premenopausal women in more detail in the substudy. It will be possible, she concluded, to study the impact of the BRCA-1 gene in premenopausal women once the gene is identified and a test for it is developed, since it is likely that the BRCA-1 gene is more active in premenopausal breast cancer.

Dr. Bettinghaus asked if it is mandatory for everyone currently in the study to re-sign the informed consent. Dr. Ford explained that all participants received a letter explaining the changes and must re-sign the informed consent. She added that there will be another informed consent change when the endometrial sampling requirements are codified. Dr. Ford noted that the FDA Oncologic Drug Advisory Committee Meeting will review the status of the trial on June 7, 1994.

In answer to Dr. Bettinghaus' second question, Dr. Ford related that approximately one-third of the 10,000 participants have signed the new consent form, and trial staff are continuing to monitor this process. OPRR originally instructed BCPT staff that participants could re-sign at their next follow-up visit; instructions were subsequently changed, and the sites are working to have all the women re-sign—some by mail consent.

Dr. Calabresi asked for an estimate of how many women dropped out of the trial after receiving the participant letter. Dr. Ford answered that these figures are not yet available and mentioned that, based on anecdotes, reactions have ranged from anger to agitation; most women have remained committed and some have decided to drop out.

Dr. Bettinghaus emphasized that the LCIS patients should be carefully monitored as to what further can be done for these patients, since this study will provide a significant amount of data on this group of subjects. When complete, the trial will probably include nearly 1,000 LCIS participants.

Ms. Mayer inquired about women who entered the trial, were randomized, and dropped out. Dr. Ford indicated that this information is presented at every Data Monitoring Committee meeting. Original sample estimates, she continued, were based on a 10 percent per year non-compliance (i.e., dropped out, stopped taking medication, not taking full medication). As of January, Dr. Ford stated, the trial was meeting the 10 percent rate. She noted that when women stop taking their study medication, they are still followed as if they were study participants. Dr. Ford remarked that some centers in Canada may decide to withdraw their participation in the study. Ms. Mayer questioned whether the side effects of tamoxifen are more prevalent than expected and whether this has affected dropout rates. Drs. Ford and Broder commented that they do not know whether the women are dropping out as a result of side effects or the effect of the placebo. Dr. Ford remarked that the Data Safety and Monitoring Committee does have this knowledge, however, and has seen no reason to make changes.

Ms. Brown asked how the BCPT is planning to recruit more minority women into the trial and if there will be a long-term effort to retain these participants in the trial. Dr. Ford explained that minority recruitment is an ongoing effort. There have been peaks in minority recruitment after group meetings at which equal representation of groups was emphasized. Efforts include provision of funds for under- or uninsured women and additional funds for data management in areas that require extra effort to access minority populations. Dr. Ford reported that an article that was published in *Jet* magazine resulted in very little response. The BCPT also utilizes public service announcements and the NSABP budget provides extra funding for research and outreach teams to organize minority recruitment. Dr. Ford emphasized that Ms. Brown's ideas would be appreciated. Ms. Brown related that she has some additional ideas that she would like to share.

XII. NEW BUSINESS: SESSION II—DRS. PAUL CALABRESI & MARVIN KALT

Dr. Wells commended NCI staff for its professional excellence in carrying out the special actions function of the Board. The Board, he noted, has consistently conducted brilliant reviews, always resolving any grant-related questions. Dr. Wells stated that NCI staff represent public service at its best. Dr. Chabner thanked Dr. Wells for his comments and added that Dr. Wells has done an excellent job as chairperson of the Subcommittee on Special Actions.

Dr. Day asked Dr. Chabner if the grants for operations and a statistical center that are to be recompeted represent the two mechanisms available for NSABP, and whether a new chair will be chosen by the executive committee. Dr. Chabner explained that these mechanisms are not mutually exclusive. The group has the right to name a new chairperson in the next few months, and this process has begun. Dr. Chabner added that the grants will be recompeted earlier than usual, allowing the group enough time to consolidate changes and reapply next year.

Dr. Broder indicated that the University of Pittsburgh is welcome to apply and recompete, commenting that a meeting between NCI and University of Pittsburgh officials went well. Dr. Day asked if any eligible group could submit a grant application that would be reviewed on its own merit. Dr. Broder stated that the goal for NSABP is to have an open

competition of all parties that desire to compete; their proposals, he added, will be judged by a peer group of non-Governmental scientists and clinicians.

Dr. Day asked when the grant will be awarded. Dr. Chabner answered that the Board of Scientific Counselors will discuss this issue, but the award will probably be made in early to mid-1996.

Dr. Bettinghaus asked if the executive committee solely selects the new chairperson, or if the University of Pittsburgh and NCI must approve the selection. Dr. Chabner explained that the University of Pittsburgh does not have the privilege of choosing the next chairperson. The existing constitution, he continued, maintains that the executive and nominating committees select the candidate and the membership approves the selection. The NSABP has a constitutional revision committee that is considering a change that would allow the executive committee to choose the chair without a vote of the membership. Dr. Chabner related that he cautioned the committee that their choice should be someone familiar with both management and science.

Dr. Correa expressed great admiration for Dr. Adamson, who is retiring. He praised Dr. Adamson for his "spectacular reorganization" of the Division of Cancer Etiology, as well as his successful work.

Dr. Salmon asked when accrual may resume for the prevention trial, at least at selected centers. Dr. Greenwald stated that a decision will not be made until an FDA review is conducted in the second week of June; however, the DCPC BSC has recommended restarting the trial as soon as possible after adoption of their recommended changes involving individualized informed consent, endometrial aspiration, and no change in eligibility criteria. Dr. Greenwald expressed his hope that the trial will resume this summer.

Motion—Resumption of the Breast Cancer Prevention Trial

Dr. Salmon motioned that the NCAB support the resumption of the Breast Cancer Prevention Trial as soon as possible, preferably this summer.

Dr. Ford pointed out that an article has been published in *Good Housekeeping* inviting women to complete a risk assessment and send it to NSABP; none of these assessments have been processed. After suspension on accrual is lifted, NCI will restart the risk assessment process (possibly in the next 1 to 2 weeks) and refer participants to centers, though randomization might not occur, she noted, until summer.

Dr. Ford agreed with Dr. Calabresi's comment that it would be helpful for the NCAB to endorse resumption of the trial. Dr. Salmon expressed concern that a significant delay could have a detrimental effect on the trial. Dr. Calabresi added that a delay raises questions about the appropriateness of the trial and stressed that the Board should go on record that it considers this an important trial that should be restarted as soon as it is safe and appropriate to do so. Dr. Calabresi then asked Dr. Salmon to draft a written motion on this issue.

Dr. Salmon read the following motion: "The National Cancer Advisory Board recommends that the breast cancer prevention trial be resumed as soon as possible, and, if at all possible, no later than this summer. Further, we consider this to be one of the most important clinical trials underway sponsored by the National Cancer Institute."

Dr. Bettinghaus seconded the motion.

Dr. Day asked how many more notification letters will be sent to participants. Dr. Ford stated that she hopes there will be no new side effects—thus, no new letters—but that women in the trial must be informed about new information. The informed consent changes of January 1994, she said, are in process; they have been approved by the IRBs and are being signed. Dr. Ford added that the letters to participants contained this same information. There will be another informed consent change related to endometrial sampling and biopsies, and no new participants can enter the study without signing this new informed consent form.

Dr. Greenwald commented that this process can be repeated so many times that it creates an impression of a higher-than-actual risk. Some prevention trials, including this one, he indicated, send information to participants via a newsletter. He suggested that unless a major issue arises, the newsletter may be a sufficient channel for evolving information. Dr. Day reiterated that women entering the trial will sign the informed consent forms that update the endometrial cancer and biopsy consents.

Dr. Broder emphasized that the NCI does not author or initiate most of the letters and modifications required for this trial; for example, the NCI is obligated to carry out the FDA's requirements. Dr. Broder remarked that some of the processes that have evolved over time are not suitable for large-scale prevention studies; thus, staff should think about more novel ways of working with the Office of Protection From Research Risk and transferring information to patients than the call-back/sign-up process. The NCI is experimenting with new methods, such as electronic bulletin boards, and would welcome the Board's suggestions on this matter. Dr. Broder noted that the process currently in place requires the trial to reconsent the patient when a substantial change occurs; discussion of procedural issues, he stressed, must not be allowed to interfere with scientific objectives. Dr. Broder observed that this study is unusual in that there are discussions concerning whether the original informed consent fully conveyed the facts. If this is true, he stressed, the NCI has an obligation to ensure that the reconsent processes occur so that the study may proceed. He related that the NCI wants this study to resume, but also wants the Board to understand its point of view. The NCI, he said, is very sympathetic to the difficulties encountered by investigators, but feels an urgency to address the problems that have arisen and get the study moving ahead without being derailed by procedural issues.

Dr. Day expressed concern about publicity surrounding these issues of the trial and its effect on the trial's validity. He also related concern about biases occurring and confidence in the findings, based on who enters and who withdraws from the study. Dr. Broder commented that he does not expect these unique circumstances to continue. He acknowledged several unexpected findings associated with the trial, such as a significantly higher-than-predicted risk of breast cancer among participants. Dr. Broder added that he does not believe the findings will change the validity of the study, since it is randomized, placebo-controlled, and double-blinded. He assured the Board that the NCI considers this trial to be the most important study it is conducting, and that a related study on ductile carcinoma *in situ* has "parallel synergy" with the Breast Cancer Prevention Trial. Dr. Broder surmised that, if allowed to continue, these two studies will have a dramatic effect on breast cancer incidence and mortality among certain high-risk women.

Dr. Day requested that the Board discuss implications of this trial's findings for the general population, particularly as women age. He asked what kind of trial is needed to demonstrate efficacy in the general population and if the BCPT's findings and recommendations are restricted to a high-risk population. Dr. Greenwald briefly answered that the most direct result would be applicable to a high-risk population. He explained that the issue of bias raised by Dr. Day concerns generalizability more than validity (i.e., limiting the focus to the segment of the population on whom it is possible to project results).

Dr. Chan asked how this trial will be reviewed. Dr. Greenwald responded that he cannot predict how the trial will be reviewed, but **[who?]** has been very supportive of the trial and worked closely with Dr. Ford and her colleagues, as well as NSABP.

Dr. Calabresi asked Dr. Kalt to reread the written motion: "The National Cancer Advisory Board recommends that accrual on the breast cancer prevention trial be resumed as soon as possible, and, preferably, by no later than the summer of 1994. The National Cancer Advisory Board considers the breast cancer prevention trial to be one of the most important trials sponsored by the NCI." The motion was approved, with one abstention.

Motion—Environmental Tobacco Smoke

Dr. Sigal suggested that the Board, as a scientific body knowledgeable about smoking and environmental tobacco smoke, has an obligation to influence policy. She read the following motion, the genesis of which was Congressman Waxman's bill, H.R. 3434:

"Whereas, the health risks of tobacco products have been established through carefully conducted biomedical research supported in part by the National Cancer Institute; and

"Whereas, the health hazards of exposure to environmental tobacco smoke have been documented through scientific research and published by the Environmental Protection Agency; and

"Whereas, the continued use of tobacco products in public and workplace settings continues to impose a health hazard to non-smokers;

"Be it resolved that the National Cancer Advisory Board supports legislation designed to restrict involuntary exposure to tobacco smoke introduced by Rep. Henry Waxman in H.R. 3434 (Senate companion S. 1680, Senator Lautenberg) and by Rep. Traficant in H.R. 881."

Dr. Bettinghaus seconded the motion.

Dr. Correa strongly supported the motion and pointed out that an article in the June 7th issue of the *Journal of the American Medical Association* showed clear findings of health risks associated with passive smoking.

Dr. Hugh McKinnon of the Environmental Protection Agency expressed support for the motion and recommended an amendment. He explained that he is the director of the group that prepared an EPA report, which NCI added to its monograph series on tobacco and which builds on 1986 reports from the National Academy of Sciences and the U.S. Surgeon General, and which was unanimously endorsed by the EPA science advisory board. To substantiate the resolution with evidence on the carcinogenic effects of ETS, he suggested adding to the second paragraph, ". . . published by the National Academy of Sciences, the U.S. Surgeon General, and the Environmental Protection Agency." Dr. Sigal agreed with Dr. McKinnon's recommendation and credited Ms. Dorothy Tisevich with drafting the motion.

Dr. Salmon seconded the amendment. The Board unanimously approved both the amendment and the motion.

Announcements

Dr. Kalt called Board members' attention to the annual report of the Division of Extramural Activities in their notebooks, which includes figures on applications and reviews

for fiscal year 1993. He described two changes that take effect by the next Board meeting. First, there will be an increased use of triage by the Division of Research Grants study section in reviewing regular R01 grants. The designation "NC," which means not competitive, will be used for applications that will be triaged out. Since there is no chance of award for these applications, Board approval is not needed; thus, members will see this designation only if the application involves human subjects or another concern. The second change involves the review of program projects. Dr. Kalt related that program project grants are currently being reviewed through a committee structure, and that NCI has initiated committees on an *ad hoc* basis, but has not received charters. Each of the program projects is initially evaluated by a site visit team or group of experts, which transmits the evaluations to a standing review committee, which then assigns the final priority scores to the program project.

Dr. Salmon asked why the Board needs to examine issues related to animal or human subjects or minorities if the grant is considered noncompetitive. Dr. Kalt explained that this information will be included on the list of applications sent to Board members, but will not concern the Subcommittee on Special Actions. Dr. Wilson commented that this information has some educational value, because applicants should be informed if they do not comply with minority or animal rights regulations.

Dr. Broder reminded the Board to provide NCI with feedback on the "just in time" concept, which would involve developing a system requiring little paperwork unless a grant is competitive. For example, he stated, the NCI would want to develop RFAs for small grant applications that require a very limited amount of paperwork; additional information would be requested only if the grant were likely to be funded.

XIII. ATBC CANCER PREVENTION STUDY—DR. DEMETRIUS ALBANES

Dr. Greenwald explained that NCI and Finnish scientists jointly conducted a lung cancer prevention trial of alpha-tocopherol and/or beta-carotene in 29,000 heavy smokers, the results of which have been published in the *New England Journal of Medicine*. Dr. Greenwald then introduced Dr. Demetrius Albanes, NCI's principal investigator for the study.

Dr. Albanes introduced the topic of his discussion, the Alpha-Tocopherol Beta-Carotene Cancer Prevention, or ATBC, study, which was published in the April 14th edition of the *New England Journal of Medicine*, entitled "The Effect of Vitamin E and Beta-Carotene on the Incidence of Lung Cancer and Other Cancers in Male Smokers." Dr. Albanes stated that the study was a collaborative effort between the NCI and the National Public Health Institute in Finland.

Dr. Albanes began the discussion by stating that epidemiologic literature in the early 1980's was strongly suggestive of the possible cancer-protective potential of vitamins. This was the same time that planning for the ATBC study began. The pilot study for the ATBC study occurred in 1984 and 1985, and recruitment occurred between 1985 and 1988. The intervention phase of the study lasted from 1985 to 1993, and, currently, analysis and reporting of study results continue.

Dr. Albanes stated that the objective of the study was to evaluate the effectiveness of vitamin E and beta-carotene supplementation in preventing lung and other cancers. He indicated that although lung cancer was the primary endpoint of the study, the occurrence of other major cancers was also of interest because these two vitamins are relevant to the prevention of other cancers.

There had been overwhelming epidemiological evidence, Dr. Albanes continued, that dietary fruits and vegetables, especially those high in carotinoids, protect against cancer, particularly lung cancer. He indicated that to date, there are approximately 200 studies that suggest a link between healthy, fruit- and vegetable-rich diets and a reduced risk of cancer. In contrast, lower blood levels of both beta-carotene and vitamin E have been associated with an increased risk of lung cancer.

The ATBC study was conducted in 14 clinics in southwestern Finland. Finland was chosen, Dr. Albanes related, because of its high-risk population with a traditionally high rate of lung cancer, particularly among males, that is due primarily to high levels of cigarette smoking. A pulmonary disease data system also exists in Finland that includes computerized smoking data on individuals, which facilitated study recruitment and logistics efforts. Dr. Albanes also stated that the ascertainment of endpoints was relatively easy through the National Finnish Cancer Registry.

Dr. Albanes summarized the study design, observing that the area of recruitment was restricted to southwestern Finland. Men between the ages of 50 and 69 who smoked at least five cigarettes per day were eligible for enrollment, and by 1988, over 29,000 men were randomized into the study. Dr. Albanes continued by saying that the trial was a double-blind, placebo-controlled, two-by-two factorial design, meaning that both vitamin E and beta-carotene were tested independently to evaluate the health outcomes for two different vitamins within the same study, making the design more cost-effective. The duration of dosage, intervention, and follow-up for study participants was 5 to 8 years. The endpoints of interest, Dr. Albanes reiterated, were lung and other cancers.

The ATBC study population was equally divided into four groups, with one group receiving 50 milligrams of only vitamin E daily; a second group receiving only beta-carotene at a dose of 20 milligrams daily; a third group receiving a combination of vitamin E at 50 milligrams and beta-carotene at 20 milligrams daily; and a fourth group receiving a placebo with no vitamins. This, Dr. Albanes stated, completed the randomized factorial design. Dosage compliance was facilitated by capsule blister packaging with calendar-imprinted backing that made it easier for study participants to take their capsules on a daily basis. Dr. Albanes added that a very specific and detailed dietary history was collected in an effort to compare the diets of individuals who developed cancer with the diets of those who did not, and to adjust data for dietary intake initially and throughout the trial. A slide was shown of the booklets used to collect the dietary information.

In regard to study follow-up, Dr. Albanes stated that the average follow-up time on the study was 6.1 years, ranging from 5 to 8 years. He observed that there was excellent compliance among participants, with an average of 99 percent of the required capsules taken over the duration of the study. Nineteen percent of participants voluntarily dropped out, and 12 percent of the men died during the course of the study. Active smoking cessation counseling was provided at each visit to study participants, Dr. Albanes stated, and a high proportion (21 percent) of participants stopped smoking during the study.

The main sources of endpoint data, Dr. Albanes continued, included the Finnish Cancer Registry for cancer incidence, the National Death Registry for major causes of mortality, and hospital discharges for incident cases of noncancer illnesses and morbidities.

Dr. Albanes then began a discussion of study results, beginning with a summary of participant characteristics at the time of study initiation. Dr. Albanes noted that none of the characteristics differed significantly by treatment assignment. The average age at study entry was 57 years, and the average number of cigarettes smoked per day was one pack, or 20 cigarettes. The average number of years of smoking by participants coming into the trial was

36 years. Participants also tended to be slightly hypercholesterolemic and overweight. Dr. Albanes summarized the average dietary intake at the beginning of the study with regard to beta-carotene intake (1.7 milligrams on average) and vitamin E intake (10.3 milligrams on average), and calories (2,730 per day). Thirty-nine percent of daily caloric intake was from fat, and participants consumed, on average, about three-fourths of one drink of alcohol per day. Dr. Albanes emphasized that there were no differences in these characteristics between treatment groups that could explain treatment effects or study results.

Changes occurred over time, Dr. Albanes noted, that did not differ significantly across treatment groups; for example, some participants smoked fewer cigarettes per day at the end of the study than they did at initiation.

Dr. Albanes then discussed compliance among participants in taking the vitamin capsules. Seventy-five percent of the study participants enrolled took over 95 percent of their capsules, and there were very few poor compliers. Capsule compliance was verified biochemically based on blood levels of both vitamin E and beta-carotene, and substantial increases for both vitamins were observed in participants' sera.

Descriptive findings with respect to baseline factors included a graph of the number of cigarettes smoked per day and the age-adjusted incidence rate of lung cancer. Dr. Albanes noted a classical step-wise increase in lung cancer incidence with the number of cigarettes smoked, and stated that this finding was cumulative through the study and was based on the number of cigarettes smoked at baseline. He added that these preliminary findings help to generalize the results of the study, and that certain variables within the study population correlate with important risk factors with respect to lung cancer.

Dr. Albanes noted that a lower incidence of lung cancer was observed among men who quit smoking during the course of the study—429 cases per 100,000 person-years, compared with 551 cases per 100,000 person-years among those who continued to smoke. Dr. Albanes acknowledged that although this comparison was not quite fair, the overall pattern was for a dramatic reduction in lung cancer among those who quit smoking.

Dr. Albanes then summarized results in terms of baseline dietary intake of vitamin E and beta-carotene and lung cancer incidence among men in the placebo group. He noted that men who had the lowest dietary intake of vitamin E at the beginning of the study had the highest incidence of lung cancer, while men with the highest level of dietary vitamin E at baseline had the lowest incidence of lung cancer in the study. Similarly for beta-carotene, men in the placebo group who had the highest levels of baseline beta-carotene had a lower incidence of lung cancer, compared with men in the lowest quartile for baseline dietary beta-carotene. Dr. Albanes stated that this information corroborated the available epidemiologic evidence that links healthy diets with reduced lung cancer. He added that similar results were found for other cancers.

In terms of treatment curves for cumulative lung cancer incidence and vitamin E supplementation versus no vitamin E supplementation, Dr. Albanes noted that the test statistic for the comparison was highly nonsignificant, meaning that there was no overall effect for vitamin E supplementation in lung cancer prevention. He mentioned that 433 cases of lung cancer were found among those receiving vitamin E, and 443 cases were found among those who did not receive vitamin E. In contrast, the curves for beta-carotene did exhibit a digression for those receiving beta-carotene, for whom lung cancer incidence was 18 percent higher than for those who did not receive beta-carotene. The difference in cumulative incidence between the two beta-carotene treatment groups was statistically significant.

A surprising finding, Dr. Albanes continued, was a highly statistically significant 34 percent reduction in prostate cancer incidence among the vitamin-E-treated group, who had 99 cases of prostate cancer, versus 151 among those who did not receive vitamin E. Dr. Albanes indicated that while there was not much prior epidemiological evidence in favor of this relationship, these results are very convincing from a trial setting and should be followed up with other studies. Dr. Albanes stated that there were no other major findings for vitamin E intake, with the exception of a reduction in colorectal cancer that was not statistically significant, but which is supported by epidemiologic information suggesting a risk reduction for higher vitamin E intake.

Dr. Albanes then focused on the beta-carotene results, which, he observed, were not as favorable. In excess of 72 cases of lung cancer were found among those who received beta-carotene. The pattern for other major cancer sites, however, indicated a null effect of beta-carotene rather than a cancer-preventive effect. In fact, Dr. Albanes continued, for some sites there may have been harmful effects of beta-carotene, since those subjects who received beta-carotene had slightly increased rates of cancer. Dr. Albanes stated that treatment codes were checked for these results and that, in fact, these are real results from the trial. Explanations for these results remain to be found from this as well as other studies, but, Dr. Albanes concluded, no cancer-preventive effects for supplementary beta-carotene were found in this group of older/middle-aged male cigarette smokers.

Other major endpoints of the trial were then discussed in terms of safety and causes of mortality. No difference was observed in terms of overall mortality for vitamin E versus no vitamin E; however, there was a slight deficit of ischemic heart disease and ischemic stroke for those who received vitamin E. Dr. Albanes noted that while this finding is not statistically significant, it fits with current hypotheses and other recently released epidemiological data.

Dr. Albanes then discussed a potentially disturbing finding related to vitamin E intake and hemorrhagic stroke. Sixty-six deaths occurred from hemorrhagic stroke in the vitamin E group, versus 44 deaths in the group who received no vitamin E, representing a statistically significant increase in hemorrhagic stroke. Dr. Albanes indicated that this fits with the known antiplatelet activity of vitamin E, which contributes to the importance of this finding.

An 8 percent excess of total mortality was observed for the beta-carotene group, compared with those who did not receive beta-carotene. Lung cancer, ischemic heart disease, and stroke were major contributors to this statistically significant excess mortality. Dr. Albanes emphasized that, as with the results from the major cancers, there was no evidence of a beneficial effect of supplementary beta-carotene in older/middle-aged male smokers in preventing either cancer or other major causes of mortality.

Dr. Albanes summarized the findings related to vitamin E as follows: there was no effect on lung cancer or on total mortality; there was a significant 34 percent reduction in prostate cancer incidence in the vitamin E group compared with those who did not receive vitamin E; and, based on 110 deaths, an increase in death from hemorrhagic stroke was observed, which fits with known mechanisms of vitamin E and platelet aggregation. For beta-carotene, Dr. Albanes reported that there was an 18 percent increase in lung cancer incidence in the beta-carotene group, and a statistically significant 8 percent increase in total mortality.

In conclusion, Dr. Albanes stated that beta-carotene supplements did not prevent lung cancer in older male cigarette smokers and showed little or no benefit for other cancers in terms of prevention; vitamin E, or alpha-tocopherol, may prevent prostate cancer, but this possibility requires further study; and beta-carotene and alpha-tocopherol supplementation may have harmful as well as beneficial health effects.

Interpretations with respect to lung cancer incidence and beta-carotene intake are being actively investigated by Dr. Albanes' group and other researchers to determine whether this result is due to chance. If so, Dr. Albanes said he anticipates that his beta-carotene results will not be replicated by others. If, on the other hand, the effect is verified with the data and found to be real, there are two possible explanations. One explanation could indicate that the effect is indirect and noncarcinogenic, possibly due to altering effects of beta-carotene on some other aspect of metabolism; for example, defense mechanisms. The second explanation is a direct, possibly carcinogenic effect that is not supported by prior information and contrasts with the nontoxic nature of beta-carotene as described over the past several decades in all other studies. Because this is a very large randomized trial, Dr. Albanes said that the observed effects cannot be ignored and should be followed up through further analysis of the study data and through analysis of data from other trials and studies.

Additional studies are needed, Dr. Albanes continued, to understand the full spectrum of these effects, both for vitamin E and beta-carotene, and some studies are already in progress and others will be started. He stated that public health recommendations regarding supplementation with vitamin E or beta-carotene for cancer prevention purposes appear to be premature at this time.

Additional analyses to be conducted for the ATBC Trial include a more detailed analysis of site-specific cancers to look at modifying effects or subgroup effects for various histologies, for stage of disease, for the modifying influence of dietary intake of beta-carotene and vitamin E, and for cigarette smoking and smoking cessation. These analyses are under way, Dr. Albanes continued, and results will be forthcoming for lung and prostate cancers before the end of this year, and for colon, stomach, bladder, and some other major cancer sites, either by the end of this year or early next year. These results will present a more detailed idea of the effects observed within the current trial.

Dr. Albanes mentioned that cardiovascular diseases will be looked at in greater detail in terms of mortality as reported in the initial preliminary report from this trial, and in terms of nonfatal cases as ascertained from hospital discharge registries to get a more complete picture of the effects of vitamins on cardiovascular disease. This effort, Dr. Albanes stated, is being led by the team of investigators in Helsinki, Finland.

Dr. Albanes indicated that the Board of Scientific Counselors of the Division of Cancer Prevention and Control approved a 7-year follow-up of the trial cohort to monitor long-term health effects. He mentioned that possible vitamin E prostate cancer trials are under consideration and, he believes, are important in order to follow-up the 34 percent reduction in prostate cancer incidence that was observed in the ATBC study. Clinical biochemical studies are also being planned to look at beta-carotene metabolism in greater detail, and the FDA is considering some laboratory studies that will elucidate possible mechanisms as well.

In terms of policy action issues, Dr. Albanes said that the NCI currently has no recommendation for vitamin supplements for cancer prevention, because the information coming from current trials will be evaluated with other epidemiologic data, and the ATBC results represent only one study. Discussions have been held with FDA to review their perspective of these results and, at present, there is no change in FDA policy related to health claims or toxicity aspects for either beta-carotene or vitamin E. Dr. Albanes concluded by saying that other NCI- and NIH-sponsored trials have been informed of the ATBC results and appropriate actions are being taken by those investigators and their Data Safety and Monitoring Boards.

Questions and Answers

Dr. Ellen Sigal stated that she is very pleased to see studies like this, but that she is disappointed with the results. She asked why only men were included in the study population since women also get lung cancer and smoke. A second question related to a possible relationship between dose, specifically dose of beta-carotene, and health outcome. She questioned whether doses administered in the study represented customary doses.

Dr. Sigal stated that she understands the need for a major follow-up on this study, given that the information is useful, and that there should be collaboration in more studies of both vitamin E and beta-carotene because they are widely used. She indicated that she would like to endorse this idea as rapidly as possible.

Dr. Albanes responded to Dr. Sigal's first question about the exclusion of women from the study by stating that it was designed as a lung cancer trial. In the early 1980's during the study's planning phase, lung cancer incidence varied widely between men and women in the United States, in Finland, and in many other countries. The combination of the very different smoking rates among men and women and the high differential in lung cancer incidence rates made the inclusion of only men much more practical from the standpoint of study size. Dr. Albanes continued by saying that smoking was a major problem at that time, and is today, and lung cancer incidence was very high and represented a high-priority site.

Dr. Broder interrupted and said that the NCI had made a mistake by not including women, and that this will not happen again. He stated that although he was not at NCI during the planning phase of the trial, he will accept full responsibility.

Dr. Greenwald mentioned that the Harvard Women's Health Study, headed by Dr. Julie Buring, is currently studying 41,000 women and includes beta-carotene and vitamin E in a factorial design. It includes an aspirin component and is looking at smoking data as well.

In response to the question about dose, Dr. Albanes stated that because this was one of the first trials in this area, the investigators did not want to use extreme dosages. He said he does not believe the observed ATBC effects from beta-carotene can be explained by a low dose, and that there is not much evidence for a preventive effect in the current study population. Less was known, he continued, about vitamin E at the time the study was planned. Vitamin E was thought to be very safe; however, investigators decided to use a slightly conservative dosage of 50 milligrams, or about three to five times the dietary intake—an amount believed to be sufficient for testing cancer prevention.

Dr. Albanes stated that follow-up is continuing, with Drs. Greenwald and Broder and the NCI leading the effort in terms of pursuing leads from the ATBC study. He stated that other studies are still actively in progress, and new studies will be planned, particularly the prostate cancer vitamin E trials that will probably be the first level of effort for cancer prevention purposes.

Dr. Becker asked whether any particular vitamin treatment group or the placebo group showed the highest rate of smoking cessation. Dr. Albanes replied that no group showed a higher rate of cessation, and that these types of behavioral changes were equivalent across each of the four individual groups and each combination group.

Dr. Becker then asked how levels of circulating beta-carotene and vitamin E induced through the use of supplements compared to levels achieved through a healthy, normal diet. Dr. Albanes responded that blood levels of the vitamins that were achieved were

pharmacologic. Dr. Becker indicated his understanding of this point, but that he still wanted an indication of the relationship of the levels. Dr. Albanes stated that blood levels of the vitamins among study participants were much higher than one would observe based on a normal, healthy diet. Dr. Becker then asked whether Dr. Albanes could provide an answer as to how much higher in terms of total percent, or in nonpharmacologic terms. Dr. Albanes replied that the vitamin E level was roughly 50 percent increased over baseline levels within the study, and baseline levels were about average for vitamin E blood levels in different populations. Dr. Albanes stated that the beta-carotene levels were increased 17- to 18-fold, which represents a more substantial increase in the beta-carotene blood levels over what is normally observed.

Dr. Becker stated that this is a very interesting point, and added that Dr. Albanes seems taken aback by the apparent promotional effect on carcinogenesis, rather than a carcinogenic effect, because it seems to accelerate or stimulate a process already under way. Dr. Becker said that Dr. Albanes has been working with huge levels of circulating vitamin E, the kind of levels that nutritionists often recommend, and comparing these levels with the salutary effects of a normal diet.

Dr. Greenwald stated that the promotional effect is a possible explanation, and that with beta-carotene there is a limiting ceiling on dosage, and that the study came close to that limit. At a higher dose of beta-carotene, a yellowing effect may be observed, and there was some yellowing among participants in this trial.

Dr. Salmon asked what dosages were given to participants in the study. Dr. Greenwald responded that 20 milligrams a day were given, which in the case of vitamin E, is a little over three times the RDA. He stated that 50 milligrams of vitamin E is about five times the RDA and is equivalent to five times the dose found in the usual diet or the upper end of the usual diet. He indicated that there is a high level of bioavailability of the vitamins observed as a large jump in blood levels, and added that there are studies under way that use higher levels, even up to 600 milligrams. Dr. Greenwald indicated that the explanation given by Dr. Becker is plausible, but has not been proven, and added that the observed effect that causes concern about risk is for beta-carotene.

Dr. Becker asked whether Dr. Albanes has examined the effect of the vitamins on cancers of the head and neck and asked whether the study participants had a high incidence of these cancers. Dr. Albanes stated that he and his group ascertained the incidence of all cancers, regardless of how small the incidence, and that these cancers were lumped together for simplicity in the "other cancer" category. He said that there were a fair number of laryngeal cancers; for example, oropharyngeal cancers, and that these are being analyzed for potential cancer-preventive results. Dr. Becker asked whether the analysis of these cancers indicated an increase, a decrease, or no change in the incidence rate. Dr. Albanes could not recall the rates; however, he indicated that he believes there are differences in the incidence of head and neck cancers.

In reference to Dr. Albanes' remarks about this study being different from the results of other studies, which were based primarily on dietary intake, Dr. Becker asked whether Dr. Albanes is aware of a single definitive study that demonstrates the beneficial or anticancer effects of supplemental beta-carotene.

Dr. Albanes responded that last fall, two Divisions in the NCI published results from the Linxian trial from China. That particular study combined beta-carotene, vitamin E, and selenium, and demonstrated a reduction in cancer mortality. Dr. Becker added that the mortality was only somewhat reduced. Dr. Albanes agreed and indicated that stomach cancer mortality, primarily, was reduced.

Dr. Greenwald stated that the Linxian trial was conducted in a population that was somewhat vitamin deficient and that there was a 21 percent decrease in stomach cancer deaths. He pointed out that there appeared to be an inverse correlation in the placebo group in this study, which could be a marker effect—the beta-carotene or vitamin E could be an indicator of potentially beneficial fruit and vegetable intake. Dr. Greenwald also indicated that there is no clear specific trial result indicating a benefit of beta-carotene.

Dr. Becker also discussed results of the Linxian study, stating that it utilized two elements for which that population was severely deficient, vitamin E and selenium. He stated that the population had no rare minerals left in their soil and were exposed to a carcinogenic stimulus of about 12 different nitrosamines and a promoting agent, Russian red. They were, therefore, a very complicated population to study. Dr. Becker said it was impossible to evaluate any potential effect of beta-carotene because it was given to the population as a complex with other agents that may have caused the observed effect. He stated that the scientific community tends to view healthy diet results and then conclude that dietary supplementation will achieve even better results. Dr. Becker stated that the study results just presented are important, however disappointing they may be, because they suggest that there are optimal levels of these supplements for normal physiology and that pharmacological enhancement may not be of further benefit. He concluded that, in a somewhat disappointing way, this study may be a real benchmark study.

Dr. Correa stated that this study has made quite an impact in the community, not only in the scientific community, but in the general public as well. He said there have been quotes saying that carotene may induce cancer, which Dr. Correa did not believe Dr. Albanes had stated, but he stressed that this is how the information is interpreted by the general public. There is no question, he continued, that beta-carotene does not reduce the incidence of lung cancer in this population, although it must be remembered that the cause of the lung cancer is not the beta-carotene; it is the tobacco. He added that the study population had been smoking for 36 years, which is indicative of long-term exposure to smoking.

Dr. Correa suggested that the design of the trial can be questioned—although it was well analyzed and very well conducted, its results may not be applicable to the general population. This trial, he said, was conducted within a special population and, perhaps, the vitamins cannot have a protective effect when a carcinogen—i.e., tobacco smoke—is constantly being delivered to the tissues. Dr. Correa stated that the general population includes people who are deficient in beta-carotene and vitamin E, and although the trial is valid, the results cannot be generalized to other populations. While the Linxian trial was very definitive about the reduction in stomach cancer, Dr. Correa stated that the current trial demonstrates an increase in stomach cancer; this discrepancy, he said, indicates that the ATBC population may not yield results that are generalizable to the public. He pointed out an additional discrepancy in the ischemic heart disease results with results from a preliminary publication of the Physician's Health Study. Although analysis of that study has not been completed, preliminary published work shows that there was a reduction in ischemic heart disease. Dr. Correa concluded that these trials should continue and stressed that an effort should be made to assure the general public that beta-carotene is not a carcinogen as far as is known.

Dr. Greenwald observed that data monitoring and quality control are major current issues, and stated that questions have arisen about why the trial was not stopped during its final year. He then elaborated on what occurs in the last year of a study, noting that for every diagnosis of cancer there is an independent review by two oncologists; if they disagree, they must meet and either come to an agreement, or call in a third referee oncologist. These oncologists may be in either Finland or America. Dr. Greenwald stated that there is also an independent review by two pathologists, who must also reach a consensus or consult a referee.

Dr. Greenwald also stated that there is an effort at close-out to get a final x-ray on each patient. Dr. Albanes mentioned that the 5,000 men who dropped out of the study were included in the effort, which was extended over a 9-month period so that the health care system would not be overwhelmed. Dr. Greenwald stated that of the total group, 90 percent had a final x-ray, and in the final year and a half of the study, approximately 245 of the 876 lung cancer diagnoses were made. Verification of study endpoints is a dynamic process not only because of age, but also because of the study design and some shifting in the totality of follow-up. Dr. Greenwald felt that the Board should be aware of this important aspect of quality control.

Dr. Adamson said it should also be remembered that in the Linxian trial, total mortality was analyzed as well as mortality from specific cancers, and that lung cancer deaths decreased in this trial. Although this decrease was not statistically significant, Dr. Adamson said it provides evidence from another trial that beta-carotene, at least in combination with two other agents, does not increase lung cancer mortality.

Dr. Broder expressed his opinion that nothing can be done to reverse the effects of smoking in those who smoke heavily. He emphasized that he did not want his comment to be misunderstood, but that individuals who smoke heavily have a high probability of dying, and that once an individual gets lung cancer, there is not much that can be done to reverse the disease process. Investigators had hoped, he continued, that beta-carotene would be a way of rehabilitating the body from smoking damage that had occurred. If, however, there has already been substantial induction and promotion, as in the ATBC study population, not much can be done to reverse these effects. Dr. Broder indicated that the only message that can be provided to the public is not to smoke, and if they do smoke, they should stop, because there are no magic bullets. Dr. Broder stated that this is how he interprets these data.

Dr. Bettinghaus stated that the public should be told that if they do stop smoking, they will dramatically diminish their chances of getting lung cancer. Alluding to the ATBC trial, he observed that this was one of the most startling sets of figures seen in people who had been smoking for 36 years.

Dr. Broder stated that this information was already known, and that it was couched within his earlier comment. He reiterated that people should not start to smoke, and if they do smoke, they should stop. No delusions should be harbored, he continued, that there is any pill or vitamin that can be taken in order to continue smoking with no adverse effects.

Dr. Salmon commented that the data presented from a powerful trial such as the ATBC study requires the consideration of an alternative hypothesis. He said that while the evidence is clear that beta-carotene is not helpful in reducing cancer, Dr. Greenwald alluded to the fact that there may be a marker effect that is not understood at this time. Dr. Salmon stated that the Linxian trial cannot be taken as contrary evidence to this hypothesis because it was done with deficient patients who received another agent, selenium, which has not been evaluated alone.

Dr. Calabresi thanked Dr. Albanes for his presentation, and called a brief recess.

XIV. STATUS REPORT: SUBCOMMITTEE TO EVALUATE THE NATIONAL CANCER PROGRAM—DR. PAUL CALABRESI

Review of the June 1, 1994, draft of "Cancer at a Crossroads: A Report to Congress for the Nation" by the NCAB's Subcommittee to Evaluate the National Cancer Program

(SENCAP) was introduced by Dr. Calabresi. He recognized the diligent efforts of the Subcommittee members and Ms. Cherie Nichols and her staff to swiftly move the Report into its final stages. The goal of this discussion, explained Dr. Calabresi, would be for appointed NCAB members to vote on approval of the Report, allowing for minor modifications pending recommendations still being made by the Board. Dr. Calabresi emphasized the importance of obtaining the Board's consensus and sending an endorsement to Congress before it adjourns. He stated that it would be helpful for members to submit written notice of any recommendations, but that the current discussion would be critical to gaining consensus.

Discussion

Dr. Becker suggested that recommendations III-6 and III-7 to increase the pool of funds for investigator-initiated research grants and to preserve the infrastructure that supports academic research become the first and second recommendations in this section. He stressed that all other suggestions for basic research rely on these two recommendations. Drs. Bettinghaus and Calabresi agreed that this is an appropriate change and will be passed on to the Committee.

Dr. Newton noted that *ex officio* members were given little time to review and comment on the Report, adding that the copy that she received did not include lists of recommendations that appear in the version under discussion.

Dr. Newton proceeded to point out ambiguous statements concerning coordination of the National Cancer Program. Under the "Executive Summary" on page iii, reference is made to the 1971 Cancer Act assignment of legislative authority for coordinating the National Cancer Program to the Director of NCI. However, on page seven of the Report, a suggestion is made to assign that authority to an overall coordinator that is not specified. Dr. Bettinghaus affirmed that the intent of the Cancer Act reference on page iii and the suggestion on page seven is to point out that although there is no current legislative authority, there was such authority in 1971 when the National Cancer Act was initiated. He emphasized that the intent is to call for coordination without specifying that it should necessarily come from the National Cancer Institute.

Dr. Day expressed concern that the Report does not clearly recognize reasons for increases in cancer incidence and mortality, nor offer suggestions to reverse the trend. The Report calls attention to the 7 percent increase in mortality and 18 percent increase in incidence, Dr. Day explained, yet no connection with the difficulties presented in cancer research, application, and translation into practice is made. He suggested clearly stating why cancer mortality and incidence figures have continued to climb and what can be done to curtail them. Dr. Calabresi agreed, noting that the Subcommittee tried to include such an explanation, but could perhaps state it more clearly. Dr. Freeman commented that the Report should admit that there is a problem and offer explanations and solutions. Dr. Calabresi added that other components, such as insufficiency in health care delivery and an increase in the aging population, also factor into the increased mortality and incidence rates.

Dr. Day emphasized that if today's knowledge were delivered across the population and behavioral changes based on this knowledge (e.g., tobacco use) were adopted, decreases in incidence and mortality would occur. In accordance, Dr. Calabresi stressed the paramount importance of basic research and the need to express this importance more emphatically in the Report to Congress.

Dr. Broder stressed that since mortality and incidence percentages are based on age-adjusted figures, the aging population cannot be used to explain the increases. He expressed

his belief that the difficulties of cancer research must not be understated and that a redoubling of research efforts is the remedy to the problem.

Dr. Yodaiken emphasized his concern that *ex officio*/alternate members had little opportunity to review the Report. Dr. Calabresi maintained that approval of the Report will come from appointed members of the NCAB. Any additional comments from *ex officio* members or alternates, added Dr. Calabresi, will be welcomed for this discussion and for consideration by the Subcommittee before the final Report is submitted to Congress.

Dr. Salmon directed the Board's attention to Figure 1, "Components of the National Cancer Program," on page three of the Report, and proposed labeling the center or "bull's eye" of the circular chart "National Cancer Program" instead of "Each Individual." Dr. Broder observed that "Each Individual" is appropriately used in an abstract sense to convey the idea that the National Cancer Program is composed of "every man or woman."

Dr. Salmon proposed an addition to the recommendations list on page seven of the Report. He mentioned that, while it is discussed in the text, there is no explicit recommendation to establish a system to ensure that translational and clinical cancer research continue to be productive in the current era of health care reform. Dr. Calabresi agreed that this thought must be followed up and specified in the section outlining recommendations. Dr. Salmon urged that even if health care reform is not enacted, the trend for revision in health care programs creates an urgency to ensure the survival of clinical and translational research.

Dr. Bettinghaus stated that comments received to date from NCI staff have been extremely appropriate and useful. Because much of NCI staff commentary has been directed to NCI and NCI programs, it has been reworked into a larger context to target the entire National Cancer Program. Though revisions, additions, or recommendations may not appear in the Report specifically as submitted to the Subcommittee, Dr. Bettinghaus explained that each comment has been diligently reviewed, thematically categorized, and either modified or incorporated to some extent.

Dr. Sigal urged the Board to read all the sections of the Report thoroughly and offer feedback. Dr. Calabresi directed Board members to send their comments to Ms. Cherie Nichols and assured members that the Subcommittee carefully considers each suggestion. Ms. Nichols requested that all comments be mailed or faxed to her office over the next few weeks, emphasizing that the Subcommittee is under a tight deadline to submit a final version of the Report to Congress by the end of the summer.

Dr. Day suggested that the fourth recommendation in the Executive Summary should begin "Expand and *broaden* the scope of the mission" rather than "Expand and *redefine* the mission."

Dr. Newton reiterated her concern that non-NCI agencies have had very little opportunity for input on the Report, and asserted that they should have another opportunity to evaluate their programs' capabilities and impact on the National Cancer Program. Dr. McKinnon concurred, adding that having received only three chapters of the Report to review, he is unable to comment on much of the later material. Dr. Calabresi stated that at the time of the initial request for commentary, only three chapters had been written. He emphasized the SENCAP's objective of obtaining voting NCAB members' approval of the Report and offered to establish a timeframe to allow submission of final comments on the Report in its entire form. Noting the tight deadline, Ms. Nichols called for a quick turnover period. Members agreed to submit written comments no later than June 22, 1994.

Dr. Chan asked who will evaluate and incorporate suggestions. Dr. Calabresi explained that a committee reviews the suggestions and the entire SENCAP votes on those chosen. If changes are substantial, he added, there will either be a mailing to Board members or a special meeting of the NCAB will be held.

Ms. Mayer commented that although omissions are inevitable in this type of report, every effort has been made to include as many examples and contributions as possible.

Dr. Becker recommended a motion for approval of the Report, and Dr. Bragg seconded that motion. Dr. Day requested that the motion be changed to approve the Report in principle or draft version subject to revision. Dr. Calabresi repeated that the intent of the motion is to approve the Report, allowing for minor revision and commentary until June 22. The Subcommittee, he continued, will redistribute the final draft to everyone in early August, at which time a final vote, either a mail ballot or agreement by consensus, can be taken. Two weeks will be allowed at that time for additional feedback. Dr. Becker suggested that the final draft mailed out for approval be highlighted where revisions are made to facilitate the review process. Dr. Calabresi agreed to this suggestion.

The Board unanimously approved the Report. Various Board members acknowledged the excellent work of the Subcommittee. Dr. Calabresi thanked Ms. Nichols, her staff, and all members of the SENCAP, and acknowledged Dr. Norman Coleman and Ms. Ellen Stovall for their contributions.

XV. RFA TO IDENTIFY THE BRCA-1 GENE—DR. CHERYL MARKS

Dr. Alan Rabson provided a brief overview of the emergence of an RFA for identifying the BRCA-1 gene. He explained that a few years ago, Dr. Mary Claire King, a geneticist at the University of California, Berkeley, identified and mapped the DNA region that contains BRCA-1, a gene for early-onset familial breast cancer. Despite intense research efforts by several groups of scientists to clone, sequence, and characterize the BRCA-1 gene, the gene has not been isolated or identified. Dr. Rabson indicated that the concept of an RFA to identify the BRCA-1 gene was suggested during a discussion among Drs. Varmus and Broder and himself as an initiative to foster and stimulate collaborations among investigators who could expedite the process of cloning and sequencing the BRCA-1 gene. Subsequently, Dr. Cheryl Marks prepared the RFA for the BRCA-1 gene research project.

Dr. Marks stated that in the last decade, genetic epidemiology studies have shown that an important genetic component is involved in the development of breast cancer. In December 1990, it was announced that this component is indicated by the genetic linkage in several families with high frequencies of early-onset breast cancer and ovarian cancer to the BRCA-1 locus on chromosome 17q21. The identification of the BRCA-1 gene is, therefore, of significant importance to understanding the etiology of breast cancer, which will lead to new research opportunities for prevention, screening, early detection, and treatment of the disease. More specifically, the identification and cloning of the BRCA-1 gene would allow further study of familial susceptibility and risk factors in patients with breast cancer. Dr. Marks reiterated that the BRCA-1 gene has not yet been identified.

Dr. Marks indicated that the ability to clone genes has been substantially improved in recent years by significant advances in molecular technologies such as polymerase chain reaction (PCR), which has enabled the localization of very small amounts of gene products found within cells, as well as a number of genetic markers. Dr. Marks explained that

investigators have no consensus on the incidence of expression of the BRCA-1 gene in familial breast cancer; the rate ranges from 15 to 45 percent. In sporadic tumors, mutations at the BRCA-1 locus are also exceedingly common (i.e., up to about 65 percent of the tumors). Therefore, the identification and characterization of the BRCA-1 gene could have a significant impact on the incidence and mortality of breast cancer, and this is the driving force of the RFA issued on April 8, 1994, to clone and sequence BRCA-1.

Dr. Marks indicated that the applications are due on June 14, 1994, at the Division of Research Grants (DRG) at NIH. The review process will be conducted in July; the summary statements will then be prepared and submitted to the NCAB for review. The grants will be funded by mid-August.

Questions and Answers

Dr. Salmon asked how many grants the DRG intends to fund under this RFA. Dr. Marks stated that the number of grants to be funded has not been specified, but will be dictated by a budget of $2 million per year.

Dr. Becker asked Dr. Marks how much the NCI currently is spending for the cloning and sequencing of the BRCA-1 gene, prior to the creation of the RFA. Dr. Marks responded that she conducted a computer search to ascertain the number of grants that are involved with this research, and she concluded that it was difficult to determine the exact number; however, approximately six grants appear to be conducting directly related studies and the funding for such grants is approximately $1 million per year. There are a number of other grants that are studying tumor suppressor genes in breast cancer that may eventually investigate the BRCA-1 gene. Dr. Becker contended that the amount of NCI funds for this area seems to be greater than the amount indicated by Dr. Marks, since he is fairly certain that a number of Army-supported grants and program projects on genetic analysis for suppressor genes are also in pursuit of the BRCA-1 gene.

Dr. Rabson explained that granting the money through an RFA mechanism would allow a number of grantees to pursue large-scale sequencing of subregions within the BRCA-1 locus through high-speed sequencing techniques, thus enabling investigators to sequence the entire region in the chromosome and identify the BRCA-1 gene more expeditiously. Dr. Rabson indicated that this approach is difficult to pursue through conventional grant support.

Dr. Becker noted that the Human Genome Project has also focused on the isolation of the BRCA-1 gene. Dr. Broder indicated that representatives of the Human Genome Project had been involved in the discussions that led to this RFA. He noted that the $1 million allocated to cofund the BRCA-1 gene RFA will support valuable research that the Human Genome Project will not have to pay for. Dr. Broder also noted that one objective of issuing the RFA is to stimulate investigators to share information and engage in collaborative efforts toward the identification of the BRCA-1 gene. Dr. Broder explained that it is hoped that by issuing an RFA through such a highly targeted approach, the gene will be identified in a shorter period of time.

Dr. Salmon asked Dr. Broder what type of research project grant is being requested for the RFA (i.e., R01, P01, cooperative agreement). Dr. Broder explained that a P01 was originally requested; however, the Division of Research Grants at NIH stated that the BRCA-1 gene RFA could not be issued as a P01. Therefore, the RFA will request an R01 as its funding mechanism. Dr. Marks noted that NCI is hoping that by issuing the RFA, new collaborations among groups of investigators will emerge. The maximum direct costs allowed for a single

grant proposal is $1.4 million, thus encouraging investigators to associate and collaborate with each other and merge their resources toward one cause.

Dr. Broder responded to a comment made by Dr. Correa concerning the identification of the BRCA-1 gene by a nongrantee, indicating that NCI will not renew the grant if that situation occurs. Dr. Broder also noted that if a grantee identifies the gene and this scientific finding is confirmed, the grant will be terminated. The sequencing of the gene is valid in its own right; thus, this aspect of the RFA might continue to be the driving force for further investigations.

XVI. POSITRON EMISSION TOMOGRAPHY (PET)—DR. RICHARD L. WAHL

Dr. Chabner introduced Dr. Richard Wahl, professor of radiology and internal medicine and head of the nuclear medicine group at the University of Michigan, to speak on the topic of positron emission tomography (PET) and its applications, particularly in breast cancer.

Dr. Wahl began by reviewing the physical properties of positrons, explaining that they are positively charged electrons emitted from the nucleus of a proton-rich radioisotope. Positrons have a very short range in tissue (in millimeters), and cannot be noninvasively imaged. Dr. Wahl explained that a positron interacts with an electron, which has an opposite charge and identical mass, which annihilates the positron; in essence, the positron is antimatter that interacts with matter and then quickly decays away. As this occurs, two 511 KeV photons are emitted that travel in opposite directions. These positron, Dr. Wahl continued, can be detected by a special device known as a PET, or positron emission tomographic scanner.

Dr. Wahl said that PET scanners look very similar to computerized tomography (CT) scanners. The patient lies in a bed that is then placed into the gantry. He stated that many of the original PET scanners were head-only devices; however, the most modern scanners have large apertures through which the entire patient may be placed. Dr. Wahl stated that this has opened new opportunities for oncologic imaging of the entire body.

Dr. Wahl explained that due to the very short half-lives of most positron emitters, the PET scanner must be located in reasonably close proximity to a medical cyclotron. He stated, however, that the 110-minute half-life of the positron emitter fluorine-18 makes the regional delivery of F-18-labeled compounds to PET scanning centers without on-site cyclotrons possible, and this procedure is now occurring at multiple urban centers. It would be possible, therefore, to accomplish this type of fluorine-18 PET scanning without an on-site cyclotron.

Dr. Wahl stated that imaging modalities proliferate constantly, and posed the question of why it is necessary to have PET scanning when CT, MRI (magnetic resonance imaging), ultrasound, and other imaging methods already exist. PET, he then explained, has several unique advantages over the other imaging methods. The radioisotopes used as emitters, including oxygen, nitrogen, carbon, and fluorine, are parts of important molecules found in the body routinely, and are different from other radionuclides. PET images tumor physiology rather than anatomy, allowing the opportunity to quantitatively assess metabolism in tumor and normal tissue. PET scanners are also very sensitive compared with other nuclear medicine cameras, and this higher sensitivity allows for detection of very small tumor foci not detected by other methods.

This higher sensitivity, Dr. Wahl continued, is accomplished through PET's use of electronic collimation. The two 511 KeV photons that are emitted define a line on which the radioactive decay occurred and which is defined by coincidence circuitry electronics. Electronic collimation means there is very little lead used in a PET scanner, thereby increasing sensitivity. The electronics and computer determine where the radioactive disintegration occurred and, thus, achieve the higher sensitivity with excellent subcentimeter resolution.

Dr. Wahl stated that the resolution of PET scanners has improved, and that scanners with 3- to 4-millimeter resolution are now available in contrast to those that were available a few years ago. Dr. Wahl explained that the combination of high sensitivity and high resolution leads to the possibility of detecting smaller tumor foci than with standard imaging methods.

Dr. Wahl discussed some of the limitations of standard imaging methods, stating that these imaging methods are largely based on anatomy. He used the example of lymph node metastases, which are detected on CT or MRI scans based on size. In general, Dr. Wahl explained, a radiologist might say that if a lymph node is over 1 centimeter in size in a patient with cancer, it would be considered suspicious for tumor, and if the lymph node is less than 1 centimeter in size it would be considered normal. This determination based on size can result in poor accuracy, causing both false-positive and false-negative interpretations of CT or MRI for the presence of nodal tumor metastases. Similarly, Dr. Wahl stated, distinguishing scar tissue verses viable cancer after treatment for a cancer can be quite difficult, and detecting a small tumor foci is a challenge for current anatomic imaging methods. Predicting responses to therapy can also be difficult using standard imaging methods, and a noninvasive mode of predicting tumor response would be most useful. The postoperative status of some patients also makes standard tumor imaging difficult, since normal anatomy is sometimes distorted and clips can degrade CT and MRI images.

Dr. Wahl stated that PET offers opportunities in all of these areas, both for research and for clinical application. He indicated that one of the reasons PET can be used in cancer diagnosis is related to the most commonly used tracer, an isotope of glucose. Altered glucose metabolism in cancer has been known for a long time, since Dr. Warburg in the 1920's realized that glycolytic rates were often increased in cancers. Most of Dr. Warburg's work was based on animal tumors; however, this same general finding has more recently been demonstrated in human brain tumors and human tumor xenografts of a wide variety of histologies.

Referring to data from his laboratory related to fluorodeoxyglucose (FDG) uptake into human tumor xenografts, Dr. Wahl reported that in autoradiographic studies, FDG uptake occurred in viable cancer cells. In tissue culture, FDG uptake was proportional to the number of living cancer cells. Dr. Wahl showed a slide that demonstrated some of his data, which were published several years ago in *Cancer*. Dr. Wahl explained that his data represent tumor-blood ratios, which are the amounts of radioactivity present in the tumor relative to the concentration in the blood. He explained that the range includes tumor-blood ratios from 6 to 1 to over 20 to 1. Dr. Wahl discussed graphs of tumor types including lung cancer, colon cancer, lymphoma, ovarian cancer, and melanoma—the relatively common histology tumors. He stated that the xenografts of these tumors have high fluorodeoxyglucose uptake. Fluorodeoxyglucose is the fluorine-18 analogue of 2-deoxyglucose.

PET, Dr. Wahl explained, can be used in two ways in oncology. In research, PET is used in measuring tumor blood flow, vascular permeability, cell proliferative rates using labeled thymidine, DNA synthesis, metabolic rates, drug delivery, and, potentially, measuring receptor expression with fluorine-labeled estradiol and other agents. Dr. Wahl stated that chemotherapeutic agents can also be labeled and imaged. The second use of PET, Dr. Wahl

mentioned, are more direct clinical applications that involve detecting tumor, characterizing masses, staging tumor, and monitoring treatment.

PET was initially used in tumor imaging at NIH. Dr. Giovanni DiChiro and others had extensive experience in brain tumor imaging, and showed that high glucose utilization is quite common in aggressive brain tumors and that, generally, glucose utilization declines with effective treatment. Dr. Wahl stated that the fluorodeoxyglucose method was developed in part through Dr. Louis Sokolov's efforts at NIH, along with collaborators from Brookhaven (Dr. Wolf and others) and the University of Pennsylvania (Dr. Kuhl). The first FDG scans were done in 1976, and over 300,000 doses have been given to patients across the world since then.

Dr. Wahl began a discussion of brain tumor imaging, using slides to review some of the tumors that have been assessed with PET. At the initial assessment of the tumor, PET can estimate the degree of tumor aggressiveness and help physicians plan biopsy sites. Dr. Wahl indicated that the most common use of PET occurs after treatment, to determine if there is residual tumor, versus tumor necrosis induced by radiation. CT and MRI often show contrast-enhancing lesions, and it is difficult to determine whether this represents a viable tumor or a scar. Dr. Wahl showed an example of an FDG scan of the brain showing an intense uptake of FDG and residual tumor. He contrasted this scan with another scan of a lesion that showed contrast enhancement on CT, but no FDG uptake. Next, Dr. Wahl showed a slide of a scar as seen in a scan. He mentioned that several studies have shown an excellent, though not perfect, predictability of FDG PET in terms of separating viable tumor and scar tissue. Dr. Wahl stated that results are better for higher-grade tumors than lower-grade tumors. He added that many insurers will pay for FDG PET scans of the brain, including CHAMPUS, a Government agency.

In regard to breast cancer, Dr. Wahl said that his group has been able to show increased uptake of fluorodeoxyglucose in breast cancers *in vitro* and in animals, and that FDG uptake, the radiolabeled glucose analogue, is inversely related to serum glucose levels.

Dr. Wahl mentioned that his group has also been able to show that part of the mechanism of this increased glucose uptake is due to overexpression of the glucose transporter-1 molecule, shown in results of immunohistochemical studies. He found these results to be consistent, at least in 12 patients that he and colleagues initially reported with an alteration in breast cancer (i.e., the alteration of glucose transporter-1), which contrasts with normal breast tissue. Dr. Wahl stated that this is part of the mechanism for increased FDG uptake in these tumors.

In addition to the known problems with therapy related to breast cancer, Dr. Wahl said there are also diagnostic issues. He stated that detecting primary lesions is problematic, particularly in younger women, and determining the presence of regional nodal metastases currently is answered only by a surgical approach. Determining the presence of systemic metastases is sometimes a challenge as well as determining the efficacy of treatment. Silicone implants also represent a diagnostic dilemma in breast cancer for mammography because the low-energy x-rays do not effectively pass through the implants. Dr. Wahl stated that PET has been applied in each of these clinical situations to some extent, although the data, while encouraging, are fairly preliminary.

A slide was then presented of a mammogram of a breast cancer and PET, which showed increased FDG uptake in the lesion. Dr. Wahl showed other slides, including results from liver. He showed a slide of a normal breast, indicating that although it was mammographically dense, the patient had complaints regarding the particular breast. On PET scan, Dr. Wahl indicated intense fluorodeoxyglucose uptake throughout this entire left breast,

whereas the right breast had low levels of FDG uptake. Dr. Wahl stated that the breast shown was diffusely infiltrated with carcinoma.

Dr. Wahl then discussed detection of axillary nodal metastases, explaining that detecting these with PET is quite possible. He showed a slide of axillary nodal metastases 1 hour after tracer injection, and another from a patient who had enlarged nodes clinically but had a negative PET scan.

Internal mammary nodes, Dr. Wahl continued, are not normally sampled surgically, but they can be detected by PET. A slide was shown of an internal mammary node in a patient with breast cancer. Dr. Wahl stated that this patient also had a positive axillary node, but that the internal mammary nodes can be involved with tumor when the axilla is uninvolved with tumor and are difficult to detect by any other method. Dr. Wahl stated that these interal mammary tumors are of comparable prognostic significance to tumors in axillary nodes, but are not assessed when a patient is diagnosed with breast cancer.

Systemic metastases can also be detected by PET. Dr. Wahl presented a slide of an axillary nodal metastasis and a bone metastasis in a woman who presented with a large primary lesion. Dr. Wahl explained that whole-body displays are becoming possible through work at the University of California in Los Angeles, where scans of larger segments of the body have revealed bony metastases in a variety of locations. Dr. Wahl added that in his initial study, 25 out of 25 known breast cancer lesions were detected using PET, including primary tumors, regional nodal metastases, and axillary nodal metastases.

Dr. Wahl mentioned that preliminary data on detecting lymph node metastases have shown sensitivities in the 80 percent range, although the studies are very small at this time. He added, however, that the specificity appears to be higher. PET has been used to separate malignant from benign breast lesions, but the data are limited and mainly show lesions of over 1 centimeter in size. Accuracies in excess of 90 percent have been reported; however, again, the studies are small in patient numbers.

Dr. Wahl then discussed treatment response, reiterating that FDG uptake is partially related to the number of living cancer cells. Dr. Wahl pointed to figures from *in vitro* studies showing amount of fluorodeoxyglucose uptake as related to the number of living cancer cells. He stated that if this is a valid relationship *in vivo*, fluorodeoxyglucose might be an excellent marker for assessing treatment response. Dr. Wahl discussed his findings in a small group of patients with newly diagnosed primary breast cancer that were recently published in the *Journal of Clinical Oncology*. He explained that patients with newly diagnosed large-diameter breast cancers received a multiagent treatment regimen, with sequential PET scans performed prior to therapy and during therapy at 8, 21, 42, and 63 days after treatment. Early after treatment was initiated, there was no change in the anatomic (mammographic) appearance of the breast cancer in many patients. With PET, however, rapid declines were apparent in fluorodeoxyglucose uptake and, in this series, the metabolic changes antedated the changes in tumor size substantially.

Dr. Wahl explained that those who responded among this small series of 11 patients had a quantitative and significant decline in glucose uptake. In responders, FDG uptake fell about 50 percent to background levels after 63 days of treatment while nonresponders did not have a significant decline. Dr. Wahl stated that treatment was continued and response was assessed by biopsy 6 months later. He referred to what he called early scintigraphic findings on PET predicting, or at least correlating with, the longer-term response in these patients. Dr. Wahl added that these findings need additional confirmation among larger groups of patients.

Another project currently under way in Dr. Wahl's group involves anatometabolic imaging, which combines tumor anatomy with metabolism. Dr. Wahl pointed to a spot on a slide that looked like a nodal metastasis, but which on fusion images with MRI could be seen to be activity within a rib lesion. It is thus possible to precisely localize some of these foci of increased fluorodeoxyglucose uptake as seen on anatomic studies, which, Dr. Wahl observed, may be important for PET-directed biopsies.

Dr. Wahl then discussed the use of PET in lung cancer, noting that approximately 45 percent of patients who do not have nodal metastases to the mediastinum survive for 5 years after diagnosis and surgical therapy. He stated that, unfortunately, this is a relatively small group of patients as most present with nodal metastases to the mediastinum. Therefore, Dr. Wahl continued, if a group of people could be identified whose survival is in the zero range, there would be a reasonable survival in that smaller population.

Dr. Wahl stated that the methods for assessing these findings are not very good. He explained that the prospective radiology diagnostic oncology group (RDOG) study showed only about a 50 to 55 percent sensitivity of CT or MRI in terms of detecting nodal metastases, and that the specificity was not much better. With PET, however, in over 200 patients in a variety of institutions, an increase in radio-glucose uptake has been demonstrated in untreated primary lung cancers. Dr. Wahl commented on a slide of a lung cancer patient with a collapsed lung in which there was reasonably good demarcation between benign and malignant pulmonary lesions. He stated that the data from Duke University and elsewhere show that the lesions in the lung that have high FDG uptake are malignant and that there is very little overlap between malignant and benign lesions.

Dr. Wahl's group recently addressed the question, in preliminary form, of whether it is possible to accurately stage the mediastinum using PET. Using anatometabolic fusion images, they have been able to show that nodes with high FDG uptake are most often cancer. Dr. Wahl stated that this is not surprising. He then showed another slide of a case with a large node that he considered to be abnormal, 14 to 15 millimeters in size, with no FDG uptake. Dr. Wahl stated that in each of seven such instances, the patient had no tumor involvement in the mediastinum, which was displayed as a false-positive CT, and a true-negative PET.

Another slide was presented of a CT of the thorax in a patient with newly diagnosed lung cancer showing normal-sized lymph nodes, with increased nodal FDG uptake and tumor involvement, which Dr. Wahl said has shown quite reliable prediction of mediastinal cancer prevalence. Another slide presented preliminary data recently published in *Radiology* from a prospective study of 23 patients with newly-diagnosed lung cancer in which PET was found to be significantly more accurate than CT in staging the mediastinum. Dr. Wahl remarked that although further follow-up is required, these are intriguing preliminary data, suggesting PET to be the imaging method of choice for mediastinal cancer staging.

Dr. Wahl then shifted his discussion to other diseases in which PET has been applied. In lymphoma, PET appears to be able to image all grades of lymphoma and to detect tumor in some instances in normal-sized lymph nodes. For example, Dr. Wahl presented a slide of a patient with obviously enlarged lymph nodes, but who also had a normal-sized supraclavicular lymph node. In a PET scan image from the same patient, Dr. Wahl pointed to tumors in the lymph nodes and commented that increased FDG uptake could be observed in all lymph nodes. He explained that this patient had low-grade non-Hodgkin's lymphoma, which is difficult to image with gallium scanning. Because of these findings, Dr. Wahl believes that PET has substantial potential for use in patients with non-Hodgkin's lymphoma. Another slide was presented showing uptake in splenic lymphoma, which Dr. Wahl said can be difficult to assess by other methods.

PET has also been used to follow up cancer treatments. Dr. Wahl displayed results from a patient that he and Dr. Mark S. Kaminski treated with I-131 anti-B1 radioimmunotherapy, showing a large tumor before treatment with a small residual mass after treatment. Dr. Wahl stated that discerning whether these residual foci are alive or dead after treatment can be a challenge that often requires biopsy, or at least follow-up, and that PET may offer potential in this situation.

Another slide showed a patient who had extensive lymphoma deposits pre-radioimmunotherapy, in which PET allowed investigators to see that the glucose metabolism in the deposits disappeared totally with the anti-B1 radioimmunotherapy. Dr. Wahl stated that this work was discussed at a recent meeting of the National Cancer Advisory Board and that the response rate has been about 80 to 85 percent in the patients treated as part of this trial.

Dr. Wahl then mentioned prior data from the nude mouse human tumor xenograft animal model, in which melanoma had the highest rate of fluorodeoxyglucose uptake of any tumor. He added that the animal model has been fairly predictive of results in patients and, in fact, has been predictive of the behavior of melanoma.

Using PET, Dr. Wahl's group has been able to find, tumor in normal-sized lymph nodes, and they have been able to find enlarged lymph nodes clinically, which on PET scan and histology are negative. He stated that his results to date, which were recently published in the *Journal of Nuclear Medicine*, have been 100 percent accurate, but he cautioned that these results are very limited.

Dr. Wahl then discussed a slide of a CT scan in which a single abnormal lesion was found. The FDG PET scan in this instance, however, showed an obvious pattern of three spots of cancer involvement 1 hour after tracer injection (two not appreciated initially on CT). Dr. Wahl stated that his group is trying to assess the overall utilization of PET in melanoma.

Dr. Wahl remarked that ovarian cancer also has increased glucose utilization, at least in the animal model. Because CT is not a very reliable test for assessing ovarian carcinoma, it is feasible to image this disease using PET. In a slide of ovarian carcinoma, he pointed out glucose uptake in a peripheral pattern along the peritoneal cavity. Dr. Wahl stated that in initial studies, the uptake of fluorodeoxyglucose is significantly (approximately four times) higher than that of normal gut, but that more study is needed.

In colorectal carcinoma, which has been evaluated by several groups, PET appears to be a reasonably reliable means to separate posttreatment fibrosis from residual tumor in patients with a history of colorectal carcinoma and radiation therapy. Dr. Wahl added, however, that the overall sensitivity of PET in colorectal carcinoma staging is unknown.

Dr. Wahl stated that head and neck cancers have been studied by investigators at UCLA and in Finland, and that PET has shown promise in staging these cancers. PET may also be useful in postoperative assessments in these cases, because of the commonly distorted anatomy among head and neck cancer patients. Dr. Wahl added that a small group of musculoskeletal tumors was studied at the NCI several years ago, and evidence now suggests that the intensity of fluorodeoxyglucose uptake can predict whether these tumors are malignant or benign.

PET, Dr. Wahl observed, appears to be emerging as an imaging method that surgical and medical oncologists prefer to have available for brain tumors, lung cancer, and selected melanoma and lymphoma cases. Its use is clearly under study in other diseases as well. For example, genitourinary cancers are being studied using PET. Because fluorodeoxyglucose is

excreted in the urine, Dr. Wahl explained, evaluation of the kidneys and pelvis is challenging, particularly for prostate cancer. He added that, while experience to date is limited, PET appears less promising in prostate cancer than in some of the other tumors.

Dr. Wahl showed a slide of bladder cancer metastatic to the lungs in which fluorodeoxyglucose uptake was over 30 times higher in these lesions than in normal lung background tissue. Dr. Wahl noted the detection of a 6-millimeter pulmonary lesion on the slide.

In addition to questions related to clinical research and efficacy, research questions remain that are related to more fundamental cancer biology. Dr. Wahl stated that some examples include studies of drug delivery, blood flow, tumor oxygenation, tumor proliferation, tumor metabolism using a variety of energy substrates, and prognosis. Dr. Wahl asserted that there are probably many other research areas, including evaluation of receptor molecules on tumors.

Researchers at Washington University in St. Louis have used fluoroestradiol compounds to image estrogen receptors and breast cancers, and have been able to separate estrogen receptor-positive and -negative tumors from one another. They have also made attempts to assess therapy in terms of the efficacy of estrogen blockade with antiestrogens. Dr. Wahl remarked that this is an interesting area of research.

Dr. Wahl then discussed research done by his group in the area of tumor blood flow. He stated that a radio-copper agent has been used that is actually made from a radioactive generator as opposed to the cyclotron; therefore, the radio-copper potentially could be available at multiple institutions. Dr. Wahl presented a slide of a PET scan showing blood flow to a breast cancer, noting that the blood flow is alternatively measured by O_{15} water, which requires cyclotron availability.

Dr. Wahl then commented on the potential availability of PET as a research or clinical tool in the United States. He noted that there are some major problems facing this technology, the most notable of which are the real and perceived costs of the methodology. He stated that there is fear of investing in a new imaging modality when major changes in health care delivery are rapidly occurring. Dr. Wahl stated that most providers are not sure whether they are able to pay for standard imaging tests, let alone new procedures such as PET. He added that, currently, there are about 60 PET scanners in the United States, many of which are of low resolution or are devoted head units and, therefore, are not specifically applicable to visceral imaging.

Another problem relates to limited reimbursement. Dr. Wahl disclosed that while many insurers pay for PET scanning, many others do not. There also exists a sort of regulatory gridlock, in that FDA is somewhat uncertain as to how to handle PET tracers. Dr. Wahl then posed the question of whether a new drug application needs to be filed at every site, or whether a compound such as fluorodeoxyglucose can be used as a drug under the practice of pharmacy. Dr. Wahl stated that this is a gray area and that, so far, the Federal Health Care Finance Administration (HCFA) does not reimburse for PET studies of any type, including brain tumors, despite the fact that other Governmental agencies, including the Veterans' Administration and CHAMPUS, pay for these studies.

Dr. Wahl commented that dissemination of the PET method has slowed somewhat because of an uncertainty regarding reimbursement. He stated that many in the field, including himself, feel that the FDA should allow PET tracers to be made available under the practice of medicine and pharmacy, using individual State regulations, the rationale being that the PET

tracers are very safe and trace normal biologic molecules. Dr. Wahl observed that the precedent for this exists in the use of other compounded medications, and that HCFA or other agencies could then perform a formal efficacy assessment of the PET technology.

An NCI-sponsored workshop was held approximately 1 year ago that addressed the use of PET in oncology, from which a summary statement was issued. Dr. Wahl explained that the consesus expressed in this statement was that multicenter prospective trials should be initiated in lung and breast cancers because of the promising data for those conditions. Head and neck cancers, in addition to ovarian cancer, were also discussed.

Dr. Wahl concluded his presentation by expressing his appreciation for NCI and NIH support of his research that has included clinical studies of a limited size. Dr. Wahl commented that PET technology appears to be promising and should have a growing role in clinical cancer imaging as well as in the study of more fundamental oncologic questions.

Questions and Answers

Dr. Wilson complemented Dr. Wahl on his presentation and stated that he had highlighted two problems—cost and availability. Dr. Wilson stated that he has found PET to be invaluable in differentiating radiation necrosis from recurrent tumor in the postoperative patient. He emphasized that judging the efficacy of any further treatment is a pivotal decision and that he is able to utilize PET only because he is part of a large program project. Otherwise, he said, he considers it unthinkable that the average person could afford the PET procedure.

Dr. Wilson also mentioned that the insurance companies at this time, including HMOs and similar organizations, are not persuaded that they should support PET. He expressed his belief that this feeling is justified and, therefore, it is up to the National Cancer Advisory Board of the NCI to support PET for cancer-related studies. Dr. Wilson added that it appears that as magnetic resonance imaging is developed, it may be shown to yield similar findings as PET; however, he cautioned that this has yet to be shown.

Dr. Wahl responded that the insurance issue is highly variable. He cited as an example Blue Cross/Blue Shield of Michigan, which pays for PET scans for brain tumors following treatment; payment, however, depends upon the specifics of the policy. Dr. Wahl stated that some companies believe PET is reasonable, but that it is an option that is negotiable on the part of the organization, which can choose to include or delete it as an option. Some insurers do pay for these procedures on a case-by-case basis, but it is highly variable.

Dr. Bragg then asked Dr. Wahl to comment on the market tending to suggest the availability of PET scanners without the cyclotron in transporting the isotopes appropriate for utilization, thereby significantly reducing the cost of acquisition of systems and making them more reasonably available. He also asked Dr. Wahl to comment on the sensitivity and specificity of single photon thallium scans, which are widely available, in separating radionecrosis from viable tumor, as opposed to PET. Dr. Bragg asked specifically how the two procedures compare in terms of accuracy.

Dr. Wahl responded, first, that because of competition in the PET marketplace, the cost of PET scanners has dropped from $2.5 million to about $1 million. Dr. Wahl added that many of these scanners are perfectly adequate, and concluded that the cost of acquiring PET scanners is falling into the range of other high-technology imaging devices such as MRI and CT.

Dr. Wahl then discussed the acquisition of radioisotopes. He explained that his earlier point about the 110-minute half-life of F18 is that this length of time is long enough so that the tracer can be regionally distributed. Therefore, if there is a cyclotron in a city or metropolitan area, it is possible that the tracer can be shipped some distance, for example from Phoenix to Tucson. PET scanners could be located in centers that do not have cyclotrons on site and still offer fluorodeoxyglucose imaging. Dr. Wahl said he believes this will be the evolution of the methodology from a clinical standpoint.

At present, each dose of FDG costs approximately $500, as a radiopharmaceutical cost, which is approximately 40 to 50 percent of that charged for commercially available monoclonal antibodies. Dr. Wahl believes that in this respect, PET is cost-competitive.

Dr. Wahl mentioned thallium and SPECT scanners, and noted that direct comparative studies in the brain are limited, but thallium appears to be a fairly good substitute for FDG in scans of brain tumors. The resolution of SPECT scanners is not as good as PET, and in general the results are not as good as with fluorodeoxyglucose. He added, however, that the results with thallium are better than those achieved with CT or MRI only. Large, comparative studies of the various technologies have not been done, but should be, Dr. Wahl continued. He stated that, based on his knowledge of the public literature, the use of thallium SPECT in tumors outside of the central nervous system generally is much less effective than FDG PET.

Dr. Wahl reported that his group has also evaluated FDG SPECT and the possibility of modifying commercially available gamma cameras that can be found in most hospitals with at least 60 beds. The cameras can be modified by placing very thick lead collimators on their crystals, so that the high-energy photons of F18 may be imaged. Unfortunately, Dr. Wahl continued, this process does not work very well. The sensitivity is about one-twentieth that of a PET scanner, and the resolution is about one-fourth as good. This is equivalent to being able to detect, in some instances, a tumor the size of a grapefruit, which does not represent a very advanced medical technique. Dr. Wahl observed that patients deserve to have their tumors found when the tumors are small.

Dr. Chan asked Dr. Wahl whether anyone has compared the FDG technique using F19 MRI versus the PET scan for imaging.

Dr. Wahl replied that he believes studies have been done in animals. He stated that one can trace F19 or F18, and that the choice of tracer does not make much difference in following the deoxyglucose; however, the resolution and sensitivity of the F19 compound is not as good as F-18 FDG PET, and a large amount of F19 is needed. Dr. Wahl added that if one switches from using tracer FDG to using nontracer quantities of FDG, high doses of F18 or high doses of fluorodeoxyglucose are actually an anticancer agent, and safety at very high doses may become an issue.

In regard to perceived cost, Dr. Salmon commented that money will be saved for the patient if only one imaging study can be performed that can successfully determine whether disease is present or not. He then asked whether there is any way that NCI can participate in evaluating the technology in such a way that it can be placed into perspective in terms of the care and diagnosis of cancer patients.

Dr. Wahl asked Dr. Shtern to respond and comment on the results of a workshop that was recently held. Dr. Shtern stated that one cannot compare MRI or PET costs with those of other modalities without looking at the impact of increased use of modalities on the quality of care, specifically in the context of management of care. Dr. Shtern stated that Dr. Wahl has demonstrated that PET can identify lymph node metastatic disease in connection with lung cancer that cannot be shown with any other modality with a great degree of sensitivity. This

procedure, Dr. Shtern stated, can prevent unnecessary surgery, which may be 10 or 20 times more expensive than the original PET study.

Dr. Shtern added that another important ability of PET, as Dr. Wahl demonstrated, is the detection of internal mammary lymph nodes with breast cancer. Dr. Shtern stated that no other imaging modality can do this yet, until the lymph nodes are very large. The bottom line, Dr. Shtern concluded, is that a technology assessment study is needed and it will be important to evaluate the cost-effectiveness of PET within the context of cancer management. Dr. Shtern added that an NIH workshop was held about 1 year ago, at which the panel unanimously agreed that the most interesting areas of investigation for clinical relation of PET and cost-effectiveness are breast cancer and lung cancer.

Dr. Freeman stated that a problem with breast cancer, particularly among women between ages 40 and 50, is the density of the breast leading to inaccuracy in the mammogram. He raised a second point about the frequency of breast cancer among women under 50 years of age. He asked about the cost-effectiveness potential for PET scanning in the dense breast tissue of younger women, who should not be screened according to current NCI guidelines.

Dr. Wahl replied that not enough data are available yet that evaluate small primary lesions, even in older women who have more fat in involved breast tissue. PET, however, is clearly less impaired by breast density than is mammography. There is, however, increased glucose utilization in the breasts of young women compared with older women, which can be measured in the normal breast and has been shown to decrease with age, falling approximately 50 percent between age 30 and age 70. Dr. Wahl stated that there is some background increase in glucose utilization in very young women. In his group's initial report on PET and breast cancer, Dr. Wahl said there were two individuals in whom the mammograms were such that the breasts were very dense and the primary tumors were not visible except by using PET.

Dr. Wahl addressed the cost-effectiveness issue, stating that better data on efficacy are needed first, and then an understanding of the prevalence of the disease in the patient group studied to complete such an analysis. He speculated that PET may have a role in very-high-risk groups of women.

Dr. Bragg asked Dr. Wahl whether, using current technology views, it is feasible to assume that PET would serve some type of screening role. Dr. Wahl replied by agreeing with Dr. Bragg that there ultimately may be a screening role for PET in high-risk patients; however, he cautioned that there is a current perception that the procedure is too expensive to perform even in patients with disease. Dr. Wahl stated that he hopes this perception will change as cost-effectiveness data emerge.

Dr. Calabresi thanked Dr. Wahl for a very interesting presentation.

XVII. SUBCOMMITTEE REPORTS

Environmental Carcinogenesis and Women's Health and Cancer

Dr. Becker began by thanking Dr. Adamson for his vital contributions to the activities of the Subcommittee and cited his expertise in the field, his ability to define crucial target areas, and his instrumental aid in locating expert contacts, often at the last minute.

Before describing Dr. Jerry Rice's presentation on the antigen bacteria *Helicobacter hepaticum*, Dr. Becker offered some background information. At the September 1993 NCAB meeting, Dr. Rice reported on an outbreak of a species of this unusual bacteria type. At that time, *Helicobacter* had been found to spontaneously produce a destructive hepatitis in a colony of C3H mice, resulting in malignant tumors, or hepatomas, in the liver of this strain of mice, which had not previously shown the hepatitis or the hepatomas. Updating the Subcommittee, Dr. Rice reported on current efforts with antibiotics that are eliminating the infection in this strain of mice and, it is hoped, will be a dependable prophylactic against tumor.

Dr. Pelayo Correa, the second speaker, reported on evidence of the involvement of *Helicobacter pylori* bacteria in human atrophic gastritis and both forms of peptic ulcer, as well as a putative effect on the genesis of human cancer of the stomach. Dr. Correa reported on the potential for an anticancer regimen by clearing suspect and known populations of the bacteria. He described the physiologic adaptation by which the bacteria survive in the highly acidic environment of the stomach. Living close to the margins of cells, the bacteria produce a urease to create a cloud of ammonia, which neutralizes gastric acid.

The final presentation was given by Dr. James Fox of MIT. Dr. Fox, a leading expert on the taxonomy of the *Helicobacter* bacteria, has linked it to disease in a large number of animal species using 16 ribosome mapping techniques. Possible animal reservoirs for this particular bacteria were indicated by Dr. Fox, one of the most interesting being the domestic cat. Dr. Becker emphasized the need for the scientific community to remain open-minded to new etiologic agents and the ramifications of infectious disease in human cancer. Dr. Broder suggested the possibility of initiating a bacterial cancer program analogous to the viral cancer program.

Dr. Bettinghaus noted that although taxonomy is perceived as a virtually exhausted area of study, many new species are being identified in a very short period of time. He suggested that college-level education may be lacking in this area.

Information and Cancer Control

Ms. Marlene Malek reported that the Subcommittee on Information and Cancer Control discussed the concept review for an extension of the Cancer Prevention Awareness at Black Colleges Resource Program. Delays in securing OMB approval of a survey instrument for one of the contracts have resulted in the need to request additional funds to complete the outlined statement of work. Subcommittee members unanimously approved the concept.

Ms. Malek reported that 20 of the 26 Regional Breast Cancer Education Summits scheduled for 1993-1994 have been held and are proving successful in reaching business and community leaders to provide information on breast cancer screening and education programs. She announced that the summits have also been outstanding in reaching minority and medically underserved women and will serve as interesting models for future activities. Local American Cancer Society leaders have played an important role in planning and funding each of the summits, Ms. Malek added.

Dr. Edward Sondik reported at the meeting on progress with the Healthy People 2000 National Health Promotion and Disease Prevention Objectives. This review for cancer progress was part of a larger review being conducted by the Assistant Secretary for Health, Dr. Philip Lee, for the entire DHHS. Dr. Sondik explained to the Subcommittee that the review is one of many strategies used to ensure that cancer control information is being applied across the nation. On May 19, 1994, Dr. Sondik presented the progress review on cancer to the Assistant Secretary, at which time community and voluntary organizations offered their perspectives on progress in cancer prevention and control. Dr. Sondik said the May 19th

review was a detailed, though not comprehensive, overview of activities directed toward meeting the Healthy People 2000 Objectives.

Ms. Malek stated that Dr. Sondik then reviewed mammography use, which has increased; smoking rates; and nutrition. Data revealed that further effort must be directed to the area of smoking among children.

During the next several meetings, Ms. Malek concluded, the Subcommittee will take an in-depth look at progress in meeting specific Healthy People 2000 goals such as the antitobacco objective. The Subcommittee, she added, has agreed to invite representatives from community and voluntary organizations to attend the reviews and share their perspectives.

Special Priorities

Ms. Deborah Mayer reported that the first combined meeting of the subcommittees dealing with aging, minorities, and women was held May 31, 1994. Ms. Valerie Setlow from the Institute of Medicine presented the report of an IOM study commissioned by NIH. The report, entitled "Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies," was described by Ms. Mayer as a "different and interesting discussion of the intent behind legislation, as opposed to the letter of the law." It also introduced issues that the Subcommittee may want to consider for discussion at future meetings, Ms. Mayer noted. Justice was a central focus in regard to ethical principles underpinning participation in clinical studies. Participant accrual, urged Ms. Mayer, should be based on an inclusionary, rather than exclusionary, model—everyone should be included unless there is sound justification to do otherwise.

Dr. Sondik, Acting Deputy Director, NCI, and Dr Robert Smith, American Cancer Society, reviewed a draft of a statement of areas of agreement between the NCI and the American Cancer Society regarding breast cancer screening. Subcommittee members were invited to submit comments to Dr. Sondik. Ms. Mayer expressed enthusiasm concerning the intent of the statement, as well as the opportunity to see it in its formative stages and obtain members' comments and feedback.

The final discussion concerned the meta-analysis of breast-sparing surgery versus mastectomy and comparable survival rates within the NSABP data.

Dr. Calabresi thanked Ms. Mayer for her efforts in bringing together the former three subcommittees.

Dr. Sondik asked that the Board also review and comment on a proposed statement on breast cancer screening drafted by Dr. Janet Osuch. He reported that NCI would work with other interested parties to create a single statement on the mammography screening issue after consideration of various proposals, including Dr. Osuch's draft and the upcoming revision of the Preventive Services Task Force report. Dr. Broder suggested that Dr. Osuch's statement be discussed at the next NCAB meeting, in October 1994.

Clinical Investigations Task Force

Dr. Calabresi began by stating that the Clinical Investigations Task Force has been renamed the Clinical Investigation Task Committee. He explained that it combines task forces on translational research and clinical trials, and is chaired by Dr. Sam Wells, while Dr. Chabner serves as the executive secretary. Chairmen from three of the six clinical trials

groups attended the meeting, including Dr. Jim Fox from ROTG, Dr. Douglas Tormey from ECOG, and Dr. Ron Heberman from NSABP.

Dr. Salmon asked for clarification on the scope of action regarding the non-NSABP groups and an estimate of the increased costs of the new monitoring procedures. Dr. Chabner estimated the previous budget for quality assurance at approximately $1.5 million by CTEP and an additional $1 million by all the cooperative groups, which is about 1 percent of the cooperative group budget. An increase of about $2 million is proposed for additional monitoring requirements for the NSABP, Dr. Chabner added. He explained that without Congressional approval, this increment cannot be taken from the current NSABP budget and must, therefore, be reprogrammed from other DCT budget requirements.

Dr. Calabresi reported that several members of the subcommittee questioned why other groups with excellent records for auditing and other quality assurance measures should be penalized by having to implement stricter auditing procedures. Ms. Visco expressed concern that the committee not be sidetracked by complaints from the groups and lose focus on the important issues of protecting and reassuring women and reestablishing public trust. Dr. Chabner stressed that in order for clinical trials to survive, all patients must be confident that the process is clean and reliable, and asked whether the group chairs agreed that certain standards for acceptable audits should be set for all clinical trials groups. Dr. Salmon expressed his opinion that standards should be established, but that each group should be completely responsible for the audit, having some flexibility to maintain minimum standards. Ms. Visco added that there should be minimal common standards for auditing and more stringent criteria for a given group, if desired, and stressed that the public will respond better to a monitoring process outside of NCI. She recommended holding a day of dialogue between clinical scientists and patient groups to inform patients on the process and to hear their concerns. Dr. Calabresi noted that this concept was previously considered and discussed as a possibility for a President's Cancer Panel program. Dr. Freeman stated during the meeting that he will speak with Dr. Broder about the usefulness of this forum.

Dr. Calabresi reported that Dr. Broder told the group that since the necessary initial actions have been accomplished, the clinical trials process is "fundamentally healthy." He reminded Subcommittee members that although cooperative group trials are science driven, their results can play an important role in the Federal regulatory process, and, therefore, action is taken to assure the public that the integrity of the processes is critical. Dr. Broder stressed that actions in response to misconduct regarding the NSABP are specific to the NSABP and should not be seen as predictors of future action.

Questions and Answers

Dr. Sigal rejected the concept of furthering efforts to focus studies, conversations, or publicity on the NSABP and expressed concern that overemphasis on the issue will further confuse the public. Dr. Calabresi agreed that the issue has been addressed and efforts should be focused elsewhere. Dr. Bragg indicated that the NSABP incident has weakened clinical trials, and there is a need to rebuild public confidence. Dr. Calabresi stated that promoting the clinical trials is precisely the purpose of the task force and assured the Board that the clinical trials groups are confident that this healing will occur.

Dr. Salmon questioned whether discussing this same issue later in the year at the President's Cancer Panel meeting would be appropriate. Dr. Broder remarked that the problem has been dealt with constructively and added that it is expected that accrual will resume in the NSABP in the near term. Dr. Calabresi pointed out that if the President's Cancer Panel focuses on the negative aspects of this experience, it could have detrimental effects; however, the Panel could reinforce the positive by examining clinical trials activity and progress.

Dr. Freeman observed that this issue may be addressed as a discussion of some current problems, such as involvement of minorities and women, rather than revisiting all of the negative aspects. Ms. Mayer urged that discussion be positive and educational to inform the public on progress and safety mechanisms that are in place.

Ms. Brown expressed concern that too much emphasis on procedure could make the process very cumbersome. She noted that holding a day-long workshop for dialogue and discussion may not be any more beneficial than issuing a public relations statement that precisely identifies the issues. She stated that efforts would be better focused on developing a positive attitude toward clinical trials among minority women who have not yet become involved in a trial. Ms. Brown expressed interest in working with NCI to facilitate more positive efforts. Dr. Broder recommended holding a joint President's Cancer Panel- and NCAB-sponsored event and inviting input on format development from members of both groups. Dr. Calabresi proposed calling it "The Benefits of Clinical Trials." Ms. Brown stressed that although the Board and NCI know how they are planning to proceed, the general public does not.

Mr. Paul Van Nevel reported that clinical trials-related public education efforts of the NCI Office of Cancer Communications (OCC) have focused on maintaining public confidence. He stressed that a greater effort must be placed on securing the understanding of the scientific leadership in clinical research, and indicated that the OCC has developed some draft communications that will be shared with Dr. Chabner. He stated that the program will be very proactive once agreement is reached with NCI staff. Dr. Sigal expressed her agreement with Mr. Van Nevel and with Ms. Brown and stressed the need for positive communication to bring some closure to the issue.

Dr. Calabresi called the Board's attention to a recent *New York Times* article that expressed a very positive view on clinical trials. He expressed his belief that, generally, the public is aware of the potential for error in any endeavor, and suggested that continued discussions of the negative aspects of the situation would not be productive.

Dr. Broder declared that a powerful force for maintaining the momentum of the NSABP study, and of clinical trials in general, is the women who volunteer for the trials. He stressed that their passionate commitment to take steps that will benefit all women is not articulated often enough nor in the right way. He emphasized that these women are intelligent, that they investigate the pros and cons before volunteering, and that they want this and other clinical trials to proceed. Dr. Correa agreed and added that particular attention must be paid to the minority populations involved in the trials. He called for investigation into better functioning with the financially less capable institutions that often provide care to underserved groups.

The Board unanimously approved the minutes of the four subcommittee meetings. Dr. Calabresi requested items for future discussion at the next Board meeting. Hearing none, he explained that any items for discussion may be mailed to Dr. Marvin Kalt and will be considered at the next agenda committee.

XVIII. ADJOURNMENT

There being no additional business, Dr. Calabresi thanked the group for their participation and adjourned the 90th National Cancer Advisory Board meeting at 1:05 p.m.

Date

Dr. Paul Calabresi, Chairman