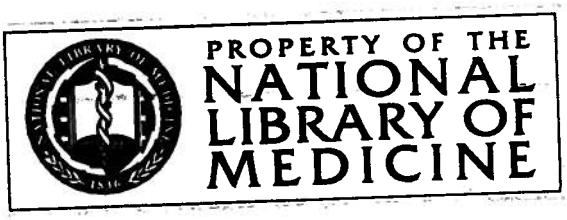
DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
November 22 and 23, 1993



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

Department of Health and Human Services
Public Health Service
National Institutes of Health
National Cancer Institute
National Cancer Advisory Board
Summary of Meeting[1]
November 22 and 23, 1993

The National Cancer Advisory Board (NCAB) convened for its 88th regular meeting at 8:00 a.m., November 22, 1993, in Building 31, C Wing, 6th Floor, Conference Room 10, National Institutes of Health (NIH).

NCAB Members

Dr. Paul Calabresi (Chairman)
Dr. Frederick F. Becker
Dr. Erwin P. Bettinghaus
Dr. David G. Bragg
Mrs. Zora Brown
Dr. Kenneth Chan
Dr. Pelayo Correa (absent)
Dr. Robert W. Day
Mrs. Barbara P. Gimbel
Mrs. Brenda Johnson
Dr. Walter Lawrence
Mrs. Marlene A. Malek
Ms. Deborah K. Mayer
Dr. Sidney Salmon
Dr. Ellen V. Sigal
Dr. Howard M. Temin (teleconference)
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
Dr. Clifford J. Gabriel, OSTP (absent)
Captain Bimal C. Ghosh, DOD
Dr. John Johnson, FDA
Dr. Theodore Lorei, DVA
Dr. Robert McGaughy, EPA
(for Dr. Hugh McKinnon)
Dr. Lakshmi C. Mishra, CPSC
Mr. Harold Mungin, DOL
Dr. Kenneth Olden, NIEHS
Dr. P. C. Srivastava, DOE

Members, Executive Committee, National Cancer Institute, NIH

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

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

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

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

Dr. Calabresi called the 88th meeting of the National Cancer Advisory Board (NCAB) to order and introduced several guests representing medical, research, and professional organizations. He welcomed members of the public and informed them that they could express their views on issues discussed during the meeting by writing to the NCAB Executive Secretary, Mrs. Barbara Bynum, within 10 days of the meeting. Changes in the proposed 1994 and 1995 NCAB meeting dates were confirmed. Dr. Calabresi called for approval of these changes and the minutes of the previous meeting, which were unanimously approved without change.

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

Dr. Freeman reported on two recent meetings held to acquire testimony on achievements of the National Cancer Program since its inception in 1971. The first meeting, held on September 22, 1993, presented the findings of a Measures of Progress Against Cancer panel, chaired by Dr. Paul Carbone. This panel examined both progress achieved and challenges faced by the National Cancer Program. This report featured six categories: mechanisms of cancer induction and progression, presented by Dr. James S. Felton; molecular medicine, by Dr. John E. Niederhuber; diagnosis and early detection, by Dr. George J. Bosl; cancer treatment, by Dr. Carbone; cancer prevention, by Dr. M. Alfred Haynes; and cancer control, by Ms. Helene Brown. Comments on barriers and challenges faced by the National Cancer Program were also presented by a number of representatives of research, academic, health care delivery, and advocacy organizations. These included the areas of environmental carcinogenesis, problems of special populations and women, issues of patient survivorship and death, as well as alternative treatments.

Dr. Freeman summarized the advances in progress against cancer described by the presenters, including:

- Identification of specific genetic alterations in cancer, which can elucidate mechanisms of cancer induction and have potential as diagnostic and treatment tools
- New molecular technologies, such as use of the polymerase chain reaction to identify tumor genes, creation of transgenic mouse models, and large-scale production of recombinant biological therapeutics
- Identification of tumor-based markers
- Elucidation of growth control mechanisms
- Improvements in understanding the relationship between mutagens and carcinogens
- Treatment advances, such as organ- and limb-sparing techniques, radiation therapy, adjuvant and neoadjuvant chemotherapy, the use of cytokines and growth factors, and bone marrow transplantation

- Quality-of-life enhancement for cancer survivors
- Advances in nutrition and diet as prevention strategies
- Chemoprevention using agents such as tamoxifen and the establishment of chemoprevention trials
- Identification of biomarkers and intermediary endpoints for use in these trials
- Examination of the impact of hormones on cancer risk
- Identification of virus-related cancers and potential vaccine development
- Public health advances in tobacco control
- Screening for early detection of breast and cervical cancers
- Strategies to reach special populations
- Increased public interest and patient activism.

Dr. Freeman also recognized that the Measures of Progress panel pointed out several challenges to be met by the National Cancer Program, including the need for sufficient funding for basic and applied research, the high costs of new technologies, ethical implications of the identification of risk factors, the need to educate physicians in translational research, and the importance of recruiting qualified young people into cancer-related research and supporting their education.

Following the panel's report, Dr. Freeman stated, Dr. Edward Sondik of the National Cancer Institute's (NCI's) Division of Cancer Prevention and Control (DCPC) reviewed cancer statistics and their implications as both a complement and a counterpoint to the achievements of the National Cancer Program. Dr. Freeman noted that while mortality has declined for some cancers, it has risen for others in spite of the advances described by the panel. Many of these diseases have a greater impact on older Americans and among certain racial and ethnic groups. These imbalances, he added, must be understood and strategies implemented to decrease mortality among these populations.

Some invited speakers, Dr. Freeman reported, reminded the President's Cancer Panel that after 20 years of war on cancer, the cures that were anticipated have not been achieved. They also pointed out that cancer treatment itself can be devastating and that cancer survivors and their families are faced with numerous psychological, social, and economic barriers. The idea that prevention is the best cure for cancer was expressed by Ms. Brown of the Measures of Progress Panel and echoed by others in attendance. It was agreed that prevention requires basic research into the causes of cancer, resources for the practical application of prevention strategies, and development of culturally sensitive outreach efforts for targeted populations.

A second meeting on measures of progress against cancer, Dr. Freeman continued, was held on November 15, 1993. At this meeting, the President's Cancer Panel heard testimony on "chronic disaster areas"—parts of the country considered to have excessive cancer-related mortality, in some cases paralleling rates in Third World countries. The panel, Dr. Freeman stated, discussed cultural, educational, economic, and racial/ethnic issues that affect rural outreach efforts in North Carolina, Kentucky, Virginia, New Mexico, and Louisiana, as well as

urban outreach in Brooklyn, Harlem, and New Orleans. Cancer screening and prevention strategies, Dr. Freeman stated, often must be modified for different geographic regions. He noted that, almost uniformly, speakers reported that the key to success in outreach is recruitment of trusted individuals within targeted communities to serve as conduits for information between caregivers and the public (e.g., the Wai'anae Coast Cancer Control Program). It was concluded at the meeting that some excessive cancer death rates may be associated with regional economic conditions and that more research should be focused on the causes of this problem and possible solutions.

A meeting of the President's Cancer Panel in January 1994, Dr. Freeman announced, will focus on the role of governmental and quasi-governmental organizations in the research mission of the National Cancer Program.

Dr. Freeman observed that when President Nixon declared war against cancer in 1971, an impression was created that such a war could be won in about 8 years. In retrospect, he stated, a misconception suggesting that the war against cancer could be won or lost through research alone has been perpetuated. Critics of the National Cancer Program, he noted, are measuring progress against cancer by mortality figures, which have, in fact, risen about 8 percent in the last 20 years. Dr. Freeman said that, ultimately, the war must be fought in the neighborhoods of America, primarily through educational efforts and early diagnosis and treatment within individual communities. Tobacco control and dietary modification, he said, are specific examples of areas that require educational efforts at the local level.

It is not in the power of the NCI alone, Dr. Freeman argued, to establish the community facilities needed for early detection, diagnosis, treatment, and education. To win the war against cancer, he stressed, other elements of the government and the private sector need to be brought into the battle. This should include efforts by the Congress to pass laws concerning universal access to health care. The people of the United States, Dr. Freeman continued, need to become foot soldiers by adopting lifestyle changes as part of the fight for their own lives.

Dr. Freeman concluded by stating that the President's Cancer Panel has made significant progress in initiating an evaluation of the National Cancer Program. The recent meetings, he said, have served to focus creative thinking on the special problems that remain, and future plans should include reshaping the conception of how the war against cancer should be fought.

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

Dr. Broder began by announcing several honors received by NCI staff. Dr. Bruce Chabner, Director of the Division of Cancer Treatment (DCT), received the 1993 Steven C. Beering Award from Indiana University for outstanding contributions to the advancement of biomedical science. Dr. Curt Harris, Chief of the Laboratory of Human Carcinogenesis, received the 1993 Alton Ochsner Award for work in the area of smoking and health. Dr. Edward Korn, head of the Clinical Trials Section, Biometric Research Branch, DCT, was recently elected to membership in the American Statistical Association.

Dr. Broder presented an update on events since the last Board meeting. He thanked Dr. Freeman for his leadership of the President's Cancer Panel during the recent meetings on measures of progress against cancer. Dr. Broder explained that the Panel's work is part of a broader process of evaluation being conducted by NCI in response to a mandate from the Congress to assess the achievements of the National Cancer Program and to develop a plan for carrying its work into the next century. The evaluation process, he added, seeks input from a broad constituency representing varying views and insights into cancer research priorities. An important goal, Dr. Broder stated, is to measure progress that reaches beyond quantitative changes in incidence, survival, and mortality, recognizing that qualitative advances in screening, treatment, and rehabilitation, as well as new directions in basic science, such as molecular medicine, also have an impact.

In addressing the problem of "chronic disaster areas" discussed at the November President's Cancer Panel meeting, Dr. Broder suggested that the National Cancer Program will be aided by the recently launched national health care reform agenda, particularly if progress is made in providing universal access to health care and eliminating the concept of preexisting conditions from insurance programs. He noted that the November meeting also highlighted the National Cancer Program's development and implementation of outreach efforts targeting underserved communities, which include the Minority Community Clinical Oncology Program (MCCOP) and the leadership initiatives.

Dr. Broder described a September 30, 1993, conference and workshop held by the Inter-American College of Physicians and Surgeons and the National Organization of Hispanic Physicians. The discussion focused on strategies to help the National Institutes of Health (NIH) increase minority participation in all phases of biomedical research, from investigator-initiated grants to outreach activities. He noted that all of NCI's funding instruments are responsive to the mandate within NIH to ensure equal access to support, regardless of race-ethnicity or gender. In effect, Dr. Broder said, all research project grants, cancer centers, cooperative groups, and activities funded through other mechanisms will not be permitted to continue regardless of their scientific evaluation if they do not meet both the letter and spirit of these guidelines.

On October 4, 1993, Dr. Broder stated, Dr. Daniel Ihde testified before the newly formed Senate Cancer Coalition, cochaired by Senators Connie Mack of Florida and Diane Feinstein of California. Dr. Ihde presented an overview of NCI's breast cancer research programs, including a number of new basic research efforts and clinical trials in nutrition, chemoprevention, and novel vaccine development. Other testimony focused on the coordination of breast cancer research between NCI and other Federal agencies, as well as between private and nonprofit organizations. Dr. Broder added that Dr. Ihde has announced plans to leave NCI for a position at Washington University in St. Louis and thanked Dr. Ihde for his superior performance.

On October 13, 1993, Dr. Broder continued, NCI held a press conference to announce the initiation of the Prostate Cancer Prevention Trial, which will compliment the Institute's tamoxifen chemoprevention trial that focuses on breast cancer. The prostate study, he explained, is a randomized trial to determine whether the 5-alpha reductase compound finasteride, a hormone-like inhibitor, reduces the incidence of prostate cancer. The trial will be coordinated by the Southwest Oncology Group, with participation by the Eastern Cooperative

Oncology Group and the Cancer and Leukemia Group B. It will be carried out in more than 200 sites across the country and will recruit about 18,000 men over age 55.

On November 1, 1993, Dr. Broder reported, a workshop entitled "Women's Health, Occupation, and Cancer" was held in Baltimore. The workshop, which grew out of the efforts of Drs. Linda Pottern and Sheila Zahm of NCI's Division of Cancer Etiology (DCE), provided an opportunity to plan an agenda for research in occupational hazards associated with women's cancers.

Dr. Broder announced the initiation of the Long Island Breast Cancer Study Project under the leadership of Dr. Iris Obrams, Chief of the Extramural Programs Branch within DCE's Epidemiology and Biostatistics Program. He explained that this study was requested by the Congress and will build on previous work involving the Centers for Disease Control and Prevention (CDC) as well as other Federal and State agencies. On November 10, 1993, Dr. Obrams and other NCI staff briefed Congressional delegates who represent Long Island. The Institute, he noted, views this project as a model for future environmental epidemiologic studies of potential cancer risk factors. The mandate, he added, requires the monitoring of specific factors, such as exposures to aircraft emissions, for which appropriate research methods do not exist; thus, the project represents a technology development effort as well as an epidemiologic study.

Dr. Broder stressed NCI's ideal positioning for work on the Long Island study, noting that a group of NCI grantees with experience in the area of environmental cancer risk has been assembled to assist in designing the study and that the Cancer Centers in the New York metropolitan area will be utilized, many of which have strong connections with Long Island. In addition to learning about environmental risks on Long Island, Dr. Broder explained that the study is intended to explore practical interventions for at-risk women, including chemopreventive approaches that could be targeted to certain risk profiles.

Dr. Broder observed that a review of the intramural research programs of NCI and other Institutes is being coordinated by the Office of the NIH Director. A panel of external advisors met on November 13, 1993, to set the following three goals: 1) to evaluate the process currently used to review the quality of intramural research programs; 2) to study the process by which the size of scientific, administrative, and training components of intramural programs are determined; and 3) to examine organizational issues that are disincentives to development of the highest quality intramural research and training efforts. The Institute is working with this panel, chaired by Dr. Paul Marks of Memorial Sloan-Kettering Cancer Center, to provide all requested data. Another meeting of the panel is scheduled for December 17, 1993; Dr. Broder offered to help arrange for interested Board members to attend the meeting.

In addition, Dr. Broder noted, an NCAB subcommittee, chaired by Dr. Calabresi, has been charged with helping to develop an overall research agenda for NCI. He stated that the subcommittee hopes to specifically help NCI address the mission, scope, and size of the intramural program. This subcommittee, Dr. Broder added, is an appropriate vehicle for all Board members who have comments or questions about the intramural program. He described NCI's intramural research program as a resource with unique capabilities for redirecting scientific expertise on short notice in response to new and emerging public health issues.

Dr. Broder announced the 20th anniversary symposium of the Surveillance, Epidemiology, and End Results (SEER) Program to be held on December 8, 1993, at the National Library of Medicine. The themes will be the genesis of the SEER Program and a summary of its contributions in cancer etiology and cancer control, as well as opportunities that new advances in cancer biology and health care reform may offer the program. Dr. Broder noted that the SEER Program is not simply a statistical archive but also an important NCI component that monitors and validates the Institute's programs and provides an integral link with other National Cancer Program activities.

It has been suggested, Dr. Broder stated, that Dr. Calabresi ask NCAB members who represent academic institutions to make a brief presentation to the Board on their research accomplishments and difficulties, focusing on their institution as a whole rather than on their own work as principal investigators. If the Board agrees with this idea, he noted, these presentations could begin at the February 1994 meeting.

Dr. Broder provided an overview of a novel approach to cancer vaccine development that is being tested in patients with colon and breast cancers and in at least one patient with lung cancer. The technique involves combining a portion of the vaccinia virus with the tumor-associated carcinoembryonic antigen (CEA) to determine whether an immune response can be generated against an established tumor and eventually can prevent tumor recurrence. He explained that a high percentage of gastrointestinal cancers and about 50 percent of breast cancers express CEA on the cell surface. When the entire recombinant vaccinia CEA is expressed, CEA is co-expressed with immunogenic, but essentially nonpathogenic, virus. Dr. Broder stated that this may provide an opportunity for generating cytotoxic T cells and, perhaps, other immune cells that could be of value to patients with these and other types of tumors.

Dr. Broder described another new project involving the use of small portions of the patient's own mutated *p53* gene product or *ras* product. A wide range of tumors express mutations or abnormalities of *p53*, including breast, lung, and gastrointestinal malignancies. This project, he noted, is almost ready to begin the phase of human administration.

Turning to the subject of the budget, Dr. Broder stated that a recision in the budgets of several Institutes might occur during the current year. For NCI, he speculated, the cut could be in the range of $5 to $18 million. Dr. Broder noted that it is better to learn about recisions as early as possible, because when cuts are announced late in the year, the number of months that have already elapsed must be factored in to calculate an annualized figure for the remaining months. He stated that the cuts pose special challenges for the Institute, since most of the cuts probably would come from the Institute's intramural program. Although this program consists primarily of investigator-initiated basic research, it is defined as overhead.

The Institute continues to operate under a hiring freeze and must reduce its work force by approximately 100 employees, Dr. Broder continued, and the Institute faces further reductions in full-time equivalent (FTE) positions in fiscal year (FY) 1995. In addition, he noted, the attrition rate has slowed recently, making it more difficult to recruit staff and to originate new programs. Another relevant issue, Dr. Broder stated, is the freeze on hiring and promotions at the GS-14 level and above. This will present a special problem, he said, in recruitment of highly trained scientists as well as in career development.

Dr. Broder mentioned that the NIH community at large is discussing the possibility of increasing the stipend level for National Research Service Awards (NRSAs). Predoctorate awards would increase from about $8,800 to about $10,000; some trainees receiving a postdoctorate award, which average about $25,000, would receive an increase of $1,000. Since the NRSA budget for NCI has remained at about $37 million, this proposal would reduce the number of trainees by approximately 60, to a level below 1,400. Dr. Broder asked the Board for its advice on this issue.

Dr. Broder reviewed recent House and Senate committee reports with language affecting NCI funding. The House report, he said, asks for expansion of all facets of breast cancer research; makes prostate cancer research a top priority; emphasizes other gender-specific diseases, such as cervical and ovarian cancers; gives basic research equal emphasis with disease-specific research; supports continued development of research in leukemia, lymphoma, and related cancers; and calls for continued proton beam research using funds in the construction line item.

The Senate report, Dr. Broder continued, mandates a balanced research program, urges continuation of vaccine research, promotes expansion of all facets of breast cancer research, encourages efforts directed toward Native Americans, suggests collaboration with the Nursing Institute on symptom management, calls for a geographic expansion of cancer centers, and asks NCI to support psychotherapeutic services through cancer centers. The Senate, he added, asks the Institute to establish leukemia centers to support educational interventions for minority and low-income adolescents, expand screening and intervention strategies for neurofibromatosis, promote DES research and education, and increase prostate research.

Dr. Broder observed that these reports do not have the force of law but are seen as a very important mandate for the Institute. The Conference Report, which he said NCI does view as having the force of law, asks the Institute to deal with equipment and planning needs, with an emphasis on Cancer Center Planning Awards. This is interpreted as placing a priority on established interdisciplinary core grant systems, including the P30 and P50 mechanisms, with appropriate P20 planning grants. Dr. Broder noted that this also may be interpreted as providing flexibility in the construction line item. The Conference Report also asks, he stated, for greater involvement of Native Americans in Federally supported clinical trials.

Dr. Broder indicated that NCI is pleased with the brevity of the Conference Report because it gives the Institute the needed flexibility to respond to scientific priorities and makes it possible to maintain an appropriate balance in its research program. He concluded that the report can be seen as a vote of confidence in the National Cancer Program.

Questions and Answers

Dr. Samuel Wells asked whether the Board was being asked to comment on the increase in National Research Service Awards (NRSA) stipends during the current meeting. Dr. Broder replied that the Board could respond at this session or at a session of its choosing, adding that time is critical because the issue is linked to an NIH-wide process. The Institute, he stressed, has a voice but will not have the final say on NRSA stipends.

Dr. Wells observed that the budget for NRSAs has not increased for several years and expressed his opinion that a reduction in the number of positions would be unfortunate. Dr. Broder agreed and noted that NCI has used other mechanisms to provide some additional flexibility in supporting trainees, including the K series and discretionary support for training and career development within Specialized Programs of Research Excellence (SPORE) grants.

Dr. Salmon predicted that there would be little controversy on this issue, suggesting that it makes sense to maintain the number of positions as an incentive for matching funds.

Dr. Calabresi announced that the Board could return to this issue during the business session. He reiterated Dr. Broder's invitation to Board members to make suggestions concerning future presentations from the extramural community, whether from their own institutions or from others receiving NCI support.

Dr. Broder then introduced Dr. Jay Harris, a clinical and educational director and professor of radiation oncology at the Harvard Medical School's Shields-Warren Radiation Laboratory. He noted that Dr. Harris' presentation on the President's Cancer Panel Special Commission on Breast Cancer would be followed by comments from Dr. Marie Swanson, professor of medicine and director of the Cancer Center at Michigan State University.

As an introduction to Dr. Harris' presentation, Dr. Freeman read a letter from Ms. Nancy Brinker, Chair of the President's Cancer Panel Special Commission on Breast Cancer, who was unable to attend the meeting. In the letter, Ms. Brinker commended Dr. Freeman, NCI staff, and members of the Special Commission for their efforts in creating the Commission's recent report. She thanked Drs. Swanson and Harris for their diligent work in gathering a consensus and authoring the report. Finally, Ms. Brinker said she had served with pleasure on the Board, the President's Cancer Panel, and the Special Commission on Breast Cancer, adding that she looked forward to working with these groups in the future.

IV. REPORT OF THE PRESIDENT'S CANCER PANEL SPECIAL COMMISSION ON BREAST CANCER—DRS. MARIE SWANSON AND JAY HARRIS

Presentation by Dr. Jay Harris

Dr. Jay Harris began by recognizing the members of the Commission and reporting that between May 1992 and July 1993, the Commission held 11 public meetings at which more than 190 experts provided testimony on a wide range of issues. He observed that during the 1990s, an estimated 2 million women will be given a diagnosis of breast cancer and more than 500,000 will die of the disease. Only a small portion of the 53 percent increase in breast cancer incidence between 1950 and 1989 can be attributed to increased screening efforts—the causes for this increase, he stated, are poorly understood.

Many poignant presentations at the Commission's meetings from members of patient advocacy groups, Dr. Harris said, demonstrated the considerable anxiety among women in this country resulting from the magnitude of the breast cancer problem. He stated that while there have been some modest improvements in detection and treatment of breast cancer over the past

few years, these gains have not been uniformly applied throughout the population. The death rate from breast cancer, he added, has not changed appreciably over the past few decades.

Dr. Harris observed that current therapies, including surgery, radiation, and chemotherapy, are relatively nonspecific in their effects and frequently diminish the quality of life for patients; however, recent advances in basic science have raised realistic hopes that more specific interventions can be developed to treat and prevent breast cancer. While prevention is the ultimate goal, he said, earlier detection through mammography and physical examination has been clearly shown to reduce mortality among women ages 50 to 59. Additional information is needed regarding the efficacy of screening in other age groups.

Improvements in detection may also be made possible through better training of technicians, better imaging technology, and the development of biomarkers. The report of the Commission asserts that access is a major concern, not only to screening but also to prompt diagnostic workups, which at present are not universally available.

Current information, according to the report, suggests the potential for developing several new strategies, including therapies directed at growth factors and their factor receptors; inhibitors of angiogenesis and metastasis; gene therapy; and immunological therapy, including vaccines. In addition, modifications in current therapies that may improve their effectiveness include development of valid prognostic and predictive factors; use of new agents and higher doses of standard agents; development of methods to overcome resistance to hormone therapy and chemotherapy; and combined use of new and traditional treatments.

It was the consensus of the Commission, Dr. Harris reported, that advances in basic science are not easily translated into practice. Advances in treatment and prevention, he stated, will require more support for translational research and clinical trials, including training of more experts in these areas. The Commission concluded that better interventions will be facilitated by additional support for Specialized Programs of Research Excellence, high-quality cancer registries, relevant animal models and cell lines, and repositories for biological specimens.

The report also acknowledges that the diagnosis and treatment of breast cancer commonly result in profound negative physical, psychological, and social effects on both patients and their families. More information on these problems and effective interventions to counteract them is needed.

The Commission identified several changes in public policy that will be necessary to implement these recommendations, including sustained support for research in breast cancer in specific and cancer in general; health care reform to ensure access to proven methods of screening, education, treatment, and supportive care; cooperative support for testing of new interventions from third-party payers, industry, academic centers, and the NCI; payment of clinical trial research costs by industry and/or NCI, while costs of patient care are covered by third-party payers; limitation of unproved interventions to well-defined clinical trials; implementation of the 1992 Mammography Quality Standards Act; and coordination of all Federal programs relating to breast cancer through an interagency task force.

Dr. Harris then relinquished the floor to Dr. Swanson for her portion of the presentation.

Presentation by Dr. Marie Swanson

Dr. Swanson explained that her portion of the report produced by the President's Cancer Panel Special Commission on Breast Cancer would focus on etiology and prevention, public communication, patient advocacy, special issues for minorities and underserved women, and implementation goals.

Presentations before the Commission by many scientists and advocacy groups, Dr. Swanson stated, emphasized the need for placing a higher priority on allocation of research funds to prevention. The best potential, she continued, lies in three areas: genetics, tumor markers, and hormones; dietary interventions; and environmental etiology.

Studies of genetics, markers, and hormones, Dr. Swanson explained, are needed to understand the transition from normal mammary tissue to premalignant and malignant tissue. Better understanding of the biology of the disease, she noted, may lead to better ways of identifying high-risk women. Intermediate markers of premalignant states may be useful for screening and prevention. The Commission also feels there is some benefit in examining low-dose hormonal contraceptive regimens, particularly focusing on the effects of estrogen and progesterone on breast tissue.

The Commission's report, Dr. Swanson continued, recommends three areas for basic research on the role of diet in breast cancer: the preventive effects of retinol and carotenoids; dietary vitamin A as a preventive agent; and energy restriction and reduction of mammary carcinogenesis. Other possible preventive factors that require further study are physical exercise at prepuberty and at puberty and non-nutritive factors in vegetables and fruits. Factors associated with increased risk of breast cancer that require further study include dietary fat and protein, moderate alcohol intake, and low levels of vitamin D.

Many public and patient advocacy groups, Dr. Swanson noted, are very concerned about environmental risk factors; very little research has been done, she added, on environmental factors in breast cancer. The Commission feels that the first area of investigation should be occupational risk. A second area of concern identified in the Commission's report is exposure to natural and synthetic estrogenic chemicals in the environment. In terms of methodology, the report recommends the development of molecular markers of exposure and susceptibility to environmental factors. Dr. Swanson called attention to ongoing studies of increased levels of breast cancer among Japanese atomic bomb survivors, noting that the cohorts that are likely to provide the most useful information are those exposed *in utero* and during adolescence.

Turning to public education, Dr. Swanson explained that the Commission's emphasis in its report is on the need for improved collaboration among the many groups involved in educating the public about breast cancer. The Commission also recommends a national work group on information for women with low literacy levels, she said, and many advocacy groups have supported this idea.

Dr. Swanson acknowledged that scientists and advocates often have different goals, but stressed the Commission's belief that these two groups can still coordinate their efforts to provide clear, accurate messages to the public. The Commission also encourages the coordination of public information efforts among the components of NIH and other Federal agencies, as well as collaboration with the news media to ensure accuracy and completeness in coverage of breast cancer issues.

Dr. Swanson reviewed several goals related to community organization and public policy that were submitted to the Commission by representatives of patient advocacy organizations. Specific goals include efforts to: support legislation funding research, treatment, and education; ensure access to care for all women; ensure that health care reform reflects local issues; collaborate with physicians to ensure that psychosocial aspects of breast cancer are included throughout the continuum of care; integrate advocates into decisions about optimal research funding; and educate all women about breast health.

The Commission's recommendations concerning special issues for minority and underserved women, Dr. Swanson continued, focus on the need for improved access and sensitivity. Specific goals include: structuring clinical trials to reflect racial and ethnic diversity; building partnerships with underserved communities; involving community leaders in the design phase of intervention projects; conducting behavioral and social research into the development of culturally sensitive approaches to prevention, screening, treatment, and rehabilitation; reducing geographic barriers to access to optimal education and care; investigating the psychosocial impact of breast cancer on women and their families in terms of ethnic, geographic, and socioeconomic diversity; determining risk factor prevalence by ethnic, cultural, and socioeconomic subgroups; making SEER incidence data available for all ethnic groups; and removing linguistic and cultural barriers to screening, treatment, and rehabilitation.

Dr. Swanson concluded with a brief statement of the Commission's recommendations for developing a national strategy for breast cancer. While many organizations contribute to the goal of preventing and curing breast cancer, she stated, the Commission feels that NCI should provide leadership for this effort. Many Commission members, Dr. Swanson observed, are frustrated at the lack of coordination of efforts ranging from research to education. Finally, she stated, the Commission recommends continuous funding at a level of at least $500 million until the goals of prevention and cure are achieved.

Questions and Answers

Dr. Salmon asked whether NCI is making any efforts to coordinate with the new breast cancer research program being initiated by the Army to avoid any unnecessary duplication of research efforts. Dr. Broder asked Dr. Susan Sieber, DCE, the NCI representative to the Defense Department, to reply. Dr. Sieber explained that the Army has established an Integration Panel, which functions in a sense as an equivalent of the NCAB, to provide an overview and policy direction for the Army's breast cancer research program. The panel, she said, has about 18 members, among whom is Ms. Fran Visco.

Dr. Ihde noted that Department of Health and Human Services (DHHS) Secretary Shalala has asked for a meeting in December 1993 at which coordination of effort among

Federal agencies and organizations in the private sector to develop a national plan for breast cancer research will be discussed.

Dr. Broder added that the $200 million budget for the Army breast cancer research program is, in effect, prepaid over the life of the project, whereas NIH grants are based on a level-of-effort budget, in which out-year costs are paid in the relevant fiscal year. Thus, he said, to compare the Army appropriation with an NCI grant, it could be described as a $50 million program on an annualized basis.

V. NEW BUSINESS: SESSION I—DR. PAUL CALABRESI

Dr. Calabresi announced that two motions had been received by mail prior to the meeting. He explained that a brief discussion of the motions during the new business session would be followed by a vote on each motion during the second day's session.

Dr. David Bragg introduced his motion on screening mammography guidelines by noting that a number of NCAB members have been concerned with the recent public debate on this issue and feel that the Board has not had an opportunity to express this concern. He stated his belief that proposed changes in recommendations for women between the ages of 40 and 49 would dilute the significant impact of mammography and create confusion concerning how mammography should be implemented. The sense of his motion, Dr. Bragg explained, is that the NCAB supports the positive role that mammography has played and recommends that NCI defer any changes in breast cancer screening guidelines. The motion also recommends, he added, that additional information is needed in the areas of evaluation, research, and development of appropriate communication guidelines. The guidelines, Dr. Bragg suggested, leave the burden on women and their health care providers without providing sufficient information to help them make decisions. Dr. Irwin Bettinghaus seconded the motion.

Dr. Salmon then presented the following motion:

> Inasmuch as the National Cancer Institute has its major focus on cancer research rather than the delivery of health care or making policy on health care delivery, the NCAB recommends that NCI limit its role in the area of breast cancer screening to the presentation and publication of information on research findings and their current status in relation to breast cancer screening. Accordingly, the NCAB recommends that NCI not involve itself in setting guidelines for breast cancer screening, but rather leave that task to those governmental and private agencies that take this as their primary charge.

Since no second to this motion was offered, Dr. Calabresi asked whether Dr. Salmon felt that his motion could be incorporated into Dr. Bragg's motion. Dr. Salmon expressed concern that the earlier motion, by deferring a decision, left the matter in limbo. His own motion, he said, presented a clearer answer to the question of NCI's role in setting guidelines.

Dr. Broder emphasized the fact that NCI is a science-based agency whose primary mission is to generate knowledge, not to determine health care policy. He noted that on controversial topics, where new scientific findings may diverge from conventional wisdom, well-meaning individuals often come to opposing conclusions based on the same scientific facts. The Institute's job, Dr. Broder stated, is to present the facts, acknowledge areas in which there is scientific disagreement, and make it clear when the debate shifts from scientific to policy considerations.

Dr. Broder pointed out that these issues will come up each time new information becomes available concerning the effectiveness of experimental agents or devices, such as PSA (prostate-specific antigen) screening or flexible sigmoidoscopy. He stressed the importance of keeping the discussion of these issues focused on scientific considerations.

VI. IDENTIFYING PEOPLE AT RISK FOR CANCER—DR. FRANCIS COLLINS

Dr. Broder introduced Dr. Francis Collins, Director of the National Center for Human Genome Research (NCHGR). Prior to heading the NCHGR, Dr. Collins directed the Human Genome Center in Ann Arbor, Michigan, where he worked on improving technologies for large-scale gene discovery. Dr. Collins is currently pursuing the gene for early onset breast cancer.

Dr. Broder commented that as the Human Genome Project progresses, new ethical, moral, and scientific issues will arise. For example, Dr. Broder said that the possibility exists that genetic disorders will be found in everyone, in essence meaning that everyone has a preexisting condition. This, he observed, would have a great impact on current insurance practices. In addition, genetic tests will soon be available to detect many diseases for which no treatment exists. These tests will be able to identify people who almost assuredly will develop a disease and yet doctors will not be able to offer treatment advice. Spinocerebellar ataxia, Dr. Broder noted, is a disease in which it is possible (by looking at the number of trinucleotide substitutions) to predict with near certainty if a patient will be stricken by the disease, and for which there is currently no intervention. This, Dr. Broder said, is an alert to all those in the prevention, diagnosis, and treatment fields.

Dr. Collins began his presentation by discussing the reasons for the human genome project, the 15-year endeavor to map and sequence all of the human DNA. The main motivation, he said, is to identify the genetic basis of all diseases, since all individuals have within their DNA certain alterations that predispose them to particular conditions. Toward that goal, Dr. Collins said, researchers are closing in on the identification of the genetic basis for many diseases, including common ones.

The chromosomes of a normal human contain approximately 100,000 genes, for some 5,000 of which scientists already know the function and location; the vast majority, therefore, remain unknown. Individual investigator-initiated research would chip away at the number of unknowns; however, the process would not be very efficient, Dr. Collins stated. Mapping and sequencing in an organized technology-driven process was thought to be much more efficient, and so the Human Genome Project was born in 1990.

A major reason behind the Genome Project, Dr. Collins said, is the realization that disease genes can be identified in one of two ways: functional cloning, in which the normal function of the gene is known; and positional cloning, in which the function of the gene is not known. In the vast majority of diseases, the normal function of the aberrant gene is not known, making functional cloning impossible. While positional cloning is more arduous, it is also more powerful, since knowledge of the function of the gene is not necessary. It is simply necessary to identify a disease with a genetic component, collect families for study, then map the position of the gene and narrow it down to the smallest possible interval. Once that is done, a search can be done for a gene that shows alterations in affected individuals. When the genome has been fully mapped and sequenced, a scientist with knowledge of the interval in which the disease gene falls will be able to use a computer to find the interval and select genes in that interval that are good candidates for study, Dr. Collins explained. Until then, however, the mapping information provided by the Genome Project can still greatly expedite the process.

Dr. Collins then addressed the progress of the Genome Project. The first 5-year plan was published in 1990, and is already somewhat obsolete. A new 5-year plan was published October 1, 1993. The first 5-year plan was replaced because advances in mapping have proceeded at a more rapid pace than anticipated and many of the goals of the first 5-year plan have already been achieved, in spite of the fact that the Project has not been fully funded. New, more ambitious goals have been set for the new 5-year plan. Dr. Collins expressed some concern that if full funding of the Project is not achieved, researchers might fall behind in the next phase of the Project—sequencing all 3 billion base pairs of human DNA. Thus, they would not be able to complete all of the sequencing by the year 2005 as expected.

Discussing the goals of the new 5-year plan, Dr. Collins said that the genetic map, a series of closely spaced signposts along each chromosome, has essentially been completed. The physical map, in which overlapping clones cover every human chromosome, is progressing, and completed physical maps exist for human chromosomes Y and 21. Within a year and a half, a relatively complete physical map of the entire human genome should be accomplished. A new goal in the current 5-year plan is to annotate the map with the location of as many of the 100,000 genes as possible, without waiting for the sequencing to be completed. This, Dr. Collins stated, is now possible because of new technologies. Sequencing the genome will be the most demanding portion of the Project and will occupy the majority of the Project's last 10 years. Further technology development is still required to accomplish the sequencing, and most of the current sequencing efforts are aimed at model organisms such as yeast, *E. coli*, and the roundworm, *C. elegans*. These organisms have smaller, more densely packed genomes. Work with these organisms has led to a better understanding of gene biology and structure, two factors that will aid in sequencing the human genome. Dr. Collins added that they expect to be able to sequence approximately 50 megabase pairs a year by 1998. With sequencing throughput increasing by a factor of two each year, the entire genome should be sequenced by the year 2005.

Dr. Collins then presented a cumulative list of the disease genes that have been identified using positional cloning, many within the past year. Included on this list are muscular dystrophy, fragile X syndrome, and Huntington's disease. These advances, Dr. Collins reiterated, are related to the genetic and physical maps produced by the Genome

Project. Genes for more common diseases such as cancers, hypertension, and diabetes will likely be added to the list in the next few years, Dr. Collins added.

Dr. Collins then turned his discussion to the search for the gene for early onset breast cancer. In the early 1980s, he reported, Mary-Claire King studied families with early onset breast cancer. Using genetic markers, she was able to pinpoint a marker that had the ability to predict breast cancer in those families. The marker was located on chromosome 17 and proved the existence of a major gene for breast cancer (BRCA1). In families with early onset breast cancer, 60 percent of cases are due to mutations in the BRCA1 gene. In families with breast and ovarian cancer, virtually 100 percent of cases map to this same region of chromosome 17. A woman with a mutation in the BRCA1 gene has an earlier age of onset of breast cancer than the general population, and a much higher risk, approaching 90 percent, of getting breast cancer in her lifetime. The risk of ovarian cancer for a woman with a BRCA1 mutation is 10 to 15 percent. Males who carry the mutation in this gene, Dr. Collins continued, appear to have an increased risk of prostate cancer, and can also pass the gene on to their daughters.

Identifying individuals at high risk for breast cancer could potentially be of great benefit and, therefore, a major effort is underway to locate the gene and develop a diagnostic test to identify carriers. Five percent of all women with breast cancer have an inherited mutation of BRCA1, which means approximately 1 in 200 women are in this category. For the remaining 95 percent, Dr. Collins said, a significant proportion probably involve a somatic mutation in the same gene.

Dr. Collins said that the location of the gene is being systematically narrowed by genetic analysis. One technique being used for locating the gene is chromosome microdissection, which was pioneered by Jeff Trent, Scientific Director of the NCHGR, and entails scraping the human metaphase chromosomes and deriving DNA, which can be used to make a library of fragments. This technique is very powerful in its ability to access a particular region of a chromosome for intensive study. Using this approach and others, the region of the breast cancer gene has been narrowed to about 1 million base pairs. If loss of heterozygosity in tumors is included, the region can be cut to 500,000 base pairs, all of which have been cloned and used in artificial chromosomes in cosmids. Roughly 20 candidate genes in that interval are being evaluated for mutations in affected persons.

The consequences of finding the breast cancer gene was the next topic Dr. Collins discussed. Dr. Collins said that in families large enough to follow the gene's inheritance, they are able to identify young women who have inherited this gene, but do not yet show signs of disease. He showed a pedigree from a Michigan study on inherited BRCA1. The mutation was inherited from the grandfather, and many of the women in subsequent generations had developed breast cancer. During the study, one woman contacted the researcher to request clinical advice. She had already made an appointment for a prophylactic bilateral mastectomy, because she had seen one sister die of breast cancer and her other sister diagnosed with her second breast cancer, and she was certain she would develop it also. She wanted to know if the results of the study would influence her decision at all. The study showed that she did not inherit the gene and, therefore, had the same risk as the general population. The woman canceled her surgery and informed her family, who also began calling to obtain their results.

Another woman, Dr. Collins stated, asked to know the results of the test. Five years earlier she had had a prophylactic bilateral mastectomy after watching two sisters die of breast cancer. This woman did not inherit the gene and had some trouble processing that information before deciding that she had made the right decision based on her knowledge at the time. She was also relieved that she would not be passing the gene on to her daughter.

In the same family, members of a second sibship assumed their risk to be low, since their closest relatives with cancer were aunts and cousins. After entering the study it was discovered that three of the six women in the second sibship had inherited the "at risk" gene from their father. One of the women, a 40-year-old who had never had a mammogram and had not practiced self-examination, wanted to know the results of the genetic test. After being informed that she had inherited the gene, she obtained a mammogram that afternoon. The mammogram showed a tumor which, upon biopsy, proved to be an intraductal carcinoma. She underwent a mastectomy; her nodes were negative and her prognosis is very good. Since this woman was still at risk for breast cancer in her other breast and for ovarian cancer, she chose to have her other breast and ovaries removed. Dr. Collins stressed that these are very difficult decisions and noted that a less drastic (but unproven) alternative is to enter an intensive surveillance program.

Dr. Collins then briefly discussed counseling for families in these situations. He said that genetic counselors employ a nondirective approach, in which the patient is informed of all her options and is then encouraged to make the decision that is best for her particular situation. Some women are comfortable only with the most aggressive therapy possible, not wanting to wait for a positive mammogram because that would mean they already have cancer. Other women view the surgical options as so unattractive that they opt for intensive surveillance, understanding the risk that decision entails.

Once the actual gene carrying breast cancer is identified, Dr. Collins said, all women will be able to undergo a simple blood test to see if they carry the hereditary breast cancer gene. This eventuality must be planned for, and NCI and NCHGR are putting together a Request for Applications (RFA) to study the effectiveness of genetic counseling in this situation. What they want to avoid, he said, is suddenly being put in the situation of providing millions of women with information without knowing the consequences of that action.

This issue applies to other diseases as well, Dr. Collins stated. The same situation, for example, has arisen with colon cancer. A mutant gene on chromosome 2 seems to be present in approximately 1 in 200 individuals with colon cancer, raising the bearer of that gene's chances of getting colon cancer by 70 to 75 percent. This is especially significant, since periodic colonoscopy can detect and remove colon cancers before they are fatal. Finding these genes will allow the medical community to focus screening efforts on those most in need.

Dr. Collins cautioned against the potential misuse of genetic information, and noted that the NCHGR spends about 5 percent of its budget on studying the ethical, legal, and social consequences of genetic research. He described the flow of information in genetic studies, from gene mapping, through cloning, to the development of a diagnostic test. In some situations these actions will lead to preventive strategies and, in others, finding the gene will provide new insight into the biological basis for a disease and, eventually, insights into developing new therapies for that disease.

Dr. Collins then concluded his presentation with a description of the new intramural program at the NCHGR. This program, he said, will act as a hub for research in genetics on the NIH campus and includes a Laboratory of Cancer Genetics, a Diagnostic Development Branch, a Clinical Gene Therapy Branch, a Laboratory of Genetic Disease Research, a Laboratory of Gene Transfer, and a Medical Genetics Branch.

Questions and Answers

Dr. Broder cautioned against assuming that once a gene is discovered, interventions will soon follow. He added that organ removal must be viewed as an interim measure until better interventions are available. Dr. Broder then commented that in the case of BRCA1, the possibility is strong that it is a gain-of-function gene and, therefore, it is theoretically possible that people will be able to be immunized against the product of the aberrant gene well before the tumor arises. The possibility also exists, he said, that customized vaccines will be developed to immunize women in their twenties or early thirties against breast cancer.

Ms. Malek asked about the percentage of fathers passing on the BRCA1 gene who themselves develop some sort of cancer. Dr. Collins responded that there appears to be a modest increase in prostate cancer for these men and that it develops at a slightly earlier age. Dr. Collins also noted that none of the fathers developed male breast cancer.

In response to a question regarding the release of information to study participants, Dr. Collins noted that his group is very concerned about this aspect. An article appeared recently in the *Journal of the American Medical Association* summarizing their experiences in this area. The general routine, Dr. Collins said, is to contact, by mail, the families being studied once results are available. The families are told that results are available concerning their future risk for developing breast cancer and asked to contact the researcher for an initial visit if they wish to know that information. At the initial visit, the study is described and it is made clear that the results are statistical statements about relative risk. The patients are then asked to contemplate the information for a few days before deciding whether they want to know their results. Individuals under 18 are not informed because there is nothing medically that can be done at that point, and informed consent is a crucial part of the process.

When the patients come back, they are asked to sign an informed consent form and, if they have decided to obtain their results, the results are explained to them along with their options. Their options are explained in a nondirective way that does not favor either surgery or surveillance. A multidisciplinary team is involved that includes an oncologist, a geneticist, a social worker, and a genetic counselor. Dr. Collins noted that this experience is time consuming, complicated, and emotionally draining for all involved. The thought of doing this on a much larger scale, Dr. Collins said, is troubling.

Dr. Wilson asked how the Board could assist the NCHGR. Dr. Collins said that the partnership between NCI and NCHGR, which represents the best assistance, is already under way.

Dr. Collins acknowledged that there is an educational problem in the medical field. Many physicians who have been in practice for a long time have never had any formal training

in genetics and are going to be on the front lines talking to individuals who are at risk. This is an issue that the various Institutes will need to join forces to address.

Dr. Bettinghaus asked if there are many situations in which more than one gene mutation is necessary to produce the lethal combination. Dr. Collins answered that, for cancer, that is usually the case.

Dr. Chabner noted that there will be a meeting in the Spring regarding the use of cooperative group programs to research and identify families at high risk.

Molecular stratification, Dr. Broder commented, is being investigated in the prevention and therapy trials. Using molecular stratification, it will be possible to tailor the chemoprevention strategy. This will be a very important requirement of the clinical trials process, he added.

VII. BREAST CANCER SCREENING GUIDELINES—DRS. PETER GREENWALD, ARNOLD KALUZNY, AND BARBARA RIMER

Before turning the floor over to Dr. Greenwald, Dr. Calabresi announced that Dr. Howard Temin, who was not present, would be able to hear the meeting and contribute comments through a speaker phone.

Dr. Greenwald explained that there would be three presentations on the subject of breast cancer screening guidelines. First, he would describe a February 1993 international workshop on clinical trials. Dr. Arnold Kaluzny, chairman of the Division of Cancer Prevention and Control Board of Scientific Counselors (BSC), would then report on the October BSC meeting, during which a full day was devoted to the issue of breast cancer screening guidelines, with a particular focus on screening for women ages 40 to 49. Finally, Dr. Barbara Rimer, Director of Cancer Prevention, Detection, and Control at the Duke Comprehensive Cancer Center, would comment.

International Workshop on Screening for Breast Cancer—Dr. Peter Greenwald

The International Workshop on Screening for Breast Cancer, Dr. Greenwald continued, was held at NCI on February 24th and 25th. He presented two slides showing information on breast cancer clinical trials among women ages 40 to 49. The first slide summarized data from eight randomized control trials on the effectiveness of screening for women ages 40 to 49, including the health insurance plan study begun in 1963, five Swedish studies, and studies from Edinburgh (Scotland) and Canada. The relative risk found by these studies ranged from 0.77 to 1.36, and all competence limits included a value of 1. The second slide presented results of a meta-analysis of these trials at 7 years of follow-up, revealing a relative risk of 1.08 for women ages 40 to 49. Dr. Greenwald noted that these findings indicating no change between cases and controls is in marked contrast to demonstrated benefits of screening for women over 50, for whom a 34 percent decrease in breast cancer mortality was found.

Dr. Greenwald read the following quote from the workshop report: "One sees remarkable consistency in the trial results for women ages 40 to 49 through the first 7 years of follow-up even though they were conducted at different times, in different countries, with varying screening intervals, and with one or two mammograms. The randomized trials of women ages 40 to 49 are consistent in showing no statistical benefit in mortality after 10 to 12 years of follow-up. This is true even with a recent meta-analysis, combined analysis of four Swedish studies based on more current data, and updated data from the Edinburgh trial." On the issue of screening intervals for women over 50, Dr. Greenwald stated that intervals of 12 to 33 months have been shown to be effective.

Dr. Greenwald mentioned two other studies on breast cancer screening. The first, a study by Dr. Carla Kerlekowsky which is soon to be published in the *Journal of the American Medical Association*, addressed the positive predictive value of screening mammography by age and family history of breast cancer among women in the San Francisco area. For women under age 50, the ratio of cancers found per abnormal screen was 1 in 26, while among women over 50, the ratio was 1 in 7. The study also found some effect of family history.

The second study, which is in the early stages of implementation in Great Britain, will randomize 65,000 women ages 40 and 41 who will be screened and then compared with 130,000 controls. Dr. Greenwald stated that NCI has been in contact with the investigators planning this study and will continue to explore constructive ways in which the Institute can assist or collaborate with the study.

Dr. Greenwald concluded his remarks by emphasizing that the Board of Scientific Counselors and the NCAB have been asked to help NCI determine whether the breast cancer screening guidelines are consistent with science, without consideration of reimbursement issues. He then introduced Dr. Kaluzny.

Board of Scientific Counselors, DCPC, October 1993 Meeting—Dr. Arnold Kaluzny

Dr. Kaluzny explained that the BSC's charge during the October meeting was to assess the appropriateness of the draft guidelines, taking into consideration the analysis of the Fletcher Committee and commentary from various advocacy and professional groups; to suggest specific information that will assist health care providers and the public in making decisions regarding breast cancer screening; and to assess the process for developing future guidelines, if necessary.

Several panels of advocacy and voluntary groups, community groups, and professional organizations made presentations, including the Breast Cancer Coalition, the Women's Health Network, WHY ME, the Black Coalition, the Appalachian Coalition, the American Cancer Society, the National Medical Association, and the American College of Radiology, among others. Each individual was given 10 minutes to speak, after which Board members had the opportunity to ask extensive questions. The three questions addressed during these exchanges were: Do the data warrant a change in breast cancer screening guidelines? If yes, how can this best be presented? And, how can this process best be carried out in the future?

Dr. Kaluzny stated that it is the consensus of the BSC that in the future, NCI should not be in the business of providing guidelines. He noted that setting guidelines goes beyond analysis of data into questions of ethics, finance, and other issues that the Institute is not structured to deal with. Dr. Kaluzny suggested that NCI originally became involved in setting guidelines as an effort to "do the right thing" during a time when the Agency for Health Policy Research, which now has a mandate to develop such guidelines, did not exist. The Board then moved on to discuss whether a change in the present guidelines is warranted and, if so, how best to proceed.

Dr. Kaluzny said Board members are confident that the data quite clearly indicate that mammography is effective for women over 50 and, thus, support the 1987 guidelines. The real challenge, he stressed, is in guidelines for the 40- to 49-year-old group. He said the Board's recommendations are based on three main issues—the lack of knowledge about the effectiveness of screening for this age group, the need for NCI to be truthful, and the need for further research in this area.

Dr. Kaluzny explained that the Board—which is composed of epidemiologists, clinicians, biostatisticians, and others—considers all existing studies to be flawed. He stated that the Board supports the philosophy that interventions are ineffective until proven effective, thus placing the burden of proof on the data to clearly show that specific recommendations should be made.

Concerning the issue of truthful disclosure of information, Dr. Kaluzny expressed the Board's belief that the Institute has an obligation to share state-of-the-art information on breast cancer screening with the American public and health care providers through a process that reflects the dynamic nature of knowledge in this area. The Board acknowledged the Physician Data Query (PDQ) system as a dynamic mechanism for providing updated information that is tailored to the needs of both professionals and various population groups.

Several aspects of the need for further research were addressed, including collaboration with European researchers to develop randomized clinical trials with sufficient power to make determinations on effectiveness and screening intervals. Questions of cost-benefit analysis were also discussed. Another issue of concern was the population of women over 70, which, Dr. Kaluzny noted, the Board considers to be a "gray area" worthy of further investigation.

Dr. Kaluzny then stated that he would respond to questions after the final segment of the presentation and relinquished the floor to Dr. Barbara Rimer.

Remarks—Dr. Barbara Rimer

Dr. Rimer opened her remarks by stating that she was addressing the NCAB as a panel member of the report writing team for the International Workshop on Breast Cancer Screening, as a breast cancer screening researcher with more than 12 years of experience, and as a 45-year-old woman. She applauded NCI for addressing the difficult issues surrounding changes in breast cancer screening guidelines, noting that maintaining the status quo would be an easier course, but would not be true to science.

Dr. Rimer stated that a review of the literature produced by the Fletcher Committee consistently reveals a lack of support for mammography screening for women in their forties in terms of a reduction in mortality from breast cancer. She said that her personal predisposition in favor of screening for this age group has been transformed because the benefits remain unproven. She observed that opponents of changes in the guidelines have not claimed that screening for this age group is beneficial, only that its effectiveness is unknown.

From an ethical point of view, Dr. Rimer suggested, a clear distinction must be made between public health recommendations and decisions made between doctor and patient, noting that a great deal of certainty is required for public health advice. She also called attention to the costs of screening—not only the dollar costs but the impact of the less precise nature of mammography in younger women. The lower sensitivity of screening among these women means that many cancers may be missed, and the excess number of false-positive results causes anxiety.

Dr. Rimer acknowledged that the tremendous momentum that has been built up in delivering the message that mammography saves lives among younger women makes it difficult to consider the idea of changing the guidelines, but she argued that medicine is dynamic and must be ready to adapt to new information. Over the years, she added, many previously accepted medical practices have been replaced by newer approaches. The public and practitioners, she noted, should be encouraged to view recommendations as an evolutionary process and not as dogma.

Dr. Rimer said that the proposed changes in the breast cancer screening guidelines are recommendations based on science, not on politics, economics, or wishes. Everyone, she pointed out, wishes that mammography could save the lives of women in their forties, but wishing will not make it happen. Giving young women false hopes about the value of mammography, she added, is a disservice. Dr. Rimer stated that while it may be possible to develop more precise guidelines in the future when further research becomes available, it would be wrong to continue the status quo indefinitely in the hope that the results of new trials will show a positive result.

Although arguments against change have been based on the assertion that not enough is known about screening effectiveness, Dr. Rimer stated that after more than 30 years and more than 800,000 woman-years of trials, it can be concluded that mammography saves lives among women in their fifties and sixties but not among women in their forties. She cited two conclusions reached by speakers at the October BSC meeting: if more data are needed, this uncertainty should be communicated to the public; and, whether existing data are viewed as inadequate or accepted as proof of a lack of benefit of screening for younger women, there is still no scientific support for guidelines advocating routine screening for women in this age group.

Dr. Rimer pointed out that the proposed guidelines do not say that women in their forties should not be screened; they state only that the benefits have not been proven. She argued that the NCI must tell women the truth and let women and their doctors make informed decisions. Dr. Rimer cited evidence from focus groups conducted by NCI and studies conducted in Washington State showing that women are willing to accept changes in screening guidelines. She strongly emphasized the importance of preparing physicians, the media, and

the public to understand the proposed changes. Because sound science does not easily reduce to "sound bites," she stated, it is necessary to communicate both complexity and uncertainty when providing information about guidelines.

Dr. Rimer concluded that disappointment over the lack of a clear benefit of screening for women in their forties should not divert attention from the importance of sending a clear message about the value of mammography for women over 50, which can have a major impact on mortality. She noted that regular screening among that age group still has not been achieved.

Questions and Answers

Dr. Salmon reintroduced his earlier motion and asked for a second. Mrs. Gimbel seconded the motion. Dr. Salmon said that deferring a decision on changing the guidelines would imply that there is no information that requires discussion. He agreed with Dr. Rimer that NCI should tell the truth based on the science available at the time, adding that this does not mean that NCI must become a public health policy-making organization.

Dr. Greenwald stated that some individuals attending the BSC meeting who had experience in setting guidelines said that this is an elaborate process requiring defined criteria and an experienced staff.

Dr. Becker asked for clarification of the phrase "no benefit"; he observed that the report does not use this phrase but uses the phrase "no improvement in mortality." Dr. Greenwald replied that all such statements are based on the meta-analysis and refer to mortality endpoints. Dr. Becker emphasized that it should be made clear whether statements concerning a lack of benefit actually refer to a lack of improvement in mortality, since improvements in quality of life and survival are often achieved and, thus, mortality is a third component in the analysis of benefit.

Dr. Rimer commented that when considering the interests of well women who may suffer from the problems of false negatives and false positives associated with this test, the best level of assurance available through randomized trials is the mortality endpoint. Problems with other endpoints, she said, include length bias, lead time, and selection of volunteers. She suggested that decisions about guidelines must be based on whether screening saves the lives of women.

Dr. Becker repeated his request that for the sake of accuracy, the phrase "no change in mortality rate" should be used instead of "no benefit" when discussing the meta-analysis of the data from screening studies. Dr. Greenwald agreed, noting that some data have shown potential benefits and potential harm in the other components of analysis that Dr. Becker mentioned earlier, adding that results are inconclusive in these areas as well.

Dr. P. C. Srivastava, an alternate ex officio NCAB member representing the Department of Energy, read a letter that had been received by his office from the Texas Cancer Council. The Council was extremely concerned about NCI's proposed changes in breast cancer screening guidelines for women 40 to 49 years of age and passed a resolution at its November 8, 1993, meeting expressing opposition to the changes. While recognizing the

inconclusiveness of data on the benefits of screening for this age group and the appropriateness of ongoing evaluation of the guidelines, the Council strongly urged NCI to continue the current guidelines until further scientific evidence has been gathered.

Ms. Zora Brown objected to a statement made earlier, during Dr. Rimer's presentation, to the effect that mammography does not save lives among women ages 40 to 49. Ms. Brown stressed the fact that treatment saves lives and argued that mammography was never intended to save lives but, rather, to detect cancer. She expressed strong concern about the idea of changing the guidelines based on studies among primarily Anglo-American women in light of a recent NCI report showing that the incidence of breast cancer among African American women below the age of 40 is higher than that among White women. Ms. Brown stated that discussions about changing breast cancer screening guidelines should not be based on flawed information and suggested that not enough studies have been done. She asserted that there is no consensus on whether screening benefits women under the age of 50, expressing her opinion that there is a benefit to these women in finding cases of cancer and subsequently treating them. Ms. Brown added that further research might be needed on whether treatment should differ for women in different age groups.

Dr. Lawrence stated that he had been the only NCAB member to attend the public meeting discussed earlier by Dr. Greenwald. He described the meeting as a very balanced presentation with excellent representation from reliable and responsible organizations interested in the issue of guidelines. He noted, also, that the overwhelming majority of those in attendance expressed regret concerning any changes in the cancer screening guidelines. Because he believed the purpose of the meeting was to determine how those groups felt about the changes, Dr. Lawrence said, he wondered why the changes were still being considered in the face of such opposition.

Dr. Greenwald agreed that many groups expressed the views voiced by Dr. Lawrence, but stated that a range of views had been presented. He identified several groups whose representatives supported a change in the guidelines, including the Women's Health Network, the Center for Medical Consumers, the American College of Physicians, and the American College of Family Physicians. He observed that groups focusing their recommendations on women over the age of 50 tended to be those whose interests were general health issues rather than issues specific to breast cancer. Dr. Greenwald agreed with Ms. Brown that the breast cancer research agenda should include a broad range of subjects, including therapy, and that better data on African American women are needed.

Dr. Bettinghaus agreed with Dr. Kaluzny that the issue before the Board is essentially a philosophical question of whether to wait until all evidence is in before making a decision. He expressed the opinion that the guidelines should not be changed until clear evidence warrants a revision. Dr. Bettinghaus asked for the opportunity to clarify statements made during Dr. Greenwald's presentation. One statement suggested that the Fletcher study found a screening interval of 12 to 33 months to be effective. Dr. Bettinghaus pointed out that the study concluded that screening from 12 to 33 months is 85 percent as effective as screening at 1-year intervals; in other words, he noted, 15 percent of the cancers will be missed if the interval is 33 months.

Dr. Bettinghaus also noted that a slide based on the Fletcher Commission study showed a relative risk of 1.08; he cited a more recent presentation to the BSC that reported a relative risk of 0.93. Dr. Bettinghaus acknowledged that the difference is not great, but noted that the change is in the right direction. He also stated that the original meta-analysis, which did not include data from the Canadian study, showed a better relative risk than a later analysis that did include Canadian data. He pointed out that the high relative risk in the Canadian study was caused by the inclusion of symptomatic women.

Dr. Greenwald acknowledged that the more recent relative risk of 0.93 is correct. In terms of screening intervals for women age 50 and older, he explained that the trials do not allow for a distinction between 12 and 33 months. The estimated 85 percent effectiveness of screening every other year compared with annual screening is an approximation reached through mathematical modeling based on a number of assumptions. Concerning the meta-analyses, Dr. Greenwald suggested that it is not appropriate to subtract data from studies "you do not like." He said that some observers felt the sensitivity in the Canadian trial was greater than in some of the Swedish studies.

Dr. Sigal stated that science and policy issues must be addressed differently. She observed that there is no consensus on the scientific aspects of this issue and questioned any decision to change recommendations when so many people of good will disagree. In terms of policy, Dr. Sigal said that she is very concerned about the implications of saying that a woman and her physician should decide on screening. That means, she argued, that women with few financial resources will be denied screening. Dr. Sigal added that she has been troubled to hear physicians speak in favor of changing screening guidelines or getting out of the business of setting guidelines and then say that they or their spouses intend to continue mammography screening for themselves.

Dr. Bragg agreed with Ms. Brown and Dr. Sigal that the information at hand is not adequate to make a decision. He stated that changing the guidelines would result in the loss of an opportunity to screen a very complex group of patients, and that screening of the more dense breast presents a challenge that will require the passage of time and development of more advanced technology to better understand. He noted that not enough is known about the alternatives, adding that NCI must not abandon its role of providing information and advice to health care providers who are being asked to take up the role of advising their patients about screening. Dr. Bragg argued that it would be a disservice to the public to change course at this time.

Dr. Freeman asked about the generic implications of this kind of policy-related issue for other policies or recommendations of NCI. He asked, for example, whether there is proof that the dietary recommendations endorsed by NCI save lives.

Dr. Calabresi noted that Dr. Salmon's motion addresses this question by proposing that NCI get out of the business of setting any kind of guidelines, whereas Dr. Bragg's present motion would only delay the decision to change the guidelines.

Dr. Broder expressed the view that dietary recommendations are in a different category because they relate to diet from a total health perspective and involve cardiovascular as well as cancer-related endpoints. In terms of mammography, he said, the issue is a safe and effective

medical intervention that can save lives. He noted that there is no debate about screening for women over 50, a group that has 80 percent of all breast cancer cases but is underutilizing mammography.

Dr. Broder explained that NCI relies on consensus in the scientific community to help determine courses of action. The situation regarding breast cancer screening guidelines is very difficult, he stated, because individuals with very good credentials do not agree. Dr. Broder emphasized the fact that NCI cannot back away from this disagreement and that the level of disagreement has to be conveyed to the public. He acknowledged that some guidelines (for example, recommendations concerning smoking cessation) are incontrovertible because of the certainty of the scientific evidence, but observed that some others (for example, those regarding PSA testing or flexible sigmoidoscopy) are as debatable as breast cancer screening guidelines. Everyone should ask themselves, he said, what additional research it would take to change the guidelines, as well as how advice should be provided to women and their families in dealing with issues about which the scientific community disagrees.

Dr. Broder agreed with Dr. Becker that quality-of-life issues are important. However, he noted, studies of new technologies often involve a profound lead time bias. When a new procedure makes it possible to detect a cancer earlier than previous methods, it automatically produces what appears to be a prolongation of survival.

Dr. Broder emphasized that NCI is not telling women to avoid mammography but is trying to find a way to deal with the fact that the studies at hand have not provided a statistically significant answer. He added that those who recommend retaining the current guidelines should, at a minimum, be thinking about what kind of footnote could be added to those guidelines.

Dr. Broder added that the same process should be followed in the testing of dietary fat in the Women's Health Intervention Study. If this study fails to show a cardiovascular or cancer-related benefit from reducing dietary fat, he said, NCI should conclude that a change in dietary guidelines is in order. Dr. Broder also urged that the issue of prudent health practices should not be mixed into the discussion of how to accommodate the reality resulting from study results. He concluded by stating that it is unwise for NCI to try to manage facts; the public, he stressed, has to be able to believe that recommendations are factually based.

Dr. Wells asked whether any questions have been raised concerning whether these studies were flawed in any way. Dr. Broder replied that flaws could be picked out in any study, but that these were generally well-conducted studies with the added strength of having been performed by investigators in different countries. He noted that the studies consistently showed a benefit of screening for women over 50 and consistently failed to show a statistically significant benefit for women under 50. Dr. Wells said that he has been somewhat persuaded as this discussion has unfolded that NCI must proceed based on the data that are available.

Dr. Ihde added, in response to Dr. Wells' question, that in all but one case the trials that showed a statistically significant benefit of screening through detection of mortality rate reductions in women over 50 were exactly the same trials that did not pick up a mortality rate reduction in women under 50.

Dr. Calabresi, noting that one of the trials was over 30 years old, asked whether any of the women received adequate adjuvant chemotherapy. Dr. Greenwald answered that none of them probably received much adjuvant therapy.

Dr. Bragg commented that none of the trials, except one, had the statistical power to analyze the impact of screening mammography in women under the age of 50. It was never the intent of these trials, he added, to examine the benefit of screening.

Dr. Kramer stated that the trial that offers the strongest support for screening is the only one in which women could have received adjuvant therapy; the others predate the adjuvant therapy era. The Swedish and Scandinavian countries began to accept standard adjuvant therapy for node-positive women in 1978, and the earliest Swedish trials did not contain adjuvant therapy as a matter of course. Three-quarters of women in the last two trials that were conducted received adjuvant therapy for node-negative disease. Dr. Kramer explained that the Canadian trial was the only study that meticulously examined the appropriateness of adjuvant therapy. Virtually all women with node-positive disease in this trial received either adjuvant hormonal therapy or chemotherapy. An independent panel of radiation therapists, surgeons, and medical oncologists examined a chart analysis of women in this study in their forties who had been diagnosed with breast cancer and concluded that the therapy was appropriate.

Dr. Kramer stated that, while no individual trial had sufficient statistical power to make a definitive statement, an in-house analysis of the combined power of the trials showed a 90 percent power to detect a 25 percent improvement in mortality and a 98 percent power to detect a 30 percent improvement in mortality among women under 50.

Dr. Wilson asked Dr. Bragg how much assurance women have that they will not be falsely reassured by screening. Dr. Bragg emphasized that mammography is not perfect, even when conducted by the most qualified individuals, and that to decrease the risk of missing mammographically imperceptible cancers, the screening must be coupled with clinical examination. Dr. Bragg added that stringent new national standards for screening will begin by October 1, 1994, that will require measurement of the professional as well as the technical quality of examination.

Dr. Wilson then inquired about the frequency of failure to detect a malignancy. Dr. Bragg answered that estimates of breast cancers that are mammographically invisible range from approximately 10 to 15 percent. Dr. Bettinghaus asked about the rate of false positives. Dr. Bragg explained that this rate varies according to the complexity of the breast tissue, the presence or absence of previous mammographic examinations for comparison, the experience of the examiner, and the quality of the study. Dr. Calabresi asked about the rate of false negatives in women under age 50 and women over age 50. Although it is difficult to answer this question specifically, Dr. Bragg explained, it is better to compare the rate of false-negative results with the mammographic surround of the stromal breast tissue. The number of false negatives would be higher in women under the age of 50 with denser breast tissue. Dr. Rimer commented that upon examination to determine the rates of false negatives by age, trial data suggest that the sensitivity for mammography in women age 40 to 49 is as low as 60 percent. This figure, she continued, indicates that breast cancers are missed in younger women, primarily due to the limits of the technology.

Ms. Brown asked about the rationale for developing the current guidelines. Dr. Greenwald explained that NCI collaborated with several organizations, including the American Cancer Society and the College of Radiology, in 1987 to reach a consensus on the data available from clinical trial results.

Dr. Salmon suggested that the effect of breast tissue density on the accuracy of screening is a possible new research issue. He commented that the individual studies that were conducted did not have the power of meta-analysis for women under the age of 50. Meta-analysis, Dr. Salmon added, markedly enhances the results of randomized clinical trials, which are often too small to provide adequate statistical power. Meta-analysis showed a modest improvement in survival in women who received adjuvant endocrine therapy or adjuvant hormonal therapy; in most of the studies, an average of 10 percent of the women appeared to benefit. Dr. Salmon remarked that it is hoped that more women will show benefit in terms of survival in the future. While extension of survival has clearly been gained through screening, Dr. Salmon noted that probably no study to date has sufficient information in case accrual of effective adjuvant therapy to show a benefit in mortality. The challenge for the future, he said, will be to show that screening performed in a research setting can change outcome and gain benefit, regardless of the measurement modality.

Dr. Ed Sondik stated that the sensitivity of mammography is at least 10 to 15 percent, possibly 20 percent. He commented that if NCI continues with the existing guidelines, it will be acting in a manner that is inconsistent with the science, in that the Institute will be unequivocally recommending mammography for women ages 40 to 49 without having the evidence to justify that recommendation. He said that the members of the February 1993 workshop drafted a set of recommendations they believe to be consistent with the science, and that these recommendations do not suggest that one should or should not be screened but, rather, stress the importance of an informed decision. Dr. Sondik suggested that the challenge is to translate the complex aspects of the science into the public policy arena and expressed concern over releasing a simple statement that does not convey the full impact of the science. He also expressed concern about the repercussions of future decisions based on the existing guidelines if the science continues to support a lack of improvement in mortality associated with screening in younger women.

Dr. Sondik discussed the harm associated with mammography as discussed in Dr. Kerlekowsky's article in *JAMA*. He explained that there are about three times more diagnostic procedures associated with cancer performed in women under age 50 than in women over age 50 and about two and one-half times as many biopsies. Dr. Sondik noted that it is difficult to recommend or not recommend this screening procedure when there are potential medical harms associated with it and no clear decrease in mortality until age 50. He stated that it seems to be more effective to state both sides of the argument and develop materials that will enable the public and their physicians to interpret and apply the information.

Dr. Broder returned to Ms. Brown's question about the basis for the original recommendations. He stated that the guidelines were probably established because there was a need to compile the best available information and create operating guidelines for recommendations while more conclusive data were formulated. Studies in this area have matured and, thus, the situation has changed.

Dr. Broder emphasized that mammography is not prevention but, rather, a form of early detection. He suggested that a balanced program of research is needed that will allow mammography research to proceed, but also will pursue other technologies, such as MRI or electron spin resonance imaging, that might be able to detect tumors at the millimeter level. If tumors could be detected at this level, it might be possible to routinely and efficiently document ductile carcinoma *in situ*, which would certainly have an effect on mortality.

Dr. Broder reminded the Board that women rarely die of primary tumors. Mortality associated with breast cancer is usually determined by micrometastatic disease that cannot be detected, and, in some women with certain types of diseases, metastatic events may occur extremely early. In this case, mammography could not realistically change the course of the disease and, therefore, more effective programs must be developed for intervention following detection. Dr. Broder cautioned that NCI should not become overly focused on mammography because, at best, it is only reducing the death rate by one-third. He stressed that NCI must have a vigorous and balanced research agenda and urged Board members not to lose sight of this goal in their capacity as advisors to the Institute.

Dr. Srivastava asked about the legal implications of the guidelines related to age discrimination. Dr. Broder answered that this concept is probably not applicable in any event and the Board should be concerned with scientific issues.

Dr. Lawrence indicated that the discussion and presentations on this topic appear to be one-sided and reiterated that there are multiple points of view, all of which are based on science. He encouraged the Board to pass a motion on the second day of the meeting and reaffirmed his support of the motion by Dr. Bragg.

Dr. Bettinghaus stated that the original guidelines—based on small studies that focused on women ages 40 to 64 and not designed for subanalysis—represented a consensus of opinion among interested groups. He expressed concern that NCI has not followed a similar procedure to develop a consensus and a common answer for presentation to the public. Accuracy of information is important, he added, but the existence of conflicting messages from different organizations confuses the decision-making process for individuals.

Dr. Bettinghaus suggested that the evidence appears to be moving in favor of screening, even on the basis of mortality. He expressed his feeling that a precise statement and decision can only be made on the basis of the point estimates or trend analyses from the available data.

Dr. Broder asked about the age range for the Edinburgh study. Dr. Bettinghaus responded that the range is 45 to 64, with a meta-analysis for 40- to 49-year-old women.

Dr. Wells asked if the Board could vote on and bring closure to this issue.
Dr. Calabresi explained that this was an important discussion to conduct in conjunction with Dr. Greenwald's presentation and the Board could resume this discussion on the second day of the meeting. Dr. Calabresi then asked for comments from Drs. Temin and Pitot, who were participating in the discussion by speaker phone.

Dr. Temin expressed his concern that the studies on which the recommendations were based did not include adequate numbers of minority women. If this is true, he continued, the recommendations should be modified for the appropriate audience—majority or minority. Dr. Pitot suggested maintaining the current guidelines and adding information stating that at the current time there is no evidence that mammography has any effect on mortality in this age group and there is uncertainty about mammography's effect on minorities included in the data as well.

Dr. Broder stated that the issue of minority recruitment is extremely important and one of the priorities of the Institute. It is hoped, he continued, that the universal access of health care and elimination of prior existing conditions promoted by President Clinton will help to address this problem. Dr. Broder encouraged the Board to support the President's health care reform agenda. The NCI as a research-based organization will frequently be forced into situations in which it will either generate new knowledge not encompassed in a prior set of policies or will have to alter its policy. All NCI can do as a science-based agency, Dr. Broder remarked, is provide the best available information. He urged the Board to make policy decisions that will create order. Dr. Broder noted that NCI needs the Board's advice in addressing the uncertainty that is present in scientific matters and the disagreement among experts.

Ms. Visco commented that she does not see the relevance of discussing false negatives, unless mammography can find no breast cancer for a woman under the age of 50. She mentioned that women under 50 would experience great anxiety upon learning that there is nothing for them in terms of screening. Ms. Visco asked the Board to advise doing something for women under 50—whether it is keeping the guidelines or not. She added that NCI should consider entering every woman under 50 into a clinical trial to test different screening modalities for women between the ages of 40 and 50 to determine what works best for this group.

Dr. Kaluzny commented that none of the studies has addressed the issue of minorities and that this issue is a central part of the research agenda.

Dr. Calabresi announced that discussion would resume on the second day of the meeting. At Dr. Bettinghaus' request, Dr. Calabresi agreed to move the second session of the new business discussion to an earlier time on the second day. Dr. Calabresi then adjourned the morning meeting.

VIII. IMPLICATIONS OF RADIOSURGERY FOR CANCER THERAPY—DR. PHILIP GUTIN

Dr. Charles Wilson introduced Dr. Philip Gutin, professor of radiation oncology and neurosurgery at the University of California at San Francisco (UCSF) and principal investigator in the UCSF Brain Tumor Research Center. Dr. Wilson related that Dr. Gutin has a long-standing interest in radioprotection and radiosensitizers, and has written a book on radiation injury to the central nervous system that has become a standard in the field. Dr. Wilson expressed his pleasure in introducing Dr. Gutin to present the latest information on

radiation surgery, which, he observed, has recently assumed a large role in the treatment of both benign and metastatic, as well as primary malignant, brain tumors.

Dr. Gutin explained that radiosurgery involves the stereotactic external beam irradiation of small intracranial targets. Radiosurgery is different, he said, from conventional external beam radiation in that it is generally delivered in one single fraction as opposed to a fractionation over a period of time, thus treating a much smaller volume than conventional radiotherapy. The dose gradient is very high for radiosurgery, and the isodose curves conform tightly to the target because of the stereotactic component, resulting in a high degree of accuracy.

Radiosurgery is delivered in a variety of ways, Dr. Gutin continued, the most common of which are with x-rays modified by conventional linear accelerators, and with gamma rays using the Leksell gamma knife. Radiosurgery can accurately and stereotactically localize a small intracranial target by imposing a coordinate system on the brain. The coordinate system is affixed to the skull with a stereotactic frame. Three-dimensional isodose surfaces are then determined around the target volume through imaging studies, including magnetic resonance imaging (MRI), computerized tomography (CT) scan, or an angiogram with the frame in place so that the target is visible. Treatment is then delivered and the patient usually remains in the hospital overnight.

Dr. Gutin presented a slide of the Brown Roberts Wells (BRW) stereotactic frame, which, he said, is a breakthrough device because it contains a base ring that attaches to the skull, to which a system of fiducial bars can be fastened, depicting a relationship between a target and the frame as visualized on x-ray. Dr. Gutin explained that this allows for calculation of a trajectory to the intracranial target by use of the operating frame. It is possible, he stated, to biopsy even difficult anaplastic astrocytoma in the dominant hemisphere and other targets deep in the brain stem using these stereotactic devices. Intracranial targets can also be accessed for the placement of radioactive sources into tumors.

Dr. Gutin next presented a slide of another type of stereotactic frame—the Leksell stereotactic frame, which was developed by Lars Leksell and is used mostly for functional work in Parkinson's disease, movement disorders, pain, and psychosurgery. It is also the frame of reference for the Leksell gamma knife. Application of the Leksell frame, Dr. Gutin explained, is a cumbersome procedure that requires anesthesia. Positioning of these frames, he noted, is a tedious and lengthy procedure. If the frame moves during treatment or is positioned incorrectly, the accuracy of the procedure can be thrown off, sometimes causing the treatment to be aborted completely.

The dosimetry developed for radiosurgery depends on what type of system is used. Dr. Gutin reiterated that the most common way of delivering radiosurgery is with a modified linear accelerator that rotates around the patient, whose head is in a stereotactic frame affixed to the floor; both the turntable of the gantry and the gantry itself rotate. He presented a slide showing that several dosimeters are chosen to deliver smooth radiation dose around the margin of the target. Then, a number of arcs are calculated by the computer to spread the dose out over the skull so that any point other than the tumor receives a low dose of radiation. The principle of arc-centered radiation surgery, Dr. Gutin explained, is that all of the arcs are concentric and the dose accrues and becomes very high.

In many centers, Dr. Gutin stated, the patient is placed in a stereotactic frame on a floor stand, and the linear accelerator with a collimator is rotated around the patient. He noted that these huge machines were not designed for treatment accuracy of within a millimeter; thus, it is incumbent on centers performing this type of work to determine in which cases these machines are best used.

Dr. Gutin explained that the best and most accurate (within a fraction of a millimeter) linear accelerator-based systems have a Gimbel bearing interposed on the accelerator head to support its oscillation. He added that the Leksell gamma knife is intrinsically accurate, since there are no moving parts in the dome, around which there are 201 fixed cobalt sources that spread the dose over the skull. Use of the Leksell frame to position the head stereotactically allows the accurate delivery of radiation to a deep target.

Dr. Gutin noted that the gamma knife has Food and Drug Administration (FDA) approval and is increasingly popular. This $3.5 million machine has several collimator sizes, with a fixed source, resulting in quick planning with simple calculations and allowing two treatments to take place on the same day. There are 51 Leksell gamma knives worldwide—22 in the Far East and 17 in the United States. There are more linear accelerator facilities in the United States than facilities with gamma knives, primarily because of the $750,000 cost to convert a linear accelerator to use for radiosurgery and the additional $3.5 million for the gamma knife. Dr. Gutin indicated that there are not enough diseases to support all of the radiosurgery units and expressed his concern that the increasing number of units will lead to misuse and inaccurate treatment, as well as dilute the research efforts of the academic centers.

The gamma knife, Dr. Gutin continued, is radiology based, and its use involves the support of neurosurgeons, a radiation oncologist, a physicist, and a full-time radiosurgical nurse who stays with the patient continuously during the procedures. Dr. Gutin explained that his unit treats four or five patients a week and must, therefore, maintain a large staff. The treatment itself is labor-intensive, he continued. Staff must reset the coordinates for every isocenter of treatment using the bars on the stereotactic frame and position the patient's head in the collimation helmet so that the target area is at the center of the collimated beams. Dr. Gutin explained that staff leave the room when the door to the gamma knife opens. The patient then is moved inside, the unit locks into position, treatment is delivered, and the patient automatically slides back down. The patient is monitored during the entire procedure and communication takes place through microphones and video cameras.

Dr. Gutin observed that the gamma knife can be applied for the treatment of arteriovenous malformations (AVMs) of the brain, pain surgery, and psychosurgery, as well as a variety of brain tumors, such as meningiomas, acoustic neuromas, malignant gliomas, and brain metastases. Dr. Gutin reported that in its first 16 or 17 months of use at UCSF, the machine was mostly used for AVMs, acoustic neuromas, and malignancies. He related that UCSF staff believe the gamma knife is not the treatment of choice for acoustic tumors, except in special circumstances.

Dr. Gutin described the use of radiosurgery for AVMs, which are not tumors but, rather, are tangles of blood vessels in the brain that can grow and cause hemorrhage, seizure, severe headaches, and progressive neurological deficits. To treat AVMs with radiosurgery, as high a dose as possible is delivered to the nidus of the malformation. The feeding arteries and

veins are ignored and, over a period of years, the nidus undergoes a hyalinization, interval proliferation, thickening thrombosis, and, eventually, obliteration. Prior to radiosurgery, there was no treatment for AVMs in the center of the mid-brain. Dr. Gutin showed slides of malformations in the dominant hemisphere that either shrank or disappeared after gamma knife treatment. The complete response rates for AVMs, he noted, are approximately 60 to 90 percent, and for smaller AVMs, very close to 90 percent at 2 years. He noted that there is a high response rate and low incidence of permanent complications in young patients who receive a high dose and have small, adequately treated AVMs. Results have been so positive that even operable AVMs are being treated with radiosurgery at some centers.

Dr. Gutin explained that his group considers the acoustic neuroma to be a surgical tumor. Although the patient's hearing will be sacrificed with the removal of this type of brain tumor, a complete cure is guaranteed. Dr. Gutin related that older patients, patients with excessive medical risk for open surgery, patients who refuse surgery, and patients with bilateral tumors were selected for early radiosurgical work with acoustic neuromas. Overall data from a number of series show that these tumors fail to progress in about 90 percent of patients. Dr. Gutin noted, however, that the longest series involves only about 9 years median follow-up; thus, it is not known if this represents a cure. He added that loss of hearing, facial palsies, and facial numbness can result from the treatment.

Dr. Gutin then moved on to discuss the radiosurgical treatment of malignancies. Of all the tumors treated with the Leksell gamma knife worldwide, he related, 35 percent are gliomas, about 50 percent are metastases, and 15 percent are various other types. Surgical resection is recommended for patients with large solitary metastases. He said that several new surgical techniques are being used in this procedure. A robotic wand, called the ISG wand, can be used to plan surgical exposure. Prior to the day of surgery, small fiducial markers are taped to the scalp and an MRI scan is performed; the tumor volume can then be recreated during surgery based on the x-ray. The wand can be used to assess the relationship between tumor margins and the target area for operation and can guarantee a more complete resection of the tumor.

Functional mapping of the brain, Dr. Gutin continued, is also being used. He explained that EEG monitors are used to avoid the risk of seizure during stimulation of the brain, and it is possible to map out the motor cortex of the brain to localize the tumor just beneath the motor cortex.

Dr. Gutin noted that researchers at the University of Kentucky conducted a randomized trial in patients with solitary metastases (mostly large-scale lung tumors) that showed the combination of surgery and radiation therapy to be more effective than delivery of radiotherapy alone. The local failure rate decreased from 50 to 20 percent, and median survival increased from 15 to 40 weeks. Median duration of independent survival based on neurologic function increased dramatically.

Dr. Gutin stated that improved local control of therapy can lead to improved survival. Because radiosurgery is a noninvasive method of increasing local control, he reasoned, it can be used to replace surgical resection in certain metastases. One question that remains is whether radiosurgery can be used as successfully in patients with multiple or inoperable metastases. Radiosurgery has been shown to be successful (90 to 95 percent) in inducing local

control with short follow-up in all series published to date, and some uncontrolled studies also suggest that the success rate of radiosurgery may be equal to that of surgery. Dr. Gutin recognized the work of Dr. Mehta at the University of Wisconsin Cancer Center, which has shown an improvement in Karnofsky Performance Score (KPS) after radiosurgery and a drop in the numbers of patients who are on steroids over time following surgery. Therefore, Dr. Gutin observed, symptomatic relief is being achieved in addition to radiographic regression.

Dr. Gutin explained that while radiotherapy is always recommended for patients with recurrent metastases, its role is unknown for patients with initial presentation of either solitary or multiple metastases. He stated that, currently, patients are being treated with a combination of radiosurgery and whole-brain irradiation because of the possible existence of hidden micrometastases. MRI scanning, he noted, is becoming more accurate with the development of double and triple dose contrasts and may reveal that no metastases are being missed. Dr. Gutin presented slides of tumors in patients who have experienced regression of disease. He proposed that it is reasonable to treat patients with radiosurgery and whole-brain irradiation if they have a good Karnofsky score, a relatively small tumor (a diameter of less than 3 centimeters), multiple metastases, no active or minimally active systemic disease, and a projected survival of more than 6 months.

Dr. Gutin indicated that while radiosurgery has been shown to result in local control, the duration of control is as yet unknown, since many of the series conducted to date are too new to address this issue. He reported that a randomized trial is under way in Pittsburgh to investigate whether radiosurgery should be combined with whole-brain irradiation, and another randomized trial is under way through the Joint Center for Radiation Therapy at Harvard to determine whether radiosurgery can replace open surgery for resectable tumors. The UCSF is participating in this latter study.

Dr. Gutin next addressed the use of radiosurgery for treatment of gliomas, which, he noted, are occurring much more frequently in older patients than in the past. Although radiation therapy is the norm for treatment of gliomas, virtually every patient who receives this treatment for glioblastoma ultimately dies. Radiosurgery, Dr. Gutin stated, is improving the therapeutic ratio for glioblastomas, but because glioblastoma is a diffusely infiltrative disease, it is optimistic to hope to draw a radiosurgical line around this type of tumor and have an impact on it.

Dr. Gutin then discussed brachytherapy, which, he said, is similar to radiosurgery in that both deliver high focal doses of irradiation in addition to the external beam irradiation delivered for these tumors.

Brachytherapy, he explained, is the implantation of radioactive sources directly into a tumor using stereotactic techniques. This kind of localized treatment is beneficial only for certain tumors that are well circumscribed radiographically, not in the midline of the brain, not in the brain stem, and not located anywhere in deep subcortical structures. One cannot treat diffuse tumors with radiosurgical or brachytherapy treatment. Dr. Gutin noted that only about 25 percent of UCSF's patients have this kind of circumscribed disease. The Northern California Oncology Group Trial, which was not randomized, found that external irradiation and implant extends survival in these patients from 10 or 12 months to about 22 months.

Implant data show that patients under the age of 30 have a 5-year survival rate of around 71 percent; patients less than 40 years of age have a 5-year survival rate of about 17 percent. Thus, Dr. Gutin pointed out that the use of these aggressive radiation techniques is improving outcome for patients with this type of tumor. However, the majority of these patients eventually experience recurrence of disease and die.

Since brachytherapy increases survival, Dr. Gutin stated, it is possible that radiosurgery will do the same. It may be most effective to provide a large dose of radiosurgery for resistant tumors to overcome the shorter arm of the survival curve. Radiosurgery can also be used in sites deep within the brain that cannot be reached with brachytherapy. Because gliomas are infiltrative, most tumors do not meet the criteria; 75 percent of patients who come to the UCSF center cannot be treated with radiosurgery. It is necessary to treat with a lower dose of radiosurgery than brachytherapy because the dose of radiosurgery must be administered all at once rather than over the course of 5 or 6 days. Dr. Gutin noted that radiosurgery has not been used much at UCSF, except in patients with good Karnofsky scores and small tumors in nonimplantable sites that are radiographically distinct and unifocal.

Dr. Gutin highlighted several successful (and one unsuccessful) cases that were treated with radiosurgery. He reported that 46 patients have been treated at UCSF with this modality—35 since June of 1992, of whom 25 had glioblastomas and 7 had anaplastic astrocytomas. UCSF's mean time for recurrence for glioblastoma is about 4 to 4-1/2 months, which, Dr. Gutin pointed out, is poor in light of the cost of radiosurgery treatment.

A group of researchers at the Joint Center for Radiation Therapy at Harvard, Dr. Gutin continued, has studied the use of radiosurgery in a more routine fashion as an initial boost in glioblastoma treatment, the results of which were published in the *Journal of Clinical Oncology*. The median survival for glioblastoma patients was around 22 months—similar to UCSF's and the Joint Center's implant data. Dr. Gutin added that he had received more recent results, and the survival curve is decreasing to a median survival of 18 or 20 months. Radiosurgery, he continued, will probably be comparable to brachytherapy in providing a boost in treatment for these tumors. Radiation necrosis, however, will probably be more severe for radiosurgery, since the dose is usually delivered all at one time.

Dr. Gutin related that a group in Boston is using a noninvasive stereotactic frame that fits in an individualized mode on the teeth and the occiput instead of being screwed into the skull. External beam stereotactic radiosurgery is being used to spread the dose over time to ameliorate the necrotic effect of this treatment. Dr. Gutin noted that a similarly good or better approach is the conformal system of delivering the dose to brain tumors, which allows fractionation without stereotactically based treatment. This so-called peacock system is being installed and tested and has not been used on patients. Dr. Gutin explained that in this procedure, as the accelerator circles over the patient, two rows of tungsten veins driven by a computer open and close. Thus, the dose is spread out contemporarily and spatially conforms to the tumor. This system can draw lines around tumors instead of irradiating a huge volume, similar to radiosurgery, except that it is simpler and fractionates treatment. Dr. Gutin commented that this approach will probably replace radiosurgery for the initial treatment of gliomas, but that radiosurgery will probably still be useful for recurrences. The next trial with radiation for glioblastoma will involve use of the peacock system in a hyperfractionated fashion.

Dr. Gutin reiterated that glioblastoma is not an ideal tumor for radiosurgery because of its diffuse invasiveness, and treatments other than radiosurgery will probably have a much greater impact on this disease. He suggested that other generalized treatment techniques, such as boron neutron capture therapy and gene therapy, are needed.

Another possible role for radiosurgery in oncology, Dr. Gutin continued, is in the treatment of cancers of the head and neck, if the frame can be positioned low enough. Various other tumors have been treated with radiosurgery, including chordomas, meningioma, and disease in the nasopharynx. Dr. Gutin indicated that external beam irradiation plays a large role in the treatment of meningioma that cannot be resected, and that radiosurgery for meningioma recurrence is a very good use of the technology. He explained that most benign tumors, such as acoustic neuromas and meningiomas, seem to stabilize rather than shrink after radiosurgery treatment.

Few side effects are associated with radiosurgery treatment, but patients do sometimes experience headaches, fevers, seizures, edema, necrosis of normal tissue, and nausea and vomiting, particularly in the posterior fossa treatments. Alopecia is rare because the dose is spread out over the scope. Generally, Dr. Gutin noted, there is some reaction in the tissue surrounding the malformation after about 5 months that disappears with steroid therapy and time, and there are some cases of focal profound and permanent necrosis and neurological deficit.

Dr. Gutin concluded that the only definite indication for radiosurgery is a nonresectable arterial venous malformation. However, it is rational to use the therapy for diseases that have no other treatment, such as deep nonresectable gliomas and recurrent metastases. Dr. Gutin predicted that radiosurgery will have a major impact on the treatment of metastases to the brain. Future goals are to decrease complications, treat larger targets, and, perhaps, develop fractionated radiosurgery for diseases such as cranial fringioma around the optic nerves or deep thalamic targets where any kind of injury with a single fraction could have significant neurological consequences.

Questions and Answers

Dr. Bragg asked what the incremental costs would be in a comparison of a traditional neurosurgical approach with radiosurgery. Dr. Gutin answered that resection of a single metastasis without complications would cost around $60,000 or $70,000 for a 4- or 5-day hospitalization. One night in the hospital for a radiosurgical treatment would cost between $15,000 and $20,000; a complication of open surgery could cost as much as $150,000.

Dr. Wilson asked about the use of radiosurgery for remedial resistant tumors like melanomas. Dr. Gutin explained that melanoma and renal cell carcinoma are showing an excellent response to the treatment. Dr. Calabresi added that his facility has treated more than 200 patients with melanoma, about half of whom are metastatic. Even radioresistant tumors, he continued, respond to the intensive radiation of this therapy. Dr. Calabresi noted that his staff has experienced 94 percent control of metastatic lesions. He then asked if Dr. Gutin has had any experience with radiosurgery and epilepsy or Parkinson's disease. Dr. Gutin expressed interest in these areas, but explained that delivering radiosurgery to these targets seems less promising than to other areas, because of the risk of hitting the wrong target.

Dr. Salmon commented that his group has applied radiosurgery to spinal cord tumors in defined areas. He then asked whether the effect of the metastatic disease is on the blood supply rather than on the tumor directly. Dr. Gutin answered that there is a lot of speculation about this issue. He added that tumors regress faster than AVMs, which affects the blood supply over the course of a couple of years.

Dr. Wells asked what makes renal cell carcinoma and melanoma so responsive to various therapies. Dr. Broder commented that melanoma is not an easily treatable disease, but it seems to be reported on more often than other carcinomas. Dr. Calabresi agreed that he has experienced excellent responses with Phase I drugs for melanoma over the years, but these responses were short-lived. This is, he said, probably due to the heterogeneity of melanoma.

IX. INTRODUCTION AND OVERVIEW, DIVISION OF CANCER TREATMENT—DR. BRUCE CHABNER

Dr. Chabner began his presentation with a brief overview of the main responsibilities of the Division of Cancer Treatment. The DCT is responsible for developing cancer therapies involving surgery, radiation, biological response modifiers, and innovative treatments. He pointed out that another major responsibility of the DCT is developing AIDS-related drugs. AIDS drug development, he added, is primarily a clinical effort in the clinical center and a contract effort at the Frederick Cancer Research Facility.

To provide an overall picture of the Division's magnitude, Dr. Chabner then discussed DCT's budget. He noted that the DCT presently has approximately 700 full-time equivalent employees, but this number is slowly declining. The Division had a budget of approximately $534 million in 1992 and $531 million in 1993, which funds research within the NIH campus as well as extramural grants, cooperative agreements, and contracts.

With respect to changes in the budget over the last fiscal year, Dr. Chabner explained that there was a reduction of approximately $3,800,000. He pointed to a 1.4 percent decrease compared with last year in the cancer budget, which accounts for approximately 90 percent of the Division's budget. The AIDS budget, however, increased about 5 percent and accounts for approximately 10 percent of the Division's overall budget.

Dr. Chabner then presented a breakdown of the Division's disbursement of funds by mechanism within cancer and AIDS research. Seventy percent of the Division's budget is spent extramurally, either in the form of research grants or cooperative agreements involving cancer. Offsite expenditures totaled about $375 million in fiscal 1993. The research and development contracts spent $35 million in fiscal year 1993, primarily in the Drug Development Program, which represented a significant drop from fiscal year 1992. Intramural research on cancer decreased by approximately 3 percent, from expenditures of $71 million in fiscal year 1992 to $68 million in FY 1993.

In the area of AIDS research, Dr. Chabner related that approximately 70 percent of the money is delegated either to contracts or intramural research. Small investments are made in other areas of interest such as cooperative group grants primarily for AIDS-related tumors.

Dr. Chabner next described scientific highlights from the past year, noting that the majority of these ventures were cooperative interactions between the DCT and the other Divisions of the National Cancer Institute, particularly the Division of Cancer Biology, Diagnosis and Centers (DCBDC). Highlights included:

- Gene therapy and cancer vaccine research projects have been initiated, including the anti-CEA vaccine and anti-*p53* vaccine efforts developed by the DCBDC and efforts by researchers in the Biological Response Modifier Program (BRMP), who have shown particular interest in the ras oncoprotein and are expecting to enter clinical trial at the end of the current fiscal year.
- Dr. Marston Linehan's laboratory has located the gene responsible for a genetic abnormality of renal cell carcinoma associated with von Hippel Lindau's disease. This abnormality has also been shown to exist in noninherited renal cell carcinoma. Mutations have been found in this particular gene in approximately 50 percent of patients with nonhereditary renal cell carcinoma, and a loss of one allele has been found in over 90 percent of patients. Dr. Chabner pointed out that this adds considerable weight to the idea that a specific gene is responsible for renal cancer in both the hereditary and nonhereditary forms.
- Significant effort has been made toward developing therapeutic agents for prostate cancer. Dr. Chabner noted that Dr. Charles Myers would discuss this subject in greater detail at the afternoon session.
- The development of taxol has received a great deal of attention, particularly in the areas of large-scale production of the drug, development of a Cooperative Research and Development Agreement (CRADA) with Bristol Myers, and the expansion of clinical trials with taxol during the past year. Adjuvant therapy trials that combine the use of taxol with the current most effective adjuvant therapy for breast cancer are scheduled to begin in the near future.
- A number of drugs have been approved on the basis of developmental activity in the cooperative groups. Dr. Chabner highlighted three agents on which the DCT has focused its attention during the past several years: Fludarabine for chronic lymphocytic leukemia; Deoxycoformycin for hairy cell leukemia; and Levamisole, as an adjunct treatment with 5FU for colon cancer.
- Dr. Chabner gave two examples of natural products that have been under investigation during the past year. The camptothecin analogs, he noted, are of particular interest because of their activity in a number of solid tumors, especially CPT-11, which is a derivative of a drug discovered through an NCI contract about 20 years ago that failed in clinical trial because of it's instability. CPT-11 is currently beginning clinical trial in the United States. Dr. Chabner also mentioned Topothecin, an analog that has shown activity in small cell carcinoma and leukemia.

Dr. Chabner moved on to review the activity of the Board of Scientific Counselors. The Board, he said, considers between $4 and $8 million worth of concepts in each of their sessions, and each concept is carefully discussed with the Board before it is actually presented. During presentation, two members of the Board act as primary reviewers for each concept and offer their suggestions. In the past year, all but about $3.5 million worth of concepts were approved. Some of these unapproved concepts were reworked and brought back to the Board at the October 1993 meeting, resulting in approval of all but $1 million in concepts.

Exceptions among the concepts that were mentioned by Dr. Chabner included a BRMP proposal for clinical trials that was cut in half from $500,000 to $250,000 and a Surgery Branch contract that was cut from $1.3 million to $900,000 after an extended discussion of the site visit before the Board.

Dr. Chabner next explained the tenure process in which he said the Board is extensively involved through site visits and presentations. Dr. Chabner outlined the two methods used to present scientists for tenured positions. The first is through site visits, in which an ad hoc board, supplemented or led by members of the Board of Scientific Counselors, visits a laboratory for 1-1/2 days and issues a report about all scientists with tenure possibility. The other process involves a direct presentation to the Board, which occurs if the tenure action does not fall within the cycle of site visits.

Dr. Chabner concluded by acknowledging those scientists who have received tenure over the past 2 years. He then introduced Dr. Clara Bloomfield, Chairperson of the DCT Board of Scientific Counselors.

X. REPORT OF THE CHAIRPERSON, BOARD OF SCIENTIFIC COUNSELORS, DCT—DR. CLARA BLOOMFIELD

Dr. Clara Bloomfield, chairperson, referred to a list of members of the DCT Board of Scientific Counselors that had been distributed to the Board and discussed demographics of the BSC. She commended Dr. Chabner for attaining broad representation in the BSC, based on gender, race, and geographic distribution. This year, Dr. Bloomfield stated, a patient advocate who is a breast cancer patient with a medical background was added to the BSC's membership. She added that various clinical modalities are represented on this body, including surgery, radiotherapy, diagnostic imaging, and pediatrics, as well as nonclinical members; only 6 of the 20 members are medical oncologists. Member expertise covers many clinical areas, such as clinical oncology, immunology, molecular biology, drug development, and diagnostic imaging.

Dr. Bloomfield then summarized approved concepts, noting that proposals have been submitted from all five DCT programs. Eighteen of 19 proposals have been approved, although some were initially deferred and there was a decrease in funding. Dr. Bloomfield observed that most of the proposals were not in the contract mechanism, but were either cooperative agreements or grants.

In addition to completing concept reviews, performing site visits is a major activity of the BSC. Dr. Bloomfield reported that each of the programs has been visited at least once every 4 years, with the recent exception of the NCI Navy Medical Oncology Branch, which has not been visited since June of 1987 because of the reorganization of this Branch and the Medicine Branch. She added that this Branch will likely be visited in 1994.

Dr. Bloomfield stated that Dr. Chabner has created five special advisory subpanels in the past 2 years. She related that she chairs the breast cancer subpanel, which was established in February 1993 as a mechanism by which breast cancer advocacy groups could participate in DCT's breast cancer research program. The goal of this subpanel is a two-way education process—to apprise breast cancer advocacy groups of DCT and NIH activities and to become aware of breast cancer advocacy groups' views. Membership of the panel includes five BSC members and Drs. Love and Dickerson from the advocacy groups.

The open meetings of the panel are held at the time of each regularly scheduled BSC meeting. Attendance, Dr. Bloomfield noted, has been excellent by BSC members, breast cancer advocates, and NCI staff. The percentage of member attendance over three meetings has been constant, but the percentage of advocates has increased from 15 to 40 percent. The first meeting of the subpanel included an overview of breast cancer research in DCT and a discussion of the Cancer Treatment Evaluation Program's (CTEP) breast cancer initiatives. At the advocates' request, the June agenda included a detailed discussion of the Drug Development Program as it relates to breast cancer and the intervention trials aimed at preventing breast cancer. Biologic response modifiers and monoclonal antibodies in breast cancer treatment were discussed at the October meeting. Dr. Bloomfield explained that the meetings have generated positive feedback, although they are relatively long, lasting 3 to 4 hours each.

Advocates have expressed interest in lobbying to eliminate the full-time equivalent restriction at NIH, which requires legislation. Dr. Bloomfield related that the advocates have a great interest in increasing the molecular and clinical evaluation of the breast cancer cell lines in the screen, which is also an interest of Dr. Grever. The breast cancer advocates have requested that more effort be given to preparing for the impact of genetic identification of highly susceptible women; a conference will be devoted to this topic. Dr. Bloomfield concluded that the meetings have been highly constructive and useful for all parties involved.

Questions and Answers

Dr. Salmon pointed out that breast cancer advocates can engage in lobbying, but BSC members cannot. Dr. Bloomfield agreed and noted that advocates' interest in lobbying for such issues as removing FTE limitations is useful. Dr. Salmon asked if Dr. Bloomfield had found the site visits to be useful and if the DCT has been responsive to critiques and specific recommendations. He noted that an article in *Science* implied that some of the NIH visits had been discarded. Dr. Bloomfield answered that Dr. Chabner and his staff have been extremely responsive. She reported that one of her tasks will be to review Dr. Chabner's performance and stated that she will feel more comfortable responding to Dr. Salmon's question after she has reviewed the facts in detail.

Dr. Sigal inquired about the date of the next meeting of the breast cancer subpanel. Dr. Bloomfield reiterated that the subpanel meetings are held on Monday nights in conjunction with the BSC meetings.

Dr. Chan asked Dr. Chabner about the number of drugs that had been moved from preclinical to clinical trials during the last cycle. Dr. Chabner answered that the number of investigative new drug (IND) submissions for biological and chemical entities varies between approximately 10 and 15 a year. More submissions are expected this year because of the large number of biological vaccines. In prior years, Dr. Chabner related, there were about three or four new drugs each year. He commented that the biological field has grown in the last 5 years and, thus, a larger number of compounds are entering clinical trials. At the same time, however, the contract program, which supports preclinical development activities, has been decreasing, making it more difficult to meet the requirements to enter a drug into the clinic.

Dr. Calabresi then introduced Dr. Steven Harms, Director of the Magnetic Resonance Imaging Department at Baylor University Medical Center.

XI. MAGNETIC RESONANCE BREAST IMAGING—DR. STEVEN HARMS

Dr. Steven Harms, Director of the Magnetic Resonance Imaging Department at Baylor University Medical Center, began his presentation by noting that pathologic studies have shown that current clinical and imaging information often leads to inaccurate assumptions as to the extent of breast cancer. This, he said, results in a tendency to overtreat the disease, leading to greater expense and morbidity. On the other hand, when attempts are made to conserve more of the breast, the likelihood of undertreating the cancer increases. Dr. Harms stated that the goal of his group's study is to develop a new method of defining the extent of cancer in the breast so that a more appropriate and accurate treatment can be determined.

Dr. Harms then briefly reviewed the potential clinical roles of magnetic resonance in breast cancer detection. In Europe, he mentioned, magnetic resonance is used in a prebiopsy role as a way of reducing the number of women having biopsies, since only 20 percent of those biopsied are positive for cancer. A second role of magnetic resonance is in evaluating the integrity of silicone implants. A third role, and one that Dr. Harms said was the primary focus of their research, is in cancer staging.

Dr. Harms reported that magnetic resonance is used following biopsy to determine the appropriate treatment regimen. Currently, lumpectomy margins are only adequate in about half the cases and repeat surgery or even mastectomy is required. Using magnetic resonance, it may be possible to make the correct decision the first time. It may also be possible to use magnetic resonance to determine whether radiotherapy or chemotherapy is the most appropriate postsurgical treatment.

One goal of magnetic resonance, Dr. Harms stated, is to improve the sensitivity of the imaging diagnosis to prevent inadequate treatment for nonvisualized cancer, particularly in patients who undergo breast conservation surgery. Toward this goal, all cancer in the breast,

including that not seen by conventional imaging, needs to be detected. False negatives must, therefore, be avoided, since they lead to untreated cancer.

The technical considerations involved in this diagnostic process are rigorous, Dr. Harms observed. To resolve all lesions, 1 millimeter, three-dimensional voxels are required. Fat suppression is also required because fat is hyperintense on T1-weighted images, and with gadolinium contrast the cancers also become hyperintense; therefore, without fat suppression, the image appears as a white lesion against a white background. The entire scan must be accomplished within 5 minutes of injection of the gadolinium contrast; after that, normal breast parenchyma starts to enhance and appears the same intensity as the tumor. Since commercial machines could not meet these technical requirements, it was necessary to develop a new method. The method uses a dedicated radio frequency (RF) coil, a nonselective three-dimensional acquisition to improve resolution, and a new pulse sequence called RODEO (rotating delivery of excitation off resonance). The isotropic voxel gives much better resolution than conventional imaging and has the advantage of being able to do image processing.

Dr. Harms explained that all magnetic resonance machines use the combination of radio fields and magnetic fields to produce an image. The commercially available magnetic resonance machines use a single type of radio frequency field, while the new method focuses on using two types of radio frequency excitations so that certain frequency ranges can be suppressed. The RODEO method can excite water with the simultaneous suppression of fat or silicone. Other magnetic resonance techniques require a longer scan time and would not be acceptable for the resolution required. The RODEO technique also provides excellent T1 weighting for gadolinium contrast enhancement, he added.

Explaining RODEO in greater detail, Dr. Harms said that fat and water are normally present within the body and the first RF pulse excites both fat and water. Since fat and water resonate at different frequencies, they move out of phase with one another. A second RF pulse in the opposite direction is then applied that drives back the fat so it does not contribute to the signal. The second RF pulse drives the water into the transverse plane, which is what creates the magnetic resonance signal. In one very efficient excitation, the fat signal is eliminated and the water signal is enhanced.

Dr. Harms then presented examples of some mammograms and magnetic resonance images for comparison. The first was from a young, premenopausal woman with dense breast tissue. She presented with a mass in her axilla that was determined upon biopsy to be metastatic adenocarcinoma, most likely from a primary breast cancer. She had no palpable masses and no masses visualized on the mammogram. He then showed precontrast and postcontrast views of the woman's magnetic resonance, which showed multifocal and multicentric breast carcinoma.

Dr. Harms then showed a videotape demonstrating the image processing capabilities of the RODEO system. He showed a woman's breast scan and commented about the noncontrasted versus the contrasted image, then showed the image processing capabilities of the machine, followed by prechemotherapy versus postchemotherapy scans. He then mentioned that magnetic resonance may play a role in the evaluation of therapy as well as in staging.

Dr. Harms then showed slides of a postmenopausal woman with an axillary mass that was positive for adenocarcinoma. Her mammogram showed no evidence of tumor, and she had no other clinical findings of breast cancer when she entered the study. Her magnetic resonance scans showed a 3-centimeter mass that was an infiltrating ductal carcinoma. After the magnetic resonance, she went back for a repeat magnification mammography and ultrasound, both of which failed to identify the mass. Blind biopsies were also negative.

Dr. Harms then turned his discussion to the use of magnetic resonance for imaging breasts with silicone implants. Silicone implants impair visualization of breast cancer because the silicone blocks the x-rays or mammogram. It is also impossible to distinguish between tumors and silicone leakage in mammography. Dr. Harms presented a chemical shift spectrum in a woman with silicone implants, showing a fat peak, a water peak, and a silicone peak. With RODEO, Dr. Harms said, the silicone peak can be turned off when silicone is on resonance. He then showed slides of scans from several patients who had palpable masses in their breasts and explained how, using RODEO, it was possible to suppress the silicone and determine whether the masses were free silicone or tumors.

In another case involving a woman with implants, her mammogram identified a suspicious area. It was not palpable, and the patient underwent a biopsy and wire localization. Prior to lumpectomy, she underwent magnetic resonance imaging. The magnetic resonance showed not just a small area of tumor, but that her entire breast parenchyma was involved. However, because of the preliminary nature of his group's study, Dr. Harms stated that clinical decisions are not currently being based on magnetic resonance data. Following the patient's lumpectomy, pathology determined that cancer was evident on all margins of the lump as predicted by the magnetic resonance. Prior to the woman's mastectomy, magnetic resonance was performed on her other breast, and it was found to have even more extensive cancer. The woman had a bilateral mastectomy that revealed infiltrating lobular carcinoma, which is notoriously difficult to detect using conventional imaging devices.

Evaluation of the new magnetic resonance methodology was the final topic that Dr. Harms addressed. He said that biopsies are performed on areas found to be suspicious with conventional imaging methods, but cannot be performed on areas seen only by magnetic resonance. Therefore, his group has used serial section mastectomy analysis as an evaluation method. With serial section analysis, it is possible, Dr. Harms explained, to identify lesions that cannot be seen by magnetic resonance. He noted, however, that it is not often that the pathologist can identify an area not seen by magnetic resonance. Using this method of evaluation, researchers can also identify lesions not detected by the magnetic resonance. Of 30 patients in his group's study who had serial section analysis, magnetic resonance identified the tumor 94 percent of the time. Three tumors were missed, two of which were in the nipple and were interpreted as normal nipple enhancement; the other was microscopic disease, which was the only false-negative result. This is compared with 55 percent for conventional breast imaging. The size of the cancers missed by conventional imaging varied from 3 millimeters to 12 centimeters, and there were a number of false positives, most of which were lesions considered to be associated with increased risk of malignancy—lobular carcinoma in situ, atypical hyperplasia, and proliferative fibrocystic change. None of those lesions were missed with magnetic resonance.

In summary, Dr. Harms stated that magnetic resonance can be used to improve staging and will be most useful in centers that favor breast conservation surgery. The greatest drawback to magnetic resonance, he said, is that no method currently exists for biopsying tumors that are detected by magnetic resonance but are undetectable via conventional means.

A potential use for magnetic resonance, Dr. Harms concluded, might be in breast conservation surgery to localize the tumor and ablate the cancer cells with a percutaneous laser. Laser oblation would continue until the margins were satisfactory as determined by magnetic resonance. This could dramatically impact not only the cost of breast cancer therapy, but also the quality of the therapy and conservation of the breast.

Questions and Answers

Dr. Broder asked if it would be possible and practical to use RODEO magnetic resonance as an early detection intervention in women who have the BRCA1 gene. Dr. Harms responded that he believes it would be practical as soon as magnetic resonance biopsy devices are commercially available, which he thinks will occur within a year. Dr. Broder reiterated his concern that in 6 months to 1 year, a test to detect the BRCA1 gene will be available and women identified as having this gene will have few alternatives other than bilateral mastectomy.

Dr. Bragg asked about the size threshold of the magnetic resonance and whether lymph nodes can be imaged clearly enough for staging. Dr. Harms stated that the resolution of magnetic resonance using RODEO is under 1 millimeter. Regarding imaging of the lymph nodes, he stated that they can be seen, but not with any degree of specificity from a staging perspective.

Dr. Harms then addressed the issue of using magnetic resonance for screening, which he said takes on a huge responsibility. There is an abundance of data on mammography, he commented, and very little on magnetic resonance imaging. He said he has heard of a television commercial in Houston that solicits women to have magnetic resonance imaging instead of mammography, and he expressed concern that this is not only inappropriate at the present time, but also dangerous. He added that he is looking to NCI for leadership in defining the appropriate uses of magnetic resonance based upon the research data.

Dr. Sigal asked if there was an age breakdown on the cancers in Dr. Harm's study that did not show up on conventional imaging but did show up on magnetic resonance. Dr. Harms responded that he did not have the data, but that any findings would most likely not be statistically significant because only 30 patients were involved.

Dr. Salmon asked how many centers have the type of equipment necessary to carry out a clinical trial. Dr. Harms said that no other center has RODEO, and it has not been picked up by a commercial vendor. He said that his group will provide the technology to NCI for multicenter trials so that more data can be obtained on magnetic resonance and recommendations can be made regarding its use.

XII. INTEGRATING ACTIVE NEW AGENTS INTO DEFINITIVE TREATMENT PROGRAMS—DR. MICHAEL FRIEDMAN

Dr. Calabresi introduced Dr. Michael Friedman, Associate Director of the Cancer Therapy Evaluation Program in the Division of Cancer Treatment. Dr. Friedman stated that his presentation would describe the efforts of the CTEP in bringing promising new therapeutic agents to the fulfillment of their promise.

Following *in vitro* and *in vivo* preclinical evaluations, Dr. Friedman explained, new agents move to clinical testing in Phase I and Phase II trials. CTEP places an emphasis, he noted, on maintaining a process that is orderly and accurate but also responsive to pressures to gain information as quickly as possible. While demonstrations of antitumor effects in Phase II trials are encouraging, Dr. Friedman continued, these effects should not be confused with more meaningful demonstrations of the benefits of long-term disease regression. Phase III trials, he stated, are the definitive instrument for demonstrating improved therapy.

Dr. Friedman presented several examples of promising agents whose antitumor activities have been demonstrated. Two of the examples involve taxol and its related compound, Taxotere, whose mechanism of action is stabilization of the microtubular system. First, he described a Phase III trial conducted by the Gynecologic Oncology Group in which 400 poor-risk patients with stage III and IV ovarian cancers were randomized to receive either cisplatin with cytoxan or cisplatin with taxol. Dr. Friedman presented data showing that after 3 years, there was a demonstrable advantage in disease-free survival for the patients receiving the platinum-taxol combination. There is also reason to believe, he added, that the platinum-taxol combination will also prove to be associated with superior overall survival. To further test this promise, Dr. Friedman continued, the Gynecologic Oncology Group plans a study of more than 400 better-risk optimal stage III patients, comparing a cisplatin with taxol treatment with a combination of carboplatin, cisplatin, and taxol.

A second example presented by Dr. Friedman focused on the use of taxol in breast cancer patients. A series of clinical trials, he stated, have shown a significant antitumor effect among patients with metastatic stage IV disease. There seems to be some evidence, Dr. Friedman noted, that patients who have received less prior therapy have a higher response rate to taxol. This suggests a hypothesis that a drug that has a temporary benefit in advanced disease could result in larger numbers of disease-free patients in an adjuvant setting.

To test this hypothesis, Dr. Friedman explained, two trials have been designed and will begin accruing patients early in 1994. Both trials will focus on stage II, resected breast cancer patients with modest risk of recurrence. An intergroup study will examine induction with cyclophosphamide and doxorubicin. Patients will then be randomized into a group with no further therapy or a group receiving four cycles of taxol treatment. It is expected, Dr. Friedman stated, that more than 3,000 patients will be accrued to this study within 2 years. Another study will focus on preoperative use of taxol. In this trial, patients will be randomized into a group receiving cyclophosphamide and doxorubicin or a group receiving that combination plus taxol, followed by the best local therapy.

Dr. Friedman briefly discussed the use of all-trans retinoic acid in patients with acute promyelocytic leukemia. High response rates to this treatment were reported by researchers in

China in 1988, confirmed in France in 1990, and reconfirmed in additional U.S. studies. Patients experienced dramatic remissions and the toxicities that occurred were quickly resolved. On confirmation of these findings, NCI began distributing all-trans retinoic acid to patients who could not benefit from conventional therapies through the special exception program. A Phase III trial, Dr. Friedman reported, was initiated in 1992 to compare a combination of cytosine arabinoside and daunorubicin with the same combination plus all-trans retinoic acid. This study is an intergroup collaboration of all the cooperative groups in the United States, including pediatric patients; although the disease is uncommon in children, Dr. Friedman noted, it appears to run the same course as in adults. He described the study as another opportunity to determine whether an agent that has a high response rate but not a high cure rate in a bad-risk setting can result in more cures in a good-risk setting.

Finally, Dr. Friedman discussed the campothecin analogs, a family of compounds that act by interfering with topoisomerase I, a critically important enzyme system for restoring the integrity of DNA. The Eastern Cooperative Oncology Group, he explained, studied the effectiveness of topotecan, one of the campothecin analogs, in a small group of patients with incurable small cell lung cancer. Of 13 patients, six had very substantial responses to this agent, and three others had at least partially positive responses. These were not cures or long-term remissions, but raised the question of whether this agent could be incorporated into a program that might benefit patients more profoundly. A clinical trial, Dr. Friedman announced, will soon be opened by the Eastern Cooperative Group. Half of the patients with small cell lung cancer will receive only conventional cisplatin and VP16 therapy and half will receive additional high doses of topotecan. Accrual, Dr. Friedman noted, will be in excess of 400 patients.

Dr. Friedman closed by observing that the cooperative groups are central to the intellectual and clinical management of these studies. Several pharmaceutical companies, he added, have also been very helpful in providing new agents for study.

Questions and Answers

Dr. Bettinghaus asked how the question of tamoxifen is being handled in the breast cancer and taxol study. Dr. Friedman replied that patients for whom tamoxifen is considered appropriate will receive the drug at the completion of chemotherapy.

XIII. NEW DRUG DEVELOPMENT IN PROSTATE CANCER—DR. CHARLES MYERS

Dr. Chabner introduced Dr. Charles Myers, who, Dr. Chabner said, is leaving NCI to become the Director of the Cancer Center at the University of Virginia. He thanked Dr. Myers for his many years of service and innovative ideas in the clinical program.

Dr. Myers stated that he would review the preclinical and clinical evaluations of two drugs against prostate cancer and glioblastoma. He noted that while this might seem like an odd combination of cancers, most drugs that work against prostate cancer also show activity in glioblastoma.

The first drug Dr. Myers discussed was lovastatin, also known as mevacor. He described the work of Dr. Jane Trepel, who began using the drug in cell synchronization studies. Lovastatin, which is widely prescribed for cholesterol management, inhibits the enzyme responsible for mevalonate formation and is a rate-limiting metabolite in the sterol synthesis pathway. Mevalonate is also used to make ubiquinone, which is essential for mitochondrial adenosine triphosphate (ATP) generation, and to isoprenylate proteins. Because of this wide range of activity, mevalonic acid has been used in the laboratory as an experimental tool in cancer biology. Therefore, Dr. Myers continued, it has long been known that mevalonic acid inhibition causes a drop in isoprenylation of proteins that results in the arrest of cell growth. It is an excellent agent for tumor cell synchronization; however, the consensus thus far has been that this drug would not be a useful anticancer agent because of its broad effects and the high concentration that would be necessary.

Dr. Trepel, in performing cell synchronization experiments, added lovastatin to prostate cancer cells in culture. Within a day, Dr. Trepel discovered mass lysis of the prostate cells. Further experiments demonstrated similar rapid cell death in other human tumors, including glioblastoma treated with lovastatin at approximately 100 times the dose used for cholesterol management. Dr. Myers hypothesized that the basis of this lovastatin activity is the inhibition of activation of the *ras* protooncogene required for cell growth. The cause of the lysis of the cells is still not understood, he said.

Using this information, Dr. Myers said, his group initiated a Phase I trial of lovastatin for 7 days. The short timeframe was chosen because of the extremely rapid antitumor activity of the drug. They started, he continued, at the high end of the dose given for cholesterol management and escalated the dose from that point. Eighteen months later, a dose of 35 milligrams per kilogram per day was reached, at which point three of the six patients in the trial developed transient muscle damage, signaled by an elevated CPK. The muscle aches lasted from 7 days to 3 weeks after drug administration. The maximally tolerated dose was determined to be 30 milligrams per kilogram per day for 7 days. The cycle was repeated each month. The drug was given orally, and except for the muscle damage and an initial dramatic drop in cholesterol, no other side effects were seen.

While investigating the cause of the muscle damage, which many of the patients described as feeling flu-like or like after running a marathon, Dr. Myers said, they looked at the relationship between creatine phosphokinase and dosage. There was a very tight exponential relationship, he reported, which was very sharp after a dose of 30 milligrams per kilogram per day.

Dr. Myers then reviewed results of a Phase I study performed on patients with high-grade glial tumors and prostate cancer.. The prostate cancer results, he said, have been disappointing, with only 1 of 34 patients showing a 50 percent reduction in prostate-specific antigen. However, in the high-grade glial tumors, 7 of 17 patients had objective disease stabilization lasting from 1 to 9 months, or minor responses. These patients are still being monitored to determine how durable the responses will be, and thus far, none have shown signs of disease progression. Dr. Myers stated that one patient with a glial blastoma multiforma had a 25 percent decrease in actual tumor volume.

Dr. Myers then turned his discussion to the muscle damage experienced by patients. He said that prior to doing this study it was known that lovastatin caused dramatic declines in circulating ubiquinone levels and that oral ubiquinone was reported to reverse the lovastatin-induced muscle damage. No proof existed, however, that oral ubiquinone is absorbed. Dr. Myers reported that his group decided to investigate the use of oral ubiquinone in a patient with glioblastoma multiforma who was a long-term responder to lovastatin. The man was confined to a wheelchair, had cortical blindness, and was severely disoriented upon initial presentation. During the lovastatin regimen, he developed severe muscle weakness and aching and had an elevated CPK. He was put on a dose of 240 milligrams a day of ubiquinone and within 12 hours he was walking. These and subsequent studies confirm that ubiquinone is readily absorbed orally and prevents the decline in ubiquinone levels associated with lovastatin administration. The man has since returned to work as a practicing attorney and is in his ninth month of clinical improvement.

The current regimen for lovastatin, Dr. Myers said, calls for 7 days of pretreatment with oral ubiquinone, which serves to prevent the dramatic drop in circulating ubiquinone. During the earlier trials, 3 of 6 patients developed muscle damage at 35 milligrams per kilogram per day, while with the new regimen none of the patients has developed the problem at 40 milligrams per kilogram per day, and the dosage is being escalated to 45 milligrams per kilogram per day.

Dr. Myers recommended that Phase II testing should begin at 35 milligrams per kilogram per day for 7 days pending the results of further dose escalation studies with ubiquinone. Dr. Myers said that oral ubiquinone's effect on antitumor activity will need to be investigated through long-term follow-up.

Dr. Myers next discussed a controversial cancer treatment being used by a physician in Houston. The physician, Dr. Brezinski, is treating patients with antineoplastons, which are purified from urine, and is charging between $10,000 and $30,000 per patient. Dr. Dvorit Samid knew of a child with glioblastoma multiforma who was treated by Dr. Brezinski, had a complete regression of his tumor, and was doing well 2 years later. Dr. Samid analyzed the antineoplastons and discovered that they were 80 percent phenyl acetate and that the phenyl acetate had profound effects on a variety of tumors *in vitro*.

Dr. Myers mentioned that phenyl acetate is available at low cost from many drug companies. It is a very simple molecule that is inexpensive to obtain, easy to manufacture in bulk, and, he added, does not warrant a $30,000 price tag for treatment.

Preclinical evaluation of phenyl acetate has determined it to be an androgenous growth regulator that forces differentiation and cessation of proliferation and is found in all living organisms. In tissue culture and animal models, phenyl acetate showed significant activity against prostate cancer, glioblastoma, and melanoma. Dr. Myers presented a slide of a fibrosarcoma before and after 5 days of treatment that showed a reversion to a more normal morphology following the treatment with phenyl acetate. Dr. Myers then showed the results of assays with PC3, an aggressive, hormone refractory prostate cancer. In an invasion assay, the PC3 cells were placed on a porous filter and the cells' ability to cross the filter was used as a measure of their mobility—the PC3 cells easily crossed the filter. After treatment with phenyl acetate, however, the PC3 cells lost that mobility. In a similar assay, PC3 cells were placed on

madrigal, a commercially available basement membrane, and evaluated for their ability to pass through the membrane. Sodium phenyl acetate again arrested the cells' ability to traverse the membrane *in vitro*.

In summarizing his group's findings on phenyl acetate, Dr. Myers said that the effects of the drug are a selective inhibition of proliferation in malignant, as compared to nonmalignant, cells in culture with no evidence of cytotoxicity to the tumor cell. In terms of clinical responses, he said, the antitumor activity was expected to be dominated by phenotypic reversion and cell differentiation, not by conventional objective tumor response criteria. During the Phase I trial, he noted, it may be difficult to demonstrate antitumor activity. The preclinical data suggest that the longer the exposure, the better the response will be. They have chosen a 14-day continuous infusion at 35 milligrams per kilogram per day with a day off every 7 days. At this level, he said there are two drawbacks. The first is that the drug is not very potent; therefore, doses of 20 to 30 grams have been administered in the form of a sodium salt. That salt load has been too great for the older patients, sometimes resulting in ankle edema and rauls at the base of the lungs. Dr. Myers noted that this does not present a serious problem, however, since the condition responds well to treatment with Lasix. The second drawback is lethargy and a retrograde amnesia of the treatment event. The drug's half-life is approximately 4 hours, so all side effects cease within 48 hours of discontinuation of the drug.

Dr. Myers presented results of the first Phase I trial for prostate cancer, in which some antitumor results were apparent even using conventional tumor response criteria. He said that 18 patients have completed at least one cycle of treatment. Two responses have been observed—one, a patient with a 50 percent reduction in prostate-specific antigen levels, and the other with a 50 percent reduction in his osteoblastic bone lesion as seen by CAT scan. Five of the patients have had stable disease for 2 to 9 months.

In the high-grade glial tumor group, 13 patients have completed at lease one cycle and two have had minor responses—a shrinkage of between 25 and 50 percent of their tumor. One patient has had stable disease longer than 9 months, which is uncommon with this disease. Dr. Myers then presented slides showing some of the responders before and after treatment. All the patients, Dr. Myers noted, have had surgery and radiation therapy and most have also had cisplatin-based chemotherapy.

The next step, Dr. Myers stated, is to escalate the duration of the therapy during Phase II studies. He suggested starting at a dose of 35 milligrams per kilogram per day for 14 days. This regimen should be well tolerated, he said, and Cancer Therapy Evaluation Program is already making plans to begin these Phase II studies.

In closing, Dr. Myers remarked that his group's approach has been different from many others, in that they have used their knowledge of tumor biology to find drugs that can interact with biological properties and processes to harm or destroy the tumor.

Questions and Answers

Dr. Calabresi said that the responses seen in these patients are good, considering that they have not responded to other treatments. Dr. Wilson characterized the results as provocative and worthy of further pursuit.

Dr. Myers remarked that he has been very cautious in his assessment of the Phase I trials because it is so difficult to accurately judge the results. Phase II will be more telling as to the drug's efficacy, especially when compared to treatment with Suramin.

Dr. Chan asked whether phenyl acetate is being used to treat any other conditions. Dr. Myers answered that it is used to treat hyperammonemia, a condition in which the urea cycle does not function and which can cause retardation in children. Phenyl acetate is used as an alternate way of cycling the urea. Dr. Myers stated that a Johns Hopkins researcher has shown that phenyl acetate preserves the IQ of the treated children. In response to a question about the drug's supply, Dr. Myers said that it is supplied through a CRADA between an industrial firm and NIH.

Dr. Myers mentioned that NCI sent an outside panel to evaluate Dr. Brezinski's claims of antitumor effects and found seven cases of unambiguous and dramatic responses in glioblastoma patients he treated. CTEP is actively testing the antineoplastons for antitumor activity.

XIV. TUMOR-INDUCED IMMUNOSUPPRESSION—DR. DAN LONGO

Dr. Longo began his presentation by discussing his involvement in the study of tumor-induced immunosuppression, making note that it is impossible to predict the direction that science will take. He stressed the need to support basic research rather than targeting specific areas.

Dr. Longo then briefly outlined the Biological Response Modifiers Program in which tumor-induced immunosuppression is being studied. The BRMP is a comprehensive program involving both intramural and extramural preclinical and clinical research, the focus of which is translational research. Dr. Longo explained that translational research is not simply a one-way process from laboratory experiment to clinical trial. It is, rather, a cyclical process involving many iterations between the laboratory and the clinic, developing a laboratory hypothesis, testing it in patients, and refining the hypothesis back in the laboratory.

Although there is little controversy concerning the idea that T lymphocytes play an important role in tumor rejection, several hypotheses exist concerning which is the most relevant mechanism to elicit T-cell responses. The fundamental question, Dr. Longo explained, is whether antigen-specific T-cell responses are required for tumor rejection.

The work of Dr. Steven Rosenberg supports the idea that T cells must be antigen specific in order to activate a response. In his research, Dr. Rosenberg found that T cells with specific tumor lysis produce better antitumor response *in vivo* which is associated with *in vitro* lysis.

Contrary to the data derived from Dr. Rosenberg's research, Dr. Longo discussed the substantial amount of evidence indicating that in humans, T-cell responses *in vivo* are not entirely antigen specific. He explained that within a delayed type hypersensitivity (DTH) response, a number of the T cells are specific for the antigen that elicits the response; however,

most of the T cells are nonspecifically recruited into the area. In fact, the affinity of the T-cell receptor for its antigen is low and several recruitment mechanisms exist for antigen-nonspecific cells in a response. From this information, Dr. Longo and his colleagues hypothesized that nonspecifically activated T cells may be manipulated to seek out tumors and destroy them.

Dr. Longo related that Dr. Jon Ashwell had performed preclinical experiments based on this hypothesis. Dr. Ashwell found that the mouse antibody, anti-CD3, recognizes the signaling complex (CD-3) associated with the antigen receptor localized on the surface of the T cells. Dr. Ashwell found that the CD3 molecule is responsible for triggering the activation of T cells after these cells encounter their antigen. High doses of this antibody given *in vivo* suppress the immune system; however, Dr. Ashwell found that when the antibody was administered in low doses, proliferation was induced and cytotoxicity was enhanced.

As a result of Dr. Ashwell's findings, a clinical trial was performed administering the antibody in low doses in order to activate the T cells and destroy tumors. Dr. Longo explained that the antibody was found to be toxic. Patients suffered severe headaches and aseptic meningitis from the activation of T cells and the production of cytokines.

Dr. Longo described the second experiment attempting to activate T cells *ex vivo* with anti-CD3. Dr. Augusto Ochoa developed an animal model in which 3×10^5 tumor cells were injected intrasplenically into mice and grown for 3 days. The mice were then treated with anti-CD3-activated T cells, also called T-cell activated killers or TAK cells. The T cells were taken from the mouse and activated with anti-CD3. The anti-CD3-activated T cells were then given to the tumor-bearing animals intravenously, together with 3 days of liposome-encapsulated interleukin-2 (IL-2). Dr. Longo explained that the animals receiving anti-CD3-activated T cells exhibited a significant reduction in the hepatic metastases by day 15 of the study, compared with animals that had no therapy, and the response was proportional to the number of TAK cells given.

The results from Dr. Ochoa's study prompted a clinical trial in which cells were taken from patients and then activated *in vitro* with anti-CD3. These activated cells were then given back to the same patients, paired with high doses of IL-2 to expand them *in vivo*. Under the influence of IL-2, Dr. Longo explained, the cells increased dramatically, ranging from 20,000 to 286,000 activated T cells per cubic millimeter of blood.

Dr. Longo presented a slide showing a melanoma lesion biopsied before and after treatment. Prior to treatment, the tumor expressed minimal cellular infiltrate; however, after treatment was administered, the tumor appeared infiltrated with CD8+ cytotoxic T cells. Unfortunately, the majority of the tumors in patients did not regress.

He found that the T cells were clearly activated and possessed activation markers, such as IL-2 receptors, and the cells appeared to accumulate at tumor sites, but the response rates were low. These low response rates led Dr. Longo to question what the differences were between the successful animal model and the unsuccessful clinical trial.

Dr. Longo revealed that the major difference between the animal and the clinical model rested in the nature of the T-cell donor. In the animal model, the donor of the T cells that had

been effective when transferred to a tumor-bearing mouse had been a genetically identical mouse that did not possess a tumor; whereas, in the clinical trial, T cells that were activated were taken from and given to the same cancer-bearing patients. This finding prompted an experiment comparing lymphocytes activated from tumor-bearing animals compared to normal animals in the hepatic metastases model in order to determine whether the tumor-bearing state influenced the success of the therapy.

The results from the study revealed that when activated T cells were transferred from animals that had possessed their tumor for more than 2 weeks, the cells were unable to produce antitumor effects. Spleen cells were taken from a tumor-bearing animal and the CD4 and CD8 subsets were isolated and mixed with cells from non-tumor-bearing animals. Dr. Longo explained that CD4+ cells from tumor-bearing animals were able to aid in the development of cytotoxic activity in normal CD8 cells. On the other hand, the CD8+ T cells from tumor-bearing mice possess a limited amount of cytotoxic activity regardless of the source of the T-helper cells. He also pointed out that low levels of mRNA encoding cytotoxic molecules, such as tumor necrosis factor (TNF) and perforin, were found within the cytotoxic T cells from tumor-bearing animals. Dr. Longo explained that this finding raised a question as to the specific defect found within the T cells of the tumor-bearing animals.

Dr. Longo went on to discuss the mechanism required for T-cell activation. This process, he explained, involves signaling through a multimeric complex. The alpha and beta chain in the T-cell receptor recognizes the antigen on the surface of other cells presented in the groove of the MHC molecule. This recognition is what normally activates a T cell. In order for the activation signal to function, a CD3 complex consisting of a delta, epsilon, and gamma chain together with a zeta zeta homodimer must be present. Dr. Longo pointed out that this homodimer is produced by the cell in rate-limiting amounts while the other chains are made in great excess. A zeta chain must be present in order to assemble the complex receptor in the cell and then mobilize it to the surface. The zeta chain is responsible for transducing signals into the cell. As a consequence of antigen recognition, several events take place which lead to the activation of transcription factors. These events include the release of calcium and phosphorylation of several different proteins. The transcription factors are then transported into the nucleus, where they bind to genes and initiate mRNA synthesis; mRNA is then translated to protein in the cytoplasm, and these new proteins are the effector molecules of lymphoid cells. Dr. Longo explained that it was necessary to analyze this complex series of events in T cells in tumor-bearing animals in order to assess the presence of defects.

The first question that Dr. Longo raised in an attempt to identify the potential defect was whether or not the tumor-bearing animals possessed fewer T cells than normal animals. He found that the T cells were completely normal in terms of their number and their CD4+ and CD8+ ratio. Furthermore, the T cells expressed normal levels of T-cell receptors. Functional studies were initiated which triggered T cells to the T-cell receptors. The activation of T cells triggers the onset of tyrosine phosphorylation. Two tyrosine kinases, lyk and fyn, coupled with the T-cell receptor, are crucial for this process. The results from these functional studies revealed the tyrosine phosphorylation process to be abnormal in the T cells of tumor-bearing animals.

Dr. Longo explained that the tyrosine kinases, lyk and fyn, were absent in the T cells of the tumor-bearing animals. These findings suggested that the T-cell receptor structure might

be abnormal in the tumor-bearing animals. The possible presence of abnormalities in the T-cell receptor structure led to two-dimensional gel electrophoresis studies looking at the T-cell structure itself. Dr. Longo found that normal T cells possess an alpha and beta chain; the delta, epsilon, and gamma chains associated with CD3; and the zeta chain responsible for the assembly of the T-cell receptor. When looking at the T cells from tumor-bearing animals, the normal alpha and beta chain and the delta and epsilon chains were apparent; however, the gamma chain appeared to either be reduced or completely absent from the T cells and the zeta chain position was altered, along with its molecular weight. This altered zeta chain finding raised the question as to whether the zeta chain was structurally altered or completely absent with another protein replacing it.

Dr. Longo then briefly summarized a component potentially responsible for the structural abnormality of T-cell receptors. He explained that the zeta chain is one of a family of proteins that are very similar to one another. Another member of this protein family, called Fc epsilon gamma, assembles a multimeric receptor on the surface of mast cells, monocytes, macrophages, and a variety of other cell types. In normal T cells, no Fc epsilon gamma protein is present; however, the T cells of tumor-bearing animals were found to possess the Fc epsilon gamma. These findings demonstrate that in the T cells of tumor-bearing animals, the Fc epsilon gamma is present instead of the zeta chain found in normal T cells. This Fc epsilon gamma protein is not associated with fyn or lyk; it decreases signaling through the cell, and although it will produce specific cytokines, the pattern of proliferation and cytokine production is abnormal, inhibiting the generation of cytotoxicity against tumors.

The question was then raised as to the mechanism of the defect. Dr. Longo explained that sufficient amounts of zeta chain and gamma chain mRNA were present; therefore, no defect could be detected in the gene transcription. When immunoprecipitation studies were done on the T cells of long-term tumor-bearing animals, the zeta protein was found to be sequestered within the T cell. Further studies revealed abnormalities involving the zeta chain. Dr. Longo explained that the zeta chain appeared to be clipped and unable to assemble a normal receptor and place it in the cell surface. The half-life of this zeta chain was also found to be shorter than in the normal T cell.

Another consequence of the abnormal receptor is the abnormal activation of transcription factors. Dr. Longo noted that these transcription factors are essential components of cytokine and effector molecule production. Under normal circumstances, the NF kappa B *rel* family of transcription factors is crucial in T-cell activation. In the T cells from tumor-bearing animals, the NF kappa B *rel* family is normal—the C *rel*, *p65*, and *p50* are the three most prominent members. However, Dr. Longo emphasized that when T-cell activation occurs, these transcription factors are translocated to the nucleus and they bind to particular genes and promote their production. What Dr. Longo found when looking at the T cells from tumor-bearing animals compared to normal T cells, was that both *C rel* and *p65* were absent from the nuclei of T cells of tumor-bearing animals. The *p50* molecule was present in the T cells' nuclei from tumor-bearing animals, but it was found to be altered in size. Characterization of this molecule revealed that it was truncated at the aminoterminal end; however, it was still functional. Dr. Longo stated that the *p50* molecule was still able to form a homodimer and bind to NF kappa B sites in the cell to block transcription. He also pointed out that instead of the T-cell activation producing the normal cytokines which are supposed to

be produced when T cells are activated, the truncated *p50* transcription factor blocks this production.

Dr. Longo explained that because of the clinical difficulties involved in producing effective adoptive cellular therapies in a large percentage of patients, studies were pursued to possibly reverse the abnormalities associated with the defective T-cell receptors from tumor-bearing animals. Dr. Robert Wiltrout's studies with a renal cell carcinoma model in mice, called RENCA, have demonstrated that the combination of Flavone acetic acid (FAA) and IL-2 is able to cure animals with bulky tumors. RENCA cells were given to animals and 2 weeks after administration, the animals were treated with FAA and IL-2. Dr. Wiltrout found that 2 weeks after the tumor cells were administered, the lck protein was missing and the T-cell receptors had no zeta chain. Seven weeks after treatment with FAA and IL-2, T cells began to regain normal functioning, and by week 13, normal functioning was fully apparent. In addition, the lck, fyn, zeta, and NF kappa B *rel* transcription factors also returned to normal.

Dr. Longo also pointed out that the FAA and IL-2 combination caused tumor regression. The zeta chain was evident 4 weeks after the administration of FAA and IL-2. After 7 weeks posttreatment, the amount of zeta chain increased, and by the 13th week the T cells had returned to normal functioning. Dr. Longo explained that these findings indicate that if an effective therapy is available, the T-cell abnormalities may be reversed.

Dr. Longo then questioned to what extent the defect is related to the tumor and to what extent the tumor influences contact cells in the body to produce the defect. Studies were initiated using hollow fibers with a molecular weight cutoff of 500,000. These fibers were filled with RENCA cells and implanted into the peritoneal cavity. By using the hollow fibers as a vehicle for the tumor products, the cellular contact between the animal and the tumor itself is eliminated. Dr. Longo found that when hollow fibers were filled with a salt solution, the zeta chain remained unchanged; however, when the tumor cells were implanted, the zeta chain and the lck disappeared. He pointed out that a soluble tumor product was fully capable of inducing the defect in the absence of direct contact between host and tumor cells. These findings raised the question of whether the material produced by the tumor was a possible mediator of suppression of the immune response.

Possible analogies between the immune and the nervous systems were then discussed. Dr. Longo related the defect found in T cells to the desensitization of neurotransmitter receptors. He explained that nerves cannot be overstimulated because, ultimately, the nerve will desensitize itself to excessive stimulus by phosphorylating the receptor so that it can no longer transduce signals. The possibility was raised that normal antigen-specific T cells exposed to their antigen may, over time, undergo desensitization in an effort to avoid overreacting to overexposure of a stimulus. Murine D10 T cells, a normal T-cell line that is specific for the antigen conalbumin, was cultured together with its antigen for a period of 7 days. The results of the study revealed that normal T cells exposed to their antigen will down-regulate the zeta chain, yet the CD3 epsilon chain remains normal. Dr. Longo explained that these findings uncovered the way in which T cells, similar to nerves, shut off and prevent themselves from overreacting. He further stated that, not only can this occur with a T cell encountering its antigen, it can occur in an heterologous way. If the T-cell costimulatory cytokine IL-1 is administered *in vivo* to normal animals, a loss of zeta chain is apparent but it returns by the fourth day after administration of IL-1. As a result of these findings, Dr. Longo

noted that studies are being pursued to determine whether a derangement in the desensitization process is responsible for some autoimmune diseases. Dr. Longo pointed out that studies that have been performed in the laboratory have also been performed in the clinic to ensure their relevance in humans.

One of the studies performed in cancer patients attempted to purify a factor produced by a tumor. Pleural fluid was extracted from a patient possessing malignant melanoma, and the fluid was cultured together with normal T cells from a cancer-free person. Dr. Longo found that after 4 days in culture with pleural fluid, the zeta chain disappeared. This finding lead to the assumption that the source of material responsible for inducing the desensitization process within the T cells was present in the fluid. Efforts to purify and identify it are under way.

Dr. Longo discussed implications involving the presence of zeta-negative T cells in cancer patients. A small number of patients with a variety of different cancers were studied. In each type of cancer represented on the study, a high percentage of these patients possessed the zeta-negative T cells. Of the patients studied who had melanoma, 46 percent had zeta-negative T cells in their peripheral blood; 52 percent of the 21 patients with breast cancer possessed the defect; 61.5 percent of Hodgkin's patients and 43.7 percent of patients with multiple myeloma possessed the zeta-negative T cell as well. Dr. Longo explained that large-scale studies are currently being performed to validate these findings.

However, Dr. Longo reported, the zeta chain findings in renal cell carcinoma appear to be different. The absence of the zeta chain appears to be a problem that originates in the tumor and becomes a more systemic problem as the tumor grows. Dr. Longo discussed tumor-infiltrating lymphocyte (TIL) specimens from primary renal cell carcinoma obtained from patients undergoing primary resection who had no prior treatment. He found from studying these T cells that 10 of 11 TIL samples had no zeta chain. Peripheral blood cells were measured in these 11 patients and only one of them lacked the zeta chain.

The results from the zeta chain studies suggest that biological consequences and prognostic implications tentatively appear related to the data. Dr. Longo pointed out that tumors in patients who had zeta-positive T cells grew at a much slower rate than tumors in patients who had zeta-negative T cells, indicating that some underlying biological consequences may exist as a consequence of having defective T cells. He also indicated that patients whose T cells lacked the zeta chain died within 21 weeks of treatment; whereas, all of the long-term survivors appeared to possess T cells that had the zeta chain.

Dr. Longo further explained that, once the mechanism that causes tumors to inhibit zeta chain production is detected, specific interventions may be developed to overcome and prevent the immunosuppression that is associated with the cancer-bearing state. In the interim, alternative solutions are being studied. A pilot experiment was performed by Dr. Larry Kwak and his colleagues with a 41-year-old woman who had serious multiple myeloma and was resistant to the conventional chemotherapy regimen, VAD. She had not done well with local radiation or thiotepa, and was considered a candidate for high-dose therapy with allogeneic bone marrow transplant from an HLA-matched brother.

Dr. Kwak thought that it might be possible to immunize the patient's brother against her tumor. Dr. Longo explained that in an effort to accomplish this, the patient's serum paraprotein, which can serve as a marker for the B cells that are producing this immunoglobin, was purified. The serum was then made into an idiotype KLH vaccine which was given with an adjuvant. The patient's clinical deterioration forced doses to be given on only two separate occasions before the bone marrow donor was harvested.

The patient underwent high-dose therapy with the bone marrow transplant. At day 60 after transplant, her peripheral blood T cells, which were phenotypically from the donor, showed that there was an idiotype-specific T-cell proliferative response. Dr. Longo stated that the patient's clinical course had been impressive even with the T-cell response generated in the presence of GVH prophylaxis with immunosuppressive agents. The patient's plasma cell number in the bone marrow has decreased to essentially zero and the patient's paraprotein is declining. He explained that this study is not evidence of therapeutic effect, but it does indicate a strategy that might be used in the future to enlist T cells into a tumor response.

In summary, Dr. Longo expressed his belief that this research has opened many possibilities for the future application of strategies to overcome tumor immunosuppression.

Questions and Answers

Dr. Salmon asked if T cells in pregnant women show the zeta chain defect and whether the defect is related to antigen-specific tolerance.

Dr. Longo explained that antigen-specific tolerance may have several mechanisms. He stated that antigen-specific T cells have been tolerized *in vitro* by blocking their costimulation through CD28. When this process was performed, the T cells were tolerized (i.e., did not proliferate in response to antigen), but their T-cell receptors still contained zeta chains, which showed that the mechanism of blocking involving CD28 did not seem to be a zeta-mediated process. However, when antigen-specific cells are stimulated with their antigen using costimulation, all T-cell clones lose their zeta chain by approximately 6 days after treatment. Thus, the zeta defect appears to require both antigen and costimulation through CD28 to induce it.

XV. QUESTION SESSION: DIVISION OF CANCER ETIOLOGY, FREDERICK CANCER RESEARCH AND DEVELOPMENT CENTER, DIVISION OF EXTRAMURAL ACTIVITIES, AND DIVISION OF CANCER PREVENTION AND CONTROL

Dr. Calabresi explained that, at the suggestion of the Activities and Agenda Subcommittee, representatives of those Divisions not scheduled to make full presentations would entertain questions from the Board. There were no questions for Dr. Richard Adamson, Director of the Division of Cancer Etiology and Acting Director of the Frederick Cancer Research Center, or for Mrs. Barbara Bynum, Director of the Division of Extramural Activities.

Ms. Mayer asked Dr. Peter Greenwald what plans have been developed by the Division of Cancer Prevention and Control to allocate the Division's anticipated budget increase. Dr. Greenwald summarized the following items:

- A substantial commitment to preclinical chemoprevention research, with special attention to breast and prostate cancers, to make up for cutbacks in this research made necessary by last year's commitment to the American Stop Smoking Study for Cancer Prevention (ASSIST) program
- Funding for smoking prevention efforts at Congressionally mandated levels
- Scaling up of the clinical study of finasteride for prostate cancer prevention
- Nine large-scale clinical trials and establishment of a prevention trials decision network
- Potential participation in a National Heart, Lung, and Blood Institute trial of capastatin to examine cancer endpoints
- Potential studies, together with DCT, of novel approaches to early detection using new imaging techniques and biomarkers.

Dr. Broder added that a mandatory 7 percent of the NCI budget must be allocated to prevention, and this portion will be increased to 9 percent next year. He noted that the Institute is prepared to react quickly to opportunities created by technological advances. For example, he explained, when an electron spin resonance (ESR) imaging system is developed, one potential application of this technology might be to identify women at high risk of breast cancer through detection of free radical formation. This would make it possible to test the application of a preventive intervention using high doses of antioxidents or other agents. Clinical trials of such an intervention, Dr. Broder noted, would probably be the responsibility of DCPC.

Dr. Broder added that $2.5 million is being devoted toward building up the clinical education program, including an increased focus on minority education, and some support is being given to the Office of Cancer Information's prevention and control efforts.

Dr. Bettinghaus asked whether it might be considered necessary in the future to expand the Surveillance, Epidemiology, and End Results program to do a better job of collecting information about racial/ethnic groups other than Whites and African Americans. Dr. Greenwald mentioned that limitations on funds available for contracts have affected the SEER program. Dr. Broder acknowledged that the SEER program is a very high priority, but reminded the Board that expanding any area of activity can be accomplished only at the expense of other programs. He noted that NCI has certain obligations concerning statistical questions that may not fall within the scope of the SEER program. For example, Dr. Broder said, the Institute has a statutory requirement to investigate reports that approximately 18 percent of the women in Suffolk County, Long Island, are presenting with metastatic disease. Dr. Greenwald commented that the equivalent figure from SEER data is about 6 percent; this indicates a problem with the 18 percent figure, he stated, but the question needs to be investigated.

Dr. Salmon, referring to Dr. Harms' presentation on magnetic resonance imaging, stated that one of Dr. Harms' colleagues told him that 30 to 40 institutions have capabilities similar to those described in the presentation. Dr. Bragg pointed out that these facilities do not have the unique features of the RODEO technology. Dr. Salmon suggested that the existing similar capabilities are sufficient to proceed with studies of the use of this technology with high-risk women. Dr. Broder explained that support was provided for Dr. Harms' work on the condition that he agree to serve as a reference center to potentially integrate his findings into NCI's clinical trials network.

Dr. Salmon then asked whether SEER could be funded through a cooperative agreement rather than a research contract. Dr. Greenwald explained that SEER is funded through the contract mechanism because it requires an absolutely consistent data set. He noted that there may be research related to surveillance, using SEER data as a tool, that could be supported through cooperative agreements or grants.

Dr. Bettinghaus suggested that cooperative endeavors could be added to the SEER program by forming groups of several State public health departments.

XVI. NEW BUSINESS: SESSION II—DR. PAUL CALABRESI

Dr. Calabresi called for discussion of the motion introduced by Dr. Bragg during session I of the New Business section. The motion suggests that NCI defer action on recommending any changes in breast cancer screening guidelines at this time, in light of the current controversy on this issue.

Dr. Bettinghaus explained that, essentially, four or five Board members drafted this motion, with Dr. Bragg as the spokesperson. The process was initiated by Dr. Robert Day, who encouraged Dr. Bettinghaus to introduce a resolution stating their position on this topic.

Dr. Temin pointed out that the motion's specific recommendations to NCI concerning evaluation, research, and communication are inconsistent with the general recommendation to defer making changes to the guidelines. Dr. Bragg explained that these specific recommendations were not intended to be modifiers of the guidelines, but are elements of uncertainty that justify a delay in changes to the guidelines. He welcomed changes to the motion.

Dr. Lawrence suggested that the Board, as an advisory body (and not a decision-making body), should shorten the resolution to a simple recommendation. Dr. Temin agreed that this change would rectify the contradiction.

Dr. Sigal indicated her agreement with the resolution in general, but suggested that a supplementary statement recognizing the disagreement among scientists should be issued. Dr. Bettinghaus pointed out that the motion refers to an agreement with the DCPC Board of Scientific Counselors and the need to follow a research agenda to clarify equivocal information.

Mrs. Bynum asked whether the motion includes only the general recommendation to defer changes and whether the subsequent items concerning recommended evaluation, research, and communication activities are not to be considered part of the motion. Dr. Bettinghaus explained that the first sentence of the motion renders the operative wording; the remainder of the material is part of the motion and urges NCI to take further action.

Dr. Temin contended that the guidelines must point out that information on mammography screening in women under age 50 is indeterminate. Drs. Salmon, Sigal, and Calabresi expressed agreement with Dr. Temin. Dr. Wells urged that if the guidelines are incorrect or if there is argument about the data on mammography screening in women under age 50, the guidelines must be modified and this information must be presented to the public. Dr. Bragg disagreed and pointed out that the scientific community has not decided whether the breast cancer screening guidelines are incorrect. Dr. Wells reiterated that screening for this age group cannot be recommended if there is no proof that it is effective. Dr. Bragg emphasized that the guidelines should not be altered at this time, since information is shifting. Recent evidence suggests that screening is effective in women under the age of 50. Dr. Wells commented that data presented during day one of this meeting did not support the guidelines and screening under the age of 50. Dr. Bragg suggested that the entire spectrum of information was not presented at this meeting.

Dr. Sigal recommended that the guidelines should not be changed. She emphasized, however, that a statement should be released explaining that scientists do not agree on the effectiveness of screening. Dr. Sigal added that people are dependent on this information, and NCI has an obligation to fully inform the public. She proposed issuing another statement emphasizing the need to come to a consensus on the science of the issue and to get better screening. Dr. Sigal expressed her discomfort with releasing a simple statement that recommends no changes in the guidelines.

Dr. Salmon recommended an amendment to the motion—to add the clause "Recognizing that there is controversy on effectiveness of mammography in women under age 50 that calls for more research," before the sentence of the motion beginning "The members of the National Cancer Advisory Board . . . ."

In light of the high false-negative rate in the under-50 age group, Dr. Wilson suggested indicating in this statement that mammography is currently the best screening technique in this group and emphasizing the value of direct self-examination. Dr. Bettinghaus stated that this information is in the guidelines. Dr. Bragg pointed out that there is no body of evidence analyzing the effect of breast self-examination or even clinical examination in terms of mortality. This would imply having a different standard for mammography than what is assumed for other examinations. Dr. Lawrence indicated that these issues have been discussed in several journals and at several conferences. The Board, he added, does not have responsibility for deliberating the pros and cons of the field; the goal of the motion is to express an opinion regarding an action.

Dr. Calabresi called for a vote on Dr. Bragg's motion with the amendment submitted by Dr. Salmon. The motion was approved with 14 in favor, 1 against, and 1 abstention.

Dr. Calabresi then moved to discussion of Dr. Salmon's motion. Dr. Salmon asked whether NCI staff feel that this motion is useful. Dr. Greenwald commented that the motion is important because it draws attention to the fact that, in addition to scientific issues, reimbursement and health care delivery issues may also play a role in the development of screening guidelines. Thus, a much more complex process, with more interaction with other Federal agencies, may be required if NCI continues to deliberate guidelines. Dr. Greenwald questioned whether NCI should continue to involve itself in setting guidelines, considering the fact that such issues interface with cost reimbursement and there are now other agencies that are directly involved in setting guidelines.

Dr. Salmon noted that if the data are equivocal and any incremental benefit might be small, NCI does not have the kind of data that would allow them to conduct a cost-benefit analysis of any given guideline.

Dr. Broder noted that this issue was addressed when NCI sent out clinical alerts and explained why he considers this a type of policy-making decision. As NCI evaluated this process, he stated, it became concerned with the factors that trigger the release of policy statements or letters to doctors and tried to determine how the Institute can avoid interfering with ongoing doctor-patient relationships while simultaneously conveying information. Dr. Broder related that NCI decided to conduct a peer review before sending out letters. However, this process will become a major issue in the future because, as new therapies or diagnostic procedures are discovered, there will be a gap between the scientific rationale for or against a procedure and associated reimbursement issues. The Institute will have to confront several issues about which it may or may not be experienced.

Dr. Bettinghaus suggested that NCI may not be able to get out of the business of developing guidelines. The Congress, he noted, will require NCI staff to testify on these issues and will demand that a consensus be reached. Dr. Sigal emphasized that people look to NCI for direction and motivation. Thus, it is necessary to have recommendations—whether they are called guidelines or not. Dr. Salmon asserted that he does not consider Physicians Data Query or clinical alerts to be guidelines because they convey information with detail, references, and background. They are generally succinct recommendations, he continued, that groups decide and vote on. Dr. Salmon explained that the other recommendations are information that the recipients read and for which they decide a plan of action.

Dr. Broder stressed that as a matter of policy, no one in the Department can disagree with the policy of the administration. Although NCI defends the policies of the President, he continued, science cannot be instructed to proceed in a certain way. The NCI is a science-based agency, and there is no "party line" or policy for science. Dr. Broder commented that reimbursement is a policy issue that will experience an unprecedented focus in the future, and NCI is not experienced in this area. He indicated that NCI has a science-based agenda and needs to reaffirm this commitment.

Dr. Salmon withdrew his motion and welcomed any input on drafting a more global statement for discussion at a future meeting.

Dr. Calabresi asked Mrs. Bynum to review the issue regarding National Research Service Awards that had been raised by Dr. Broder. Mrs. Bynum explained that all NIH

Institutes were asked to consider a proposal to increase predoctoral stipends by $1,200 each per annum from $8,800 to $10,000, and by $1,000 each for the first 2 years of postdoctorals. She noted that this proposal would cost NCI $1.7 million; if the change were made only for predoctoral awards, the cost would be about $700,000. Dr. Broder asked that the Board consider these increases in terms of their equivalence to formal positions—$1.7 million would be equivalent to about 60 positions and $700,000 to about 28. The NCI has already stated that it is not in favor (as an Institute) of the proposal as NIH-wide policy.

Dr. Broder added that NCI cannot have its own NRSA program; thus, it may have to adhere to NIH policy. Dr. Wells asked if it is correct to assume that an increase in stipends is associated with a reduction in the number of available awards. Dr. Broder noted that Board members cannot vote to increase both the stipends and the number of awards. Mrs. Bynum explained that the Institute has the statistical latitude to compensate for an increase in stipends and trainee slots, but not in this fiscal year. She indicated that the Institute could increase the money in that line, and Dr. Hartinger specified that this change would require reprogramming.

Dr. Bettinghaus suggested that the Board not support the increase in stipends in order to retain the current number of awards. The current amount of funding is not enough to attract quality people, he continued, and departments must supplement NRSAs. Dr. Bettinghaus stated that the Board should recommend that funding is insufficient. Mrs. Bynum noted that the NIH recommendation enjoins NCI to pass the increase along to the student, although NCI cannot make that a requirement.

Dr. Salmon asked whether the Board can submit a motion encouraging Institutes to supplement or require matching a proportion of the awards. Dr. Broder explained that NCI cannot have a policy that is separate from that of the NIH, but, if it chose to, the NIH could develop a matching program. Dr. Salmon suggested that the Board merely express its support of a position to the NIH. Mrs. Bynum clarified that a predoctoral award costs NCI (on average) between $18,000 and $20,000, $8,800 of which composes the student stipend. Dr. Cairoli added that NCI pays $6.8 million for tuition to the universities.

Dr. Wells recommended a motion that the Board not support an increase in stipends because it would result in a reduction in the total number of NRSA slots. Dr. Bettinghaus seconded the motion. Dr. Becker suggested recasting the motion to recommend the maintenance of the present number of slots and not recommend an increase in stipends. Dr. Wells agreed that Dr. Becker's suggestion yields a positive, although nonspecific, statement. Thus, Dr. Wells submitted a motion, which Dr. Becker seconded, recommending that the number of National Research Service Award slots (pre- and postdoctoral) not be reduced—not that they be maintained but, rather, that they not be reduced. The motion was unanimously approved.

Dr. Broder distributed copies of an article that appeared in the November 22, 1993, edition of the *Washington Post* regarding negotiations of the General Agreement on Tariffs and Trade (GATT) treaty and its effects on business and research. He suggested organizing a presentation on this matter for one of the subcommittee's next meetings. One implication of an expansion of the GATT would be limitations on Federal contributions to private research, allowing governments to subsidize up to 50 percent of basic research projects and 25 percent of applied research. The international GATT disputes panel would review cases in which

governments exceeded those limits; disregard for the panel's findings could result in trade sanctions against the offending nation. Dr. Broder noted that the United States in general and the NCI specifically have made a great effort to encourage strong collaborations between the public and private sectors under the Bayh-Dole Act and the Stevenson-Wydler Technology Innovation Act as amended in 1986. He said NCI feels that its clinical trials program is a type of applied research and stressed that the Board may want an update on this issue, since treaties have the force of law that supersedes any other law, except for constitutional issues.

Dr. Becker asked if NCI played a role in the discussion of limitations on certain chemicals or agents that international treaties have deemed to be threatening, but which are important in the synthesis of certain chemotherapeutic agents. Dr. Broder answered that NCI has not played such a role.

Considering the December 15th deadline for negotiations, Dr. Salmon introduced a motion, which was seconded by Dr. Chan, recommending that health research be exempt from the GATT treaty.

Dr. Sigal questioned the validity of this article in light of the magnitude of these implications. Dr. Broder confirmed the veracity of the article and explained that the expansion concerns an overall limitation for nondefense types of government subsidy. The idea is to prevent the subsidy of a project in one country, while the same project is conducted entirely by free enterprise in another country; it is meant to make production fully competitive. Dr. Broder explained that this matter primarily concerns domestic security issues and should not affect health care issues, for which he feels a government should be able to expend as much effort as possible.

Dr. Calabresi expressed the Board's interest in this issue and suggested that it be discussed at the February NCAB meeting.

Dr. Salmon repeated his motion, which was approved unanimously: "The National Cancer Advisory Board recommends that health research be exempt from the clauses on government limitations in funding as proposed in the GATT treaty."

XVII. INTRODUCTION AND OVERVIEW, DIVISION OF CANCER BIOLOGY, DIAGNOSIS, AND CENTERS—DR. ALAN RABSON

Dr. Rabson identified the three major programs of the Division of Cancer Biology, Diagnosis and Centers—the Intramural Research Program, the Extramural Research Program, and the Centers, Training, and Resources Program. He explained that there are 12 laboratories in the intramural program, ranging in work from research in bacterial genetics to cancer vaccine development. The extramural program administers all of the grants in tumor biology, immunology, and diagnostic research. The Centers, Training, and Resources Program is the newest section and has been quite active in the past year, Dr. Rabson reported.

In reference to the anticipated presentations, Dr. Rabson introduced the speakers and applauded their accomplishments in the field of cancer research. He noted that the first

speaker would be Dr. Albert Owens, Chairman of the Division's Board of Scientific Counselors and former Director of the Johns Hopkins Cancer Center. Dr. Owens is now Distinguished Service Professor at the Johns Hopkins University School of Medicine, added Dr. Rabson, and is responsible for many of the advances in oncology coming out of Johns Hopkins.

Dr. Rabson explained that the second speaker, Dr. H. Shelton Earp, Deputy Director of the University of North Carolina Cancer Center and a leader in the breast cancer SPORE program, would present an overview of the Centers Program and the SPORE program. Dr. Rabson called the breast cancer SPORE one of the most interesting, as it illustrates the use of molecular genetics in a community outreach program. Dr. Jo Anne Earp, Professor of Education at the University of North Carolina, and Dr. Shelton Earp's wife, was present, at Dr. Rabson's request, to answer questions.

Dr. Martin D. Abeloff, invited to describe NCI's training programs and the K12 award, directs the Johns Hopkins Cancer Center. Dr. Abeloff selected Dr. Elizabeth Jaffee to attend the proceedings as a representative of the trainees. Dr. Jaffee is an assistant professor of oncology at Johns Hopkins University.

From the Extramural Research Program, Dr. Rabson reported, Dr. Olivera J. Finn, associate professor of immunology at the University of Pittsburgh, would address cancer vaccine development and Dr. Jean Y. J. Wang, professor of biology at the University of California at San Diego, would discuss the molecular basis of the malignant cell cycle.

The final speaker, Dr. Elise C. Kohn, is a medical oncologist from the Intramural Research Program's Laboratory of Pathology.

XVIII. REPORT OF THE CHAIRPERSON, BOARD OF SCIENTIFIC COUNSELORS, DCBDC—DR. ALBERT OWENS

Dr. Albert Owens explained that the Board of Scientific Counselors is responsible for maintaining a general surveillance over the activities of the Division and providing advice to Dr. Rabson, as requested. He emphasized that the BSC spends a great deal of time reviewing the Division's initiatives and, with the assistance of outside experts, conducting lengthy reviews of the Intramural Research Program. Dr. Owens noted that copies of the minutes of the most recent BSC meetings, a list of BSC members, and detailed reports on DCBDC programs were included in Board members' notebooks.

In fiscal year 1993, the DCBDC had a budget of $532 million, of which 12 percent was expended on the Intramural Research Program. The remainder, Dr. Owens reported, was divided among extramural investigator-initiated research and the Centers, Training, and Resources Program.

Dr. Owens credited the extramural program with playing a very significant role in the "knowledge revolution" that currently defines the molecular genetics of human tumor progression. Dr. Owens expressed optimism that, in the coming years, an understanding of the

molecular mechanisms by which altered genes cause the cancer phenotype will be realized. The extramural program has also nurtured the increasing understanding of tumor-initiated angiogenesis.

Dr. Owens highlighted the activities of the Diagnosis Branch, under the direction of Dr. Sheila Taube. This Branch is involved in developing techniques to further identify genetic changes in tumor cells, linking together breast cancer tissue registries, and validating diagnostic and prognostic markers to aid their proper utilization in clinical practice. Dr. Owens noted other efforts by the Branch, including research on prostate cancer, markers of bladder cancer, and brain tumors.

Dr. Owens briefly remarked on cancer immunology, noting that activity is focused on developing cancer vaccines or stimulating tumor immunity by engineering tumor cells. He referred specifically to modifying tumor cells to produce various cytokines with the intended result of achieving a more effective immunity than that obtained using unmodified tumor cells alone. A number of trials based on this laboratory work have begun to evaluate this approach clinically.

Dr. Owens stressed that the various complexities of the immune system continue to be examined. He cited the use of "knock-out" mouse models to elucidate the role of gamma interferon. Dr. Owens mentioned X-linked gamma globulin anemia as another emerging theme related to understanding the pathogenesis of human immune deficiency disorders.

Dr. Owens emphasized the significant role of the Centers, Training, and Resources Program, including the construction program, in the National Cancer Program. He indicated that in these programs, over half of all peer-reviewed funded cancer research is pursued, as well as over half of the training. Dr. Owens listed the major SPOREs that have been awarded, including breast, prostate, and lung cancer SPOREs. Dr. Owens noted that the SPOREs are approaching their second year and, in addition, there are several planning grants in each of these major areas.

The construction budget, Dr. Owens reported, is not adequate for the needs. Over the past several years, concerns have surfaced about the need for new and updated cancer research facilities. Dr. Owens projected that increased support for construction may be available in 1994.

The major accomplishments from the 12 intramural laboratories were presented on slides. Dr. Owens observed that despite the variety of accomplishments emerging from the labs, there is a salient genetic focus—a focus on human disease. Dr. Owens identified a developing biologic basis for immunotherapy, as well as for gene therapy, and noted that advances in the development of vaccines for treatment, as well as for prevention, are also numerous.

The BSC conducted three reviews of intramural sites during the 1993 fiscal year, Dr. Owens explained. Reviewed sites include the Metabolism Branch, under the direction of Dr. Thomas Waldmann; the Laboratory of Biochemistry, directed by Dr. Claude Klee; and the Laboratory of Tumor Immunology and Biology, directed by Dr. Jeffrey Schlom. Reviews

scheduled during the 1994 fiscal year include the Laboratory of Mathematical Biology, the Laboratory of Pathology, and the Laboratories of Cell Biology and Cellular Oncology.

Dr. Owens praised the quality roster of personnel working in the intramural program. He referred to awards made to intramural program staff during his term as chairman of the BSC. He mentioned that a number of DCBDC staff are members of the National Academy of Sciences and the Institute of Medicine, including Dr. Rabson.

Dr. Owens concluded his report by acknowledging Dr. Rabson's "special characteristics" in leadership. He said that Dr. Rabson listens carefully to advice and criticism, which he solicits frequently, and that he always considers the activities of his Division in the context of the National Cancer Program. Finally, Dr. Owens observed, Dr. Rabson's personal example of patience, resourcefulness, and commitment to the task has contributed to the accomplishments of the DCBDC.

XIX. UNIVERSITY OF NORTH CAROLINA BREAST CANCER SPECIALIZED PROGRAM OF RESEARCH EXCELLENCE—DRS. SHELTON EARP AND JO ANNE EARP

Dr. Rabson introduced Dr. Shelton Earp, Principal Investigator of the University of North Carolina (UNC) Breast Cancer SPORE, and Dr. Jo Anne Earp, Principal Investigator of the North Carolina Breast Cancer Screening Program (NCBCSP).

Dr. Shelton Earp described the UNC Specialized Program of Research Excellence, which is organized by the Cancer Center and involves the Schools of Public Health and Medicine, various North Carolina State health agencies, and a consortium of collaborating institutions, including Duke University, East Carolina State University, and the Mayo Clinic. The SPORE became available at a time when UNC had been preparing for an organ site type of effort. Over the past 5 years, UNC had thus established a path for the SPORE through faculty recruitment via State support, a private endowment for breast cancer pilot projects, a collaboration between UNC's Schools of Medicine and Public Health and the Comprehensive Cancer Center, and core grant money used to build a laboratory to facilitate the transfer of molecular technology to the epidemiology research effort. As the basic components for a SPORE were in place, the opportunity arose for UNC to create a unique grant consisting of basic biology and molecular epidemiology, as opposed to the SPORE's directive of taking basic biology into treatment trials.

Dr. Earp described the population-based molecular epidemiologic study of the State of North Carolina, covering 24 counties, which focuses on breast cancer in minority women and, in particular, on finding ways to decrease mortality in older minority women in rural areas. Presently, screening mammography is known to decrease mortality in women over age 50. However, Dr. Earp reported that Blacks and older women in this target rural area receive few mammograms, and Black women are dying from breast cancer at a higher rate than White women. He attributed these statistics to late screening and tumor detection, thus resulting in larger tumor size at the time of reporting.

The UNC SPORE led a large-scale intervention program in an effort to correct this situation. Based on grants previously funded by NCI, Dr. Earp continued, the consortium grant allowed UNC to work in New Hanover and Pitt counties where breast cancer screening was publicized through a media-based practice. They found that a gap existed between Blacks and Whites in screening behavior, and although the intervention was successful at increasing screening mammography, it increased the gap in screening behavior between Black and White women.

Realizing that it was not reaching the minority women in this area through the intervention program, the UNC utilized an NCI minority cancer control research program grant to enhance an innovative approach using lay health advisors, natural helpers in the community, senior citizens, and Black women within the community networks to instigate a system of behavioral change within the community. Dr. Earp explained that the program tested in New Hanover and the small pilot projects subsequently set up in several other counties evolved into the North Carolina Breast Cancer Screening Program.

Dr. Earp then introduced his wife, Dr. Jo Anne Earp, to continue the presentation and discuss the NCBCSP.

Dr. Jo Anne Earp stated that the NCBCSP's specific objective was to increase early detection of breast cancer. Specifically, the program aimed to increase screening by an absolute 20 percent above the secular trend in the proportion of Black women aged 50 and older who reported screening mammography in the past year.

The NCBCSP consists of five intervention counties and five comparison counties, with Pitt County serving as the pilot site for both the evaluations and interventions. The intervention and pilot counties each have a greater proportion of women in poverty, especially older women, than found in the State as a whole. The three intervention components of the NCBCSP include an outreach effort, an inreach effort, and an access intervention. Dr. Earp highlighted the goal of building structures and strategies that can be maintained by both the communities and the agencies involved, thereby enabling the continued dissemination of information even after the grant has expired.

The outreach component of the NCBCSP consists of three community outreach workers who are based in the agency and spend about 80 percent of their time in the communities. The outreach workers implement a lay health advisory network within the communities to assist with advice, referrals, emotional support, recommendations for screenings, and transportation. Once established, Dr. Earp continued, it is hoped that the advisory groups and local networks will remain available to the communities and become their own intervention program. Additionally, in order to assist in the program design of outreach mechanisms, five focus groups within each county provide the NCBCSP an opportunity to elicit information from the women to identify barriers to screening that exist in the community on both the individual and the agency levels. Focus groups and outreach efforts will be coordinated from Bethel Baptist Church, which, Dr. Earp observed, is in the largest church in Bertie County. She added that the "Save Our Sisters" effort in New Hanover County has trained 90 women in outreach techniques and received media coverage nationwide.

The inreach component works parallel to the outreach component in an effort to expose nurses, health educators, and health care technicians to breast cancer education. By doing so, screening can become a preventative measure in underprivileged populations with the assistance of trained, skilled, and educated health care personnel in hospitals, health departments, and community health care centers. The NCBCSP is offering skills training in clinical breast examinations and mammographic technology and prompting strategies to encourage yearly checkups. The program is also helping agencies to set up tracking and follow-up systems to ensure that women obtain recommended checkups.

Dr. Earp explained that the access component of the intervention involves improving the quality of the mammogram testing process. Accreditation and quality assurance, she stressed, are essential to the success of the entire project. Coupled with this is an effort to make testing accessible to women by providing transportation to facilities.

The evaluation component uses a face-to-face structure and a 45-minute questionnaire, which is currently being fielded and will be distributed again in 3 years. The interventions are scheduled to last 2 years and be reevaluated in 4 years. A systematic random sample of 1,000 Black and 1,000 White women in a large rural area (10 counties) involved visits to 24,000 women by 65 trained census workers. Only 2,500 women interviewed met the eligibility criteria for the study protocol—being without breast cancer and over age 50. The subsequent random sample of 2,000 women is being interviewed by 50 trained interviewers; 200 interviews are complete to date, with approximately 14 refusals.

The NCBCSP covers a large geographic area and involves 40 staff and 20 agencies. Dr. Earp asserted that the NCBCSP's goal is not only to increase the annual mammography rate among Black women at 20 percent above the secular trend, but also to institute linkages between Federal and State agencies, health departments and radiology centers, and within the communities themselves. Essentially, Dr. Earp concluded, the project is trying to make a series of social and organizational changes that will last beyond the life of the grant.

Dr. Shelton Earp then resumed his portion of the presentation to discuss molecular epidemiology and its relative importance in the UNC SPORE. He reported that, in the major population-based study in this area, a rapid case ascertainment was devised with which all cases of breast cancer in the study area were used to select a random sample within 2 weeks. Dr. Earp argued that the population-based epidemiology was chosen rather than information from the hospital because it avoids the biases of referral patterns, includes early or late disease, and allows the selection of controls from the population; it thus produces a better amalgam of generalizable data.

Dr. Earp explained that in molecular epidemiology, scientists examine cancer tumors for genetic changes. Both germ line DNA from the patients as well as any genes that predispose them to cancer are collected, and the tumors are analyzed to determine whether they contain a particular molecular signature. In this way, the heterogeneous disease can be broken down into molecular subsets from which further analysis may determine whether a specific inherent environmental or behavioral factor leads to cancer.

The molecular epidemiologic approach involves several steps. First, a pathology report in one of 26 hospitals in the 24 counties involved in the study triggers the hospital database in

the State's central cancer registry; thus, rapid notification is received regarding the cancer detection. Second, staff go to the hospital, obtain the patient's permission for testing, and a random sample is made on a home visit. (In this study, Blacks have been oversampled to attain a sample size equivalent to Whites.) The patient home visit consists of an epidemiologic interview, a blood sample to obtain germ line DNA, and a signed release form for acquisition of the paraffin blocks for laboratory testing. Based on analysis, defined molecular subsets may correlate either to traditional risk factors (i.e., family history, pregnancy, hormone exposure) or to hypothetical risk factors (e.g., pesticide exposure).

Dr. Earp stressed the power of the SPORE program in enabling scientists to rely on a fully funded grant lasting 8 to 13 years in which an integrated, longitudinal population study may be achieved. Therefore, the tumor registry, rapid case ascertainment, collection of cancer data in the State area, and disease correlation to a progressive set of interventions focused on minority women in a largely rural population will result in research that could not be supported by any other type of grant. The grant combines cancer control and epidemiology to allow cumulative data collection of all cases over time and stratification of the tumors by molecular markers to reveal genetic risk. Through continued monitoring of the mammography registry over an 8-year period, codified tumors may show whether the interventions are reducing tumor size and, eventually, reducing mortality. Dr. Earp emphasized that the flexibility of the SPORE program engages utilization of core resources in a team approach, hiring of developmental faculty, pilot testing of developmental projects, reallocation within major projects, and setup of large-scale projects that could not be achieved with other types of grants.

Questions and Answers

Dr. Samuel Broder expressed his enthusiasm for the innovative model of the SPORE program, reaffirming its relevant impact on cancer research efforts. He stressed the importance of the UNC's natural control population to an NCI statutorily mandated study and requested participation of this SPORE to serve as a model in the epidemiological study of Nassau and Suffolk counties in New York State. Dr. Earp responded affirmatively that the UNC SPORE would serve as a control for NCI, and emphasized that the UNC's prepared infrastructure paves the way for other studies.

Dr. Broder noted that the SPORE will be successful if it serves as a catalyst to bring in new funding instruments, and said that the program presents an opportunity for UNC to participate in NCI's research project grant pool.

Dr. Harold Freeman inquired how the program ensures that those who are diagnosed or detected by mammogram actually receive treatment in a short period of time. Furthermore, he noted that it may be dangerous to screen patients without assuring treatment and requested that UNC consider the possible negative impact on the population.

Dr. Earp responded that this issue has not been rigorously addressed in the entire population, and that a UNC renewal grant for a project in New Hanover will look specifically at treatment in the future. The Save Our Sisters network will be used to determine how positive mammograms will be acquired and will serve as an active mechanism to urge women into treatment. Thus, the research from one county will potentially influence that of the SPORE collectively.

XX. CAREER AWARDS FOR CLINICAL INVESTIGATORS: THE JOHNS HOPKINS EXPERIENCE—DR. MARTIN ABELOFF

Dr. Calabresi introduced Dr. Martin Abeloff, Director of the Johns Hopkins University's Cancer Center, to describe his Center's new Clinical Oncology Research Career Development Program.

Dr. Abeloff began by observing that for several years, there have been concerns that clinical investigators are becoming an "endangered species" due to factors such as the competition among academic institutions for limited grant support, increasing dependence on clinical practice income, a decreasing number of role models, and the severe indebtedness of trainees. While institutions have little control over most limiting factors, it was perceived at Johns Hopkins that one factor could be changed within the training program. Trainees had frequently been apprenticed to individual faculty members rather than participating in a defined training program and lacked the rigorous training in research methodologies provided for those interested in epidemiology.

In the mid- to late 1980s, Dr. Abeloff reported, faculty from several Johns Hopkins departments, particularly the Oncology Center in the Department of Medicine, discussed the need for a new approach to educating clinical investigators. This group developed a white paper on the topic and eventually launched the Graduate Program in Clinical Investigation, a joint program of the School of Medicine and the School of Hygiene and Public Health. The 4-year program, Dr. Abeloff continued, is designed to yield a Master of Health Science and Clinical Investigation degree through the School of Public Health, with specialties in disciplines such as medical, radiation, pediatric, or surgical oncology. The program will feature a rigorous curriculum dealing with the principles and methods of clinical research, and will require a thesis mentored by a senior clinical investigator.

The first year, Dr. Abeloff explained, is a clinical fellowship; the second year features course work; and the final 2 years focus on the mentored clinical research and thesis development. In addition to methodology, Dr. Abeloff stated, the curriculum will include computer data management, ethics of clinical trials, biomedical writing, grantsmanship, and drug development. Trainees are also encouraged to take electives relevant to their own interests.

Dr. Abeloff stated that the major problem in establishing this ambitious program involved funding. When NCI issued an RFA for its K12 awards for research career development in 1991, the timing was perfect for the Johns Hopkins Clinical Oncology Research Career Development Program. The proposal developed by Johns Hopkins, as noted earlier, combined the resources of the Cancer Center, the School of Medicine, and the School of Public Health, and incorporated the input of 58 faculty members, including both clinical and basic science investigators from 12 different Cancer Center programs.

The program, Dr. Abeloff mentioned, is still in its early phases, and the response from applicants for fellowships as well as from within the institution has been gratifying. The first fellow was appointed in September 1992, and there are currently four fellows involved in the program. Three of the fellows are supported by an NCI grant that provides a stipend for 3 years, including tuition, modest research support, and some travel funds; the other—a foreign

national—is supported by University funds. Additional support for young investigator grants has been made available by Sandoz and Bristol Myers Squibb. Areas of investigation being pursued include drug development and molecular biology.

Dr. Abeloff stressed that the K12 awards have not only encouraged young physicians to study clinical investigation but have also significantly enhanced the quality of their training. More and more faculty members, he noted, are becoming involved in the program at Johns Hopkins. The linkages between the School of Medicine and the School of Public Health amplify the quality of the training, and the involvement of industry is very helpful in meeting the high costs of the program.

Dr. Abeloff then introduced Dr. Elizabeth Jaffe, Assistant Professor of Oncology at Johns Hopkins University. He explained that Dr. Jaffe is a recipient of an NCI K11 Physician Scientist Award and began work in August 1992 on genetically engineered tumor vaccines.

XXI. GENETICALLY ENGINEERED TUMOR VACCINES—DR. ELIZABETH JAFFE

Dr. Jaffe explained that her interest in tumor immunology began in 1979 when, as a college student, she studied mechanisms of antibody production. In addition to her medical school training and residency, which focused on clinical training, Dr. Jaffe received an NIH Physician Investigator Award, which allowed her to spend a year in laboratories learning the basic tools of science. During this time, she also began a small project in tumor necrology, assisted by several individuals who provided role models for pursuing a career in tumor immunology research.

Dr. Jaffe began a fellowship at Johns Hopkins in 1989, during the first year of which she studied a number of clinical problems in medical oncology. Her next 2 years, supported by the oncology center training grant, were spent in the laboratory learning about basic immunology and exploring ways to apply this knowledge to cancer research.

A major question being addressed in the laboratory at that time, Dr. Jaffe related, was whether the immune system can be activated to eliminate tumors. During her research training, Dr. Jaffe was able to investigate the antitumor immune response by building on a hypothesis developed at Hopkins suggesting that tumor cells, if provided with the right stimulus, can stimulate the T-cell arm of the immune system to recognize and eradicate tumors. During the second and third years, Dr. Jaffe began to develop information from mouse models into a design for human tumor vaccine trials.

It was learned, Dr. Jaffe continued, that tumor cells can express tumor antigens that have the ability to distinguish between tumor cells and nonmalignant cells. These antigens are small peptide fragments that are derived from cytoplasmic proteins in the tumor and then brought to the cell surface, where they should be recognizable by the T-cell arm of the immune system. The question, Dr. Jaffe explained, is why the immune system does not recognize these antigens. One hypothesis is that there is no signal to activate T cells, particularly cytotoxic

lymphocytes, to recognize the major histocompatibility complex (MHC) class I molecule that contains the antigen.

Dr. Jaffe described a study in which a murine colon cancer tumor was transfected with an interleukin-2 (IL-2) gene. One role of IL-2, she explained, is to activate T cells. This brought T cells to a local area of the tumor, where they could be activated to recognize the tumor antigens. The T cells then circulated systemically, recognizing other areas of tumor cells that were expressing similar antigens.

A series of evaluations was then performed, Dr. Jaffe stated, to examine all of the known cytokines for their ability to activate the immune system. One that seemed promising was granulocyte-macrophage colony stimulating factor (GM-CSF). She described a study using GM-CSF with the B16 murine melanoma, which, unlike human melanoma, is nonimmunogenic. Mice were vaccinated and later challenged with a parental tumor. Those with a normal immune system were able to reject the subsequent injection of tumor cells; this response was dependent on the presence of CD4 and CD8 T cells. Natural killer (NK) cells did not appear to play a major role, at least in this model, in helping to reject tumor cells.

Based on this model, Dr. Jaffe addressed several issues relevant to developing a strategy for cancer vaccine clinical trials. The first important question, she stated, was the amount of tumor antigen required. A second question was how to get the GM-CSF gene into tumor cells so that they could produce GM-CSF locally and attract the immune cells to the tumor. The third question was how to safely deliver tumor cells back to the patient.

Dr. Jaffe described the process used to prepare the cancer vaccine. Tumor specimens, she explained, are obtained during surgery and subsequently treated with a transviral vector to introduce the cytokine genes into the tumor cells. These cells are irradiated so that they will not grow further and are then returned to the patient through subcutaneous vaccination approximately 1 month after surgery. Significant success has been achieved, Dr. Jaffe stated, in growing renal ovarian tumor cells and introducing the cytokine gene into them. In renal cell carcinoma, she noted, the gene has been introduced into at least 40 percent of the cells, although, she added, more than 60 percent of cells can usually be genetically altered to express the cytokine gene.

This trial, Dr. Jaffe continued, is being reviewed by the FDA and has already received approval from the Recombinant DNA Advisory Committee. She added that there are plans to study whether *in vivo* and *in vitro* assays can be identified to help monitor the antitumor response expected to be generated by this vaccine.

Dr. Jaffe concluded by describing her work since completing her fellowship, in the context of her recent receipt of a K11 award. A problematic aspect of the current approach to cancer vaccine development, she said, is that it requires working with whole tumor cells from individual patients. This is a cumbersome process and involves some risk if tumor cell growth is not inhibited. In the long run, Dr. Jaffe observed, the goal is to develop generalized vaccines that can be more easily dispensed to multiple patients. The relevant research question, Dr. Jaffe explained, is whether tumor antigens can be isolated, making it possible to learn more about the cytoplasmic proteins from which they derive.

The current theory, Dr. Jaffe stated, is that tumor antigens are peptide fragments of whole cytoplasmic proteins that are expressed as the result of genetic alterations in the tumor cell. New technology has made it possible to isolate tumor antigens, and vaccine development studies are being used to determine which antigens are relevant. Dr. Jaffe described a mouse colon cancer model developed with the support of her K11 award. Mice that receive a GM-CSF-secreting vaccine subsequently generate T cells that can identify tumor-specific peptides, which can be examined in very small quantities. Using mass spectrometry and treatment with digestive enzymes, Dr. Jaffe continued, the mass of the model tumor antigen can be determined. She noted that her team is currently trying to sequence its first naturally occurring tumor antigen in CT26 colon cancer.

In summary, Dr. Jaffe stated, NIH funding, and specifically NCI support, have made it possible for her to begin training in the clinic, proceed into the laboratory to address the questions of interest, and return to the clinic to test whether new therapies actually produce a response in patients.

XXII. BREAST CANCER IMMUNITY AND VACCINE DESIGN—DR. OLIVERA FINN

Dr. Finn thanked Board member Dr. Ellen Sigal and her husband, Jerry, for their contribution to the Duke Comprehensive Cancer Center for breast cancer research. Dr. Finn explained that she was one of the recipients of this donation.

Dr. Finn presented a slide of a breast cancer cell fragment. She pointed out long strands—mucin molecules—protruding from the fragment. About 5 years ago, Dr. Finn said, she and her group discovered that they could easily grow T cells from lymph nodes in breast and pancreatic cancer patients that could kill their tumors. These T cells had a specificity for breast and pancreatic cancer. Dr. Finn and her colleagues determined that the target antigen that could be recognized and used by the T cells to destroy the tumor was the mucin molecule. The molecule protrudes far from the cell membrane and is heavily glycosylated. The molecule is also expressed on normal ductal epithelial cells, which are the origin of breast or pancreatic cancer cells. In a normal situation, the mucin molecule will polarize its expression on one side of the ductal epithelial cell, facing into the duct, and is never presented to the immune system.

The only time that the immune system sees this molecule is when one of the ductal epithelial cells is malignantly transformed and becomes a tumor. In this situation, the molecule loses polarity of expression and is expressed all over the tumor cell. Perhaps because it is produced in such large amounts, it is not fully glycosylated and, therefore, begins to express novel epitopes. It expresses parts of its polypeptide core that are recognized by T cells. Dr. Finn stated that this molecule seems to be immunogenic and tumor specific; otherwise, the immune system would not see it.

The tumor as an immunogen has a very low capacity to stimulate the immune system, even if it has immunogenic molecules on it. Dr. Finn and her group decided to try to use the molecule at a site away from the tumor to stimulate the immune system and generate an immune response, leading to destruction of the tumor cell.

Dr. Finn found that this molecule is encoded by a gene that had not been seen before—one with very few unique sequences. The gene has a transmembrane region and a cytoplasmic region, but is mostly encoded by 60 base pairs tandemly repeated between 20 and 200 times. The final molecule as encoded by this gene is basically a 20 amino acid sequence repeated many times. The site recognized by the T cells is a small site from the 20 amino acids. A cytotoxic T cell can bind to this molecule through multiple T-cell receptors on its surface, leading to a strong activation of the T cells and a high degree of tumor cell lysis.

Initially, Dr. Finn explained, she did not understand the reason for the specificity of the T cells because the amino acid sequence of the mucin made by normal cells and the mucin made by tumor cells are identical. A cytotoxic T cell derived from a breast or pancreatic cancer patient will kill a tumor cell. However, normal ductal epithelial cells in primary culture that express a substantial amount of mucin are not seen or killed. *In vitro*, the cytotoxic T cells that are mucin specific are tumor specific as well. The mucin molecule is also immunogenic in the mouse; most of the antibodies, however, are to sugar determinates, which do not distinguish between normal and tumor mucin.

Dr. Finn then presented a slide of antibodies that can distinguish between normal and tumor cells and recognize a very specific region of the polypeptide core. Dr. Finn related that her group obtained isolated antibodies from sera that recognize this mucin and the synthetic peptide in about 20 percent of all breast and pancreatic cancer patients. Only the synthetic peptide that shows a certain type of retreat can block the reactivity. The other half of the peptide that does not have that repeat is inert. The tumor that expresses this mucin recognizes it through both its T cells or antibodies via exactly the same epitope of the mucin molecules; thus, it is a very immunogenic epitope.

Dr. Finn reported that this gene has been cloned and this particular mucin is expressed extensively in breast, pancreatic, colon, some renal cell, some nonsmall cell lung, and prostate cancers. The ability to manipulate the immune response of this particular molecule in breast cancer may lead to manipulation of the same immune response in all of the aforementioned cancers.

Dr. Finn and her team decided to separate the molecule from the tumor, since the tumor is not a good immunogen. They have conducted several *in vitro* studies in which they have isolated the cDNA of the molecule and inserted it into an expression vector. Dr. Finn related that if the whole molecule is expressed on the tumor, a mucin-transfected cell, immortalized B cells, or fibroblasts, CD8-positive and CD4-positive T cells recognize these cells. The human leukocyte antigen (HLA) type of the patient does not control the T cells' ability to recognize this molecule; therefore, this particular vaccine does not experience the MHC restriction that is common to other vaccine protocols. Dr. Finn stated that her group has created a shorter molecule composed of only two repeats. The tumor cell and mucin-transfected cell are also destroyed in this situation as long as this shorter molecule (two repeats) is expressed on the surface.

Dr. Finn explained that her group has conducted biochemical and biophysical analyses of the polypeptide core sequence. They created a peptide that is 105 amino acids long, which contains six epitopes (repeated five plus times) that are recognized by T cells. The peptide is under consideration at the Food and Drug Administration, and, Dr. Finn stated, an

investigational new drug application for use of this peptide as a vaccine in patients should be awarded by December 1, 1993. Based on nuclear magnetic resonance analysis, Dr. Finn found that this peptide stimulates the T cells as if it were a purified mucin molecule. She suggested that it might be possible to boost an immune response in cancer patients or generate a *de novo* immune response in noncancer patients by vaccination with the peptide. With the use of a good adjuvant, the antigen-presenting cells would migrate to the vaccination site. Achievement of immunity to this peptide will translate into immunity against the cancer cell. Dr. Finn said that this procedure has been successful in *in vitro* studies, and she and her colleagues are attempting these experiments in clinical trials and primate studies. Three types of vaccines have been generated, including cells transfected with whole mucin and cells transfected with truncated or two-repeat mucin.

Dr. Finn stated that this approach might be successful *in vivo* because of mucin-specific immunity. This mucin epitope that is recognizable by T cells and antibodies is usually only expressed in malignancy, though it is also expressed during pregnancy and lactation. Dr. Finn pointed out the fact that breast cancer risk for women (even those with a high predisposition) decreases by half if they have been pregnant and lactated once. If a woman has been pregnant and lactated twice, the risk decreases by half again. Dr. Finn related her belief that a level of immunity to the mucin develops during pregnancy and lactation and, perhaps, the mucin on breast or ovarian cancer as they develop in women who have lactated may boost that immunity enough to reject the cancer. The protective value of pregnancy or lactation may result from a combination of factors, including this preformed immunity to mucin.

Dr. Finn described a patient who had cancer at the age of 21, resulting in a mastectomy. The patient's tumor was positive for the epitope that Dr. Finn was studying. Approximately 2 years after her mastectomy, the patient became pregnant and experienced mastitis in her remaining breast during lactation. There was concern that the mastitis was a recurrence of the tumor, but biopsies revealed that the breast was tumor free and had a tremendous infiltrate of T cells. Her lactation and pregnancy provided a strong boost to her immunity, which was expressed by the mastitis in the lactating breast. Both the tumor and the biopsy of the lactating breast stained positive for the tumor-specific epitope of the mucin molecule. Although it is usually not possible for T cells to infiltrate breast ducts, even in a normal lactating breast, the lactating ducts were heavily infiltrated by T cells. Dr. Finn presented a slide showing that the T cells were actually destroying the ducts. She showed another slide in which the T cells were sitting on top of a mucin molecule inside a duct. Analysis of the patient's peripheral blood established the presence of cytotoxic T cell lines that kill transfected cells, but not control cells.

Most breast and pancreatic cancer patients have antibodies of the IGM type; however, serum from this patient showed both IGM and IGG antibodies. Dr. Finn explained that IGG is a type of antibody produced during a strong immune response. If a patient has enough anti-mucin immunity, she continued, it might be possible to control that patient's tumor. Dr. Finn concluded that her group's clinical trials are designed to boost preexisting mucin immunity in patients to measurable levels and examine the effect on patient survival and tumor recurrence.

Questions and Answers

Dr. Becker asked if the mucin expressed during lactation would actually be exposed to immune cells. Dr. Finn explained that mucin usually remains intraductal because normal ductal cells have very tight junctions, but all the junctions are looser during lactation. It is difficult to biopsy a lactating breast, she added, but it is possible that there is a low-level infiltration and a change of ductal architecture that allows mucin presentation.

XXIII. MOLECULAR BASIS OF THE MALIGNANT CELL CYCLE—DR. JEAN WANG

Dr. Calabresi introduced Dr. Jean Wang, professor of biology at the University of California at San Diego (UCSD).

Dr. Wang began her presentation by stating that investigation of the difference between a normal and a malignant cell cycle drives the research in her laboratory. Mammary epithelial cells, she stated, are a good example of this difference. During pregnancy, there is a continuous proliferation of mammary epithelial cells in preparation for lactation, and pregnancy reduces the risk of breast cancer development. However, deregulation of the process of mammary epithelial cell proliferation later in life results in the development of malignant cancer.

Dr. Wang expressed hope that understanding of this regulatory process will cause cancer therapy to progress from the killing of proliferating cells to the restoration of cell growth regulation. Understanding how to convert abnormal to normal proliferation would provide an opportunity to enhance proper functioning, such as reviving skin and hair.

Dr. Wang described the three fundamental processes that all eukaryotic cells undergo, and which are essential to completing a successful proliferative cycle or event. During the G1 phase, cytoplasmic growth occurs and metabolism is mobilized so that cells double their content. This phase is followed by the replication of cellular DNA. Following DNA synthesis, the cells rest for a brief period and then undergo a rapid process of mitosis in which the replicated DNA is divided faithfully into two new daughter cells. The cancer cell experiences the same process of cytoplasmic growth, DNA replication, and mitosis.

In recent years, Dr. Wang related, research mainly in yeast and frog oocytes has led to the identification of the basic machinery that drives the regular cell division process. Simple enzymes called protein kinases drive the cell cycle progression. Cyclin-dependent kinases (CDKs) phosphorylate a variety of other proteins to modify their functions.

There is only one CDK in a simple yeast, and three types of basic cyclins drive one enzyme and activate the kinase activity. The cyclins that regulate cell growth are expressed only during the G1 phase, the cyclins that maintain and regulate DNA synthesis are expresesd in the S phase, and the cyclins that drive the mitotic process are expressed late in the cell cycle.

In the mammalian system, there are at least four distinct types of CDK cyclins that work at discreet points in the cell cycle. The D-type cyclins in complex with the fourth member of this family, CDK4, regulate G1 progression. Cyclin E in complex with the second member, CDK2, catalyzes the commitment step, after which the cells are committed to DNA synthesis. Cyclin A in complex with CDK2 maintains regulation throughout DNA synthesis, and cyclin B in complex with CDK1 drives mitosis. These, Dr. Wang stated, are the evolutionarily conserved machineries.

Dr. Wang explained that because these molecules phosphorylate other proteins, they can be viewed as a simple transducer signal. A variety of cellular parameters regulate the cyclin CDKs on a variety of molecular levels, such as expression, protein synthesis, assembly of the complex, and activity of the complex. Upon activation and during the cell cycle, these proteins will selectively phosphorylate their substrates to mobilize the cells forward. A majority of these substrates are the machineries for DNA synthesis or mitosis, and cancer cells rely on the same machineries to grow. Some of the substrates are components of feedback regulatory loops. Thus, these molecules, Dr. Wang indicated, can trigger a third set of regulatory events. This, she said, is the key to regulation.

Dr. Wang outlined the cellular parameters from G1/S during progression from cytoplasmic growth to DNA synthesis. First, she emphasized, the cell has to know that mitosis has been completed. If a cell undergoes successive DNA synthesis without mitosis, the cells become polyploid, or will have multiple contents. This is a scheme utilized by megakaryocytes—the precursors of platelets. The second important control is cell size; a cell must gain a critical size before it will enter DNA synthesis—if there is not enough cytoplasmic content, there is not enough energy for DNA synthesis. Growth factors regulate the attainment of the critical size. Third, mammalian cells must know contact information (i.e., how much space there is to grow, if it is proper to grow) and, finally, the cells must know the chromosomes are intact.

At the transition into mitosis, cells check that the S phase events are completed and the chromosomes are intact so that there will be no mistakes during the segregation of the chromosomes. The growth factors always promote entry into the cell cycle, regulate metabolism, and stimulate cytoplasmic growth. Dr. Wang pointed out that cardiomyoocytes never develop cancer. Cardiomyoocytes respond to growth factors and become larger, but never proliferate because there is complete uncoupling of the growth factor signals from the cell cycle machineries in their genetic program.

Dr. Wang discussed pro-oncoproteins and anti-oncoproteins, two classes of genes that play a major role in carcinogenesis. Pro-oncoproteins encode proteins that are activators of proliferation and, presumably, inhibitors of differentiation. These proteins should activate the cell cycle machinery, and they promote positive activity and drive the activity of cyclin CDKs. Tumor suppressor genes, such as *p53* and the retinoblastoma suppressor protein, are anti-oncogenes and inhibit cell proliferation. Dr. Wang reported that her laboratory was one of the first to discover that the CDK cyclins actually "talk" to proto-oncoproteins and tumor suppressor proteins. She and her staff found that the proto-oncoprotein, as well as tumor suppressor genes (such as *RB* and *p53*) are substrates of the cell cycle-driven kinase. Thus, when the CDK cyclins are activated, they actually target the phosphorylation. The targets of these enzymes include proto-oncoproteins and tumor suppressor proteins.

Dr. Wang explained that she and her group believe that these phosphorylation events set up a feedback loop. The proto-oncoproteins are activators of proliferation and should activate CDK cyclins by one of a variety of mechanisms. Meanwhile, the tumor suppressor proteins are inhibitors of CDK cyclin. Dr. Wang related that evidence suggests that when anti-I proteins (or tumor suppressor proteins) are phosphorylated, they become inactivated. This inactivation sends a positive feedback signal to the CDK cyclins. Dr. Wang explained that when these inhibitors are activated, they phosphorylate and inactivate an inhibitor, setting up a positive loop of CDK cyclin. This activity occurs at G1/S transition. When a bit of CDK is activated, it will actively eliminate the tumor suppressor proteins and cause a positive event that drives entry into DNA synthesis. Conversely, phosphorylation of the activated proteins serves as an inhibitory event so that the CDK cyclins can turn themselves off.

Dr. Wang described two genes that encode the retinoblastoma protein and a pro-oncoprotein called abl. The retinoblastoma protein was first identified as the suppressor of a childhood cancer, retinoblastoma, and has been found to be mutated in a variety of adult tumors. This product exhibits growth suppressor activity.

Dr. Wang noted that a dominant active mutation in *c-Abl* has been discovered to be the cause of human chronic myelogenous leukemia and a fraction of childhood acute lymphocytic leukemia (ALL). Children with acute lymphocytic leukemia that involves *abl* are refractile to conventional chemotherapy.

Dr. Wang explained that abl, a complex protein with hundreds of thousands of amino acids, is ubiquitously expressed in mammalian cells. She noted that this is the main protein of study in her laboratory. It is localized in the cytoplasm where it binds to actin filaments. Actins, Dr. Wang stated, are part of the skeleton of the cell. Abl is the only protein tyrosine kinase that not only resides on actin, but also migrates into the cell nucleus, where it binds to specific DNA sequence. The mouse is dependent on the *abl* gene for survival—if the gene is knocked out of the mouse genome, completely deleted, or mutated, the mouse will die 10 days after birth for unknown reasons.

Activated tyrosine kinase, Gag-v-Abl, of Abelson murine leukemia virus or BCR-ABL of chronic myelogenous leukemia can stimulate growth or cause cell cycle arrest, depending on the cell context. Dr. Wang noted that not all tyrosine kinases drive proliferation. The majority of protein tyrosine kinases are associated with cell surface receptors either directly as a receptor protein (such as the new oncogene product) or as a protein coupling with the receptors.

The RB protein is a tumor suppressor whose activity is regulated by cell cycle-dependent phosphorylation; thus, it is a target of the cell cyclin machinery. Dr. Wang reported that Drs. David Livingston and his associates found that the RB protein has an important pocket, which Dr. Livingston calls the A-B pocket, that allows the RB protein to bind cellular transcription factors that may be important for the growth inhibitory activity of this protein. RB is a target of viral oncoproteins, such as SV40 T antigen, which can inactivate RB. Dr. Wang reiterated that RB is associated with a wide variety of adult cancers and might contribute to tumor progression.

Dr. Wang related that before starting her study, she hypothesized that RB is an important regulator and carries out this activity by binding other cellular proteins. These proteins are important for controlling cell cycle progression and must be free of RB for the cells to continue cycling. When CDK cyclins are activated, they phosphorylate RB and inactivate RB's ability to sequester cellular proteins. Thus, when RB is phosphorylated, proteins are released and cells can progress. As cells enter mitosis, RB is continually phosphorylated until two new cells arrive. RB is then dephosphorylated and resequesters cellular proteins; the cell is now ready for the next set of signals. A viral oncoprotein binds RB and disregards cellular proteins, leading to cell cycle deregulation.

Dr. Wang reported on the work of a graduate student at UCSD, which was recently published in *Cell*. This work led not only to the discovery of a cellular protein, but a separate function of RB. The UCSD group found that the c-Abl tyrosine kinase that sits on the cellular DNA forms a complex, one-to-one interaction in direct contact with the retinoblastoma protein product. This direct interaction is mediated through two new protein-binding domains in both proteins. They discovered that, in addition to the so-called A-B pocket, RB also has a C pocket at the C terminal region of the protein. The C pocket is involved in touching this tyrosine kinase. The ATP-binding mode is on the *abl* side of the tyrosine kinase. In order to work properly, any kinase needs to bind ATP and transfer the phosphate onto its substrate. RB sits directly on that place. When c-Abl is bound by RB, the tyrosine kinase activity of c-Abl is inhibited, both for autophosphorylation and substrate phosphorylation.

Dr. Wang presented a slide of the basic structure of all protein kinases, which was published by a group at UCSD in 1991. There are, she stated, probably a thousand protein kinases in the cell being investigated, and they all follow a basic floating diagram for protein kinase A (a metabolic kinase). Dr. Wang related that the *abl* protein has a similar, but not identical, floating diagram. Her group, she continued, believes that the alpha-helices allow RB to mount and they hope to understand the direct molecular location of RB on the specific cell lobe.

Dr. Wang reported that the RB-*abl* cycle was discovered within the cell cycle. While cells are preparing for DNA synthesis and carrying out the G1 phase, there is an inactive complex in which RB holds on to c-Abl through the C pocket and the kinase is kept off. When cells enter into the S phase and one of the CDK cyclins is driven, it phosphorylates RB, releases this abl, and activates the kinase. The kinase is turned on through S and G2 until mitosis. The CDK cyclins are also capable of phosphorylating abl protein, which, Dr. Wang observed, "kicks the abl protein off DNA." Dr. Wang and her group found that the polymerase cells are the substrate for abl. The RNA polymerase II causes all of the mRNA to express all of the genes, and is a direct target of this activated tyrosine kinase. The abl protein has to bind to DNA in the nucleus to regulate transcription.

Dr. Wang summarized that her group has found a second protein-binding domain in the tumor suppressor protein RB, which indicates that RB may act as a molecular matchmaker. RB is an important regulator of many proteins, and there is evidence supporting the hypothesis that a protein such as RB acts as a promoter that supervises the assembly of DNA-sequenced specific protein complexes binding to RB. A fundamental regulatory program of gene expression is that cells know which proteins should be assembled on which DNA sequences, since there are many different X proteins that can bind a given sequence.

Dr. Wang explained that the c-Abl tyrosine kinase can be inhibited by RB. Her group, she stated, discovered a protein-protein interaction as a way of regulating the kinase. Phosphorylation of RB can lead to the activation of *abl*; thus, this enzyme is actually a cell-cycle-regulated tyrosine kinase, which can regulate transcription.

Dr. Wang reiterated that her group believes that c-Abl not only binds DNA, but also sits on the cytoskeleton. c-Abl is the signal transducer that allows the cell nucleus to sample information conveyed by cell contact. When actin filaments are reorganized under morphogenesis, there is an inclination transfer system in which *abl* is involved. Dr. Wang said her group also concludes that the abl-RB interaction is a mechanism by which the cell can integrate a space inflammation, or integrate the affected signal with the cell cycle control program. This integration, Dr. Wang pointed out, is jeopardized in the malignant cell cycle.

Dr. Wang concluded that the malignant cell cannot live without CDK cyclins, so the cells do not want to mutate them. The cells mutate regulatory schemes, but a malignant cell ignores contact information—an important regulatory scheme. The major difference between a normal growth and a malignant growth is infiltration metastases. Dr. Wang and her group propose that c-Abl RB regulation, or the integration of the cell cycle program with the contact information, is an important aspect involved in understanding cell cycle regulation. Further research, she stressed, is needed on the compromise of DNA integrity. She expressed hope that understanding the cellular integration of contact information with the cell cycle program through *abl* and RB interactions will contribute to the design of therapies that can convert a malignancy to a benign growth.

XXIV. SIGNAL TRANSDUCTION THERAPY: A NEW PARADIGM—DR. ELISE KOHN

Dr. Elise Kohn, Senior Investigator in the Laboratory of Pathology within the Division of Cancer Biology, Diagnosis, and Centers, stated that her presentation would provide an example of translational research, in which laboratory studies are translated into applications that benefit cancer patients. Her laboratory, she explained, identified signal transduction pathways on the cell surface as a novel target for intervention. Working from the hypothesis that inhibiting such pathways could inhibit tumor cell migration, Dr. Kohn's team screened 25 compounds and chose an agent called carboxyamido-triazole (CAI) as a prototype. The pathway selected for study was influx of calcium, the regulation of which is important to a number of biological functions.

Having demonstrated that CAI inhibits calcium influx, Dr. Kohn continued, her laboratory examined whether this resulted in inhibition of proliferation. This effect was demonstrated *in vitro*, she observed, for a wide variety of tumor cell types, including hormone-dependent, hormone-independent, and drug-resistant breast cancers, as well as prostate, colon, pancreas, and ovarian cancers.

Dr. Kohn presented results of a study of the effect of CAI on angiogenesis, or the formation of new blood vessels, a process important not only in metastasis but also in tumor initiation and proliferation. She presented slides showing abundant vascularization in controls,

compared with the breakdown of vessels and prevention of proliferation of small vessels with the application of CAI. Dr. Kohn noted that studies of signal transduction have demonstrated that there is a calcium-dependent phosphorylation event in angiogenesis in response to fibroblast growth factor (FGF), a key angiogenic stimulator that plays a role in a wide variety of cancers.

CAI, Dr. Kohn explained, has been taken into the arena of animal studies and, subsequently, into the clinic. Results of an experiment in which nude mice were inoculated with human melanoma cells and then given oral doses of CAI showed that the agent not only inhibited tumor proliferation, but also affected the ability of tumors to be initiated.

These studies, Dr. Kohn continued, led to the establishment of a Phase I clinical trial. One goal of the trial is to explore the range and severity of toxicities for oral administration of CAI. A metabolite that may be active has been identified. Another goal is to look for objective responses to the agent, although Dr. Kohn noted that CAI is expected to result in disease stabilization before producing tumor decreases.

Dr. Kohn presented anecdotal data concerning one patient in the study. Two of the patient's three lesions had a positive growth rate prior to treatment. All three lesions, she noted, had a negative growth rate during therapy, and two of the lesions decreased in size from 20 to 30 percent. During the observation period following therapy, regrowth and changes in growth rates confirmed that a cytostatic effect had taken place. When the patient went back on the drug, stabilization was again achieved.

Dr. Kohn stated that her laboratory is also exploring novel combination approaches and has identified paclitaxel as the agent most likely to synergize successfully with CAI. She presented preliminary data showing a moderate inhibition of proliferation of two ovarian cell lines with CAI alone and a marked additive effect with a very low dose of paclitaxel. The effect, Dr. Kohn noted, is probably schedule-dependent, requiring administration of CAI before paclitaxel.

This approach, Dr. Kohn related, has potential not only for treatment but also for chemoprevention. She explained that a multidivisional project being conducted by DCBDC, DCT, and DCPC, is showing that CAI can inhibit intermediate endpoint markers that are very important in the prevention of cancer. Efficacy has been found, Dr. Kohn noted, at concentrations well below those known to be toxic. Inhibition of the aberrant colon crypt assay, an animal model of colon cancer initiation, has been demonstrated in preliminary studies, and plans are under way to study breast and lung cancer chemoprevention models. These and other animal studies, combined with evidence from Phase I trials of CAI showing minimal toxicity, should make it possible to initiate chemoprevention trials in the near future.

Questions and Answers

Dr. Becker asked for clarification of the mechanism of inhibition of calcium influx into cells. Dr. Kohn replied that studies of CAI show that it inhibits calcium influx through several channels. While it affects one of the slower voltage gated channels, she said, it predominantly affects nonvoltage gated calcium influx, as well as receptor-operated calcium influx, refilling channel calcium influx, and possibly also the nonspecific cation channel.

XXV. GENERAL DISCUSSION OF DIVISION OF CANCER BIOLOGY, DIAGNOSIS, AND CENTERS PROGRAMS—DR. ALAN RABSON

Dr. Rabson expressed his gratitude for Dr. Broder's support of the DCBDC over the past 2 years. He commended Dr. Broder for his ingenuity in creating the SPOREs program and for enthusiastically supporting the K12 program. Finally, Dr. Rabson thanked Dr. Broder for his support for translational research.

Dr. Calabresi asked Dr. Rabson for recommendations on making the field of clinical investigation more attractive in terms of support and career development. Dr. Rabson commented that it is difficult to combine scientific endeavors with clinical responsibility. Dr. Broder urged Board members to ensure that NCI receives and/or stimulates good research project grant applications related to clinical investigation. He added that NCI will continue to investigate a possible reconfiguration of its study sections, and emphasized the importance of encouraging investigators to submit applications for clinical research.

Dr. Calabresi thanked Dr. Rabson and the other speakers for their presentations, and Drs. Vincent Oliverio and Paulette Gray and their staffs for arranging this program review meeting.

Dr. Calabresi then introduced Dr. William Harlan to provide an update on the NIH Women's Health Initiative.

XXVI. UPDATE ON THE NIH WOMEN'S HEALTH INITIATIVE—DR. WILLIAM HARLAN

Dr. Calabresi introduced Dr. William R. Harlan, Associate Director for Disease Prevention, Office of the Director, NIH. Dr. Harlan stated that his presentation would include an overview of the Women's Health Initiative (WHI), a summary of its Institute of Medicine (IOM) review and the NIH response to that review, and a report on the WHI's status and next steps.

The WHI, Dr. Harlan explained, has three components: testing promising interventions through a clinical trial; searching for new predictors and descriptors of disease through an observational study; and examining the application of healthful behaviors through a community trial approach. Two of the components—the observation study and the clinical trial—are closely linked. All of the components, Dr. Harris said, are dedicated to examination of the principal causes of mortality, morbidity, and impaired functioning among women in the postmenopausal years.

The clinical trial, which Dr. Harlan said has received the most attention, has a partial factorial design and features three components. The first is an examination of hormone replacement therapy with a primary endpoint of coronary heart disease and secondary endpoints of osteoporosis and the development of breast cancer. The second is a large dietary modification component with principal endpoints of breast, colon, and rectal cancers and a secondary endpoint of coronary heart disease. Dr. Harlan stated that there is an overlap of

about 15 percent between the hormone replacement and dietary modification trials. Overlapping both of these, he said, is the third component, a trial of calcium and vitamin D supplementation to determine its effect against hip and other fractures, as well as the effect against colorectal cancer. The anticipated sample sizes for these components are 25,000, 48,000, and 45,000, respectively. Dr. Harlan stated that no detectable interactions of any particular magnitude are expected with this design, with the possible exception of hormone replacement and supplementation as regards osteoporosis.

Dr. Harlan provided further detailed information on the dietary modification component, which he suggested would be of greatest interest to the NCAB. The trial tests a diet with 20 percent of calories from fat, increased intake of fruits and vegetables up to five servings per day, and increased intake of grain products. This diet, Dr. Harlan noted, has been tested in feasibility studies in the colon polyp prevention trial, the initial Women's Health Trial, and the Women's Health Trial Minority Feasibility Study, as well as studies in Canada. Results of these early studies, with sample sizes of up to 2,000, have shown that over a period of 2 to 5 years, women can adhere to the dietary pattern well enough to reduce their calories from fat to about 23 to 25 percent.

In the design of this study, Dr. Harlan explained, breast cancer was selected as the principal endpoint against which to determine sample size and duration of follow-up. It was found that the ability to detect or prevent colorectal cancer and coronary heart disease requires about 9 years of follow-up, approximately the same as that for breast cancer. While the estimates of power are rather low at 6 years of follow-up, they are well over 80 percent for all three endpoints at 9 years.

When the IOM reviewed the WHI and issued a report on November 1, 1993, Dr. Harlan stated, they asked whether coronary heart disease should be the primary endpoint instead of breast cancer. He described this as more than a semantic difference in light of another IOM recommendation that there be a programmed examination of the data at 6 years of follow-up with an eye toward stopping the study at that point. Dr. Harlan said that the NIH believes the coronary heart disease endpoint is unlikely to be achieved at 6 years. At this time, he stated, the NIH view is to keep the endpoints as planned, perform structured analyses of the data at 3 and 6 years to examine adherence to the diet and conditional probabilities of success in answering the study questions either in a positive or negative manner, and subject data to review by a safety monitoring board at 6-month intervals.

Dr. Harlan stated that a major recommendation from the IOM review of the hormone replacement study was that the design failed to clearly identify risks or benefits for women who are randomized to receive therapy or a placebo. Changes are being made in the informed consent agreement, he said, by adding information on the magnitude of risk; this will include both descriptive and quantitative language concerning risk to account for the fact that the information conveyed in an educational presentation may overwhelm some people.

Dr. Harlan noted that the calcium and vitamin D portion of this study will have sufficient power to test approximately a 30 percent effect of prevention of colorectal cancer, based on the observational studies that have been conducted.

Concerning the dietary modification portion of the study, Dr. Harlan explained that there is good evidence, based on the first set of studies, including geographical correlational studies and experimental animal studies, that diet has an effect on breast cancer prevention. On the other hand, he said, some analytical epidemiological studies are conflicting in their views on the effect of diet. Dr. Harlan suggested that the principal benefit of the diet for coronary heart disease would come from the decreased intake of saturated fat. He added that it is now widely believed that the increased servings of fruits and vegetables as well as the increased antioxident intake may also provide a benefit for this disease.

Dr. Harlan emphasized that a great deal of commitment was made in the study design to developing adequate minority representation. Noting that minorities comprise about 17 percent of age-eligible women in the United States, he stated that the study's goal is to recruit 20 percent or more of minority women. In order to do this, he said, a separate pool of contracts will be awarded to clinics that focus on recruitment of 60 percent or more minorities.

The observational study, Dr. Harlan observed, received laudatory comments in the IOM report. Women coming into the study will be asked to join the clinical trial; those who are not eligible or willing to join will be invited to participate in the observational study, which will then become the cohort for follow-up. It is estimated that 100,000 women, or two out of three women who come to the clinic with an interest in the clinical trial, will join the observational study. Baseline information and biological samples will be collected and stored. Information collection will be repeated with annual follow-ups, and these data will help identify markers for disease and quantify disease risk factors. Dr. Harlan described this as an extraordinary resource for testing new measurements that require very large cohorts of well-characterized individuals.

Dr. Harlan stated that this study is currently in the vanguard phase. The Fred Hutchinson Cancer Research Center, he said, is the coordinating center, and 16 clinical centers around the country are involved. Protocol recruitment plans were developed and the first participants were enrolled in September 1993. Dr. Harlan noted that without any active recruitment, the 16 centers already have about 20,000 women who have indicated an interest in joining the study. He added that another 29 clinical centers will be awarded in September 1994, for a total of 45 centers. The clinical trial, Dr. Harlan observed, will undergo final analysis between 2005 and 2007, and the observational study will yield useful results well before this.

Dr. Harlan concluded by noting that the community prevention study will evaluate strategies to achieve the adoption of healthy behaviors and provide a public health approach to reduction of mortality and morbidity from chronic diseases. A particular focus will be on diverse racial/ethnic groups and various socioeconomic strata. The concept review for this study, Dr. Harlan stated, occurred in early November 1993 and, following the release of an RFA, about 15 grants will be awarded.

Questions and Answers

Dr. Ellen Sigal asked whether advice on alcohol consumption will be included in the study. Dr. Harlan replied that in the clinical trial, women will not have a structured intervention about alcohol. He added that women with alcohol problems that could hinder

follow-up, particularly regarding dietary modification, may be excluded from the study. Dr. Harlan added that in previous studies, problems arose in measuring compliance with alcohol reduction programs. Liver enzyme tests, he said, are useful when alcohol intake is high but are not useful in measuring modest reductions.

Dr. Sigal asked how women will be educated concerning fat intake. Dr. Harlan stated that the dietary modification program, which is similar to one already in use at the Fred Hutchinson Cancer Research Center, will involve frequent group meetings that will become less frequent over time. The program involves a change in dietary pattern, Dr. Harlan explained, in which women will be taught about the handling and processing of foods and will learn to identify sources of fat as they purchase foods and select foods in restaurants.

Dr. Calabresi asked how the recommendation of six servings of grains and cereals per day will be implemented. Dr. Harlan answered that this particular diet will probably not be able to reach that level of grain intake. He noted that in women, whose caloric intake is lower than that of men, it is difficult to achieve a large number of portions of grains without increasing fat intake.

Dr. Bragg asked whether Dr. Harlan felt that participants would be any more accurate in their reports of dietary intake than they seem to be about alcohol intake. Dr. Harlan suggested that there are fewer moral judgments associated with diet than with alcohol. He also explained that an additional instrument in the dietary modification study will be a 4-day food record that is expected to give a much better indication of fat intake than previously used methods. Dr. Harlan noted that measures of weight reduction and lowering of serum cholesterol levels are also indications of reduction of fat intake. Measures of carotenoid, he added, will give indirect evidence of intake of fruits, vegetables, and fat.

In light of the fact that the WHI is the world's most ambitious women's health trial and is not likely to be repeated on this scale, Dr. Broder asked whether the apparatus being assembled could integrate new scientific ideas and new opportunities for prevention, early detection, diagnosis, and treatment. Would it be possible, he wondered, to use this costly commitment to help NCI in its clinical trials process—for example, by incorporating needed chemoprevention studies into the WHI?

Dr. Harlan replied that the observational study will develop a very large resource of stored materials, providing the opportunity to look at new questions that might arise over the course of follow-up. For example, he suggested, it might be possible to go back in time and look at DNA as it relates to disease development. A number of investigators, he noted, have applied for ancillary studies, which can be done at a small fraction of the usual cost when the work of building a cohort and follow-up is already accomplished. Regarding the clinical trial, Dr. Harlan suggested that there are problems associated with changing treatments during the course of such a study. This might be feasible, he observed, if part of the structured treatment were stopped because a beneficial or adverse effect has been demonstrated; at that point, some participants could be rerandomized.

Dr. Broder emphasized the scientific concerns that must be addressed with long-term studies, such as the WHI, that involve commitment to many years of follow-up. During this period, science could change radically; he mentioned, as an example, the likelihood that the

BRCA1 gene will be cloned and sequenced within the next year. Dr. Broder argued that unanticipated advances could change the way data are stratified and analyzed. Dr. Harlan expressed confidence that adaptation to new measurements could be made early on, during the first 6 months. He said the real problem occurs when full recruitment has been achieved and all sites are committed to a particular set of approaches.

Dr. Broder stressed the generic problem of conducting large-scale studies, such as prevention studies, that take 7 to 10 years. What is the algorithm, he asked, for retaining the original hypothesis while maintaining the flexibility necessary to ensure that a germane question is still being asked in the out years of the study? Dr. Harlan replied that if a new test stratified an individual in terms of increased risk, the test could be incorporated at the baseline to determine whether response to the particular intervention differs among those with the same characteristic. He said he could not see any way to do this other than to stop the trial at a specific point and initiate a new intervention.

Dr. Becker asked, hypothetically, whether a new test that was not involved in the study design but was found to be protective in animal experiments could be incorporated into the trial. He suggested that it could not be incorporated without great difficulty because of the momentum a trial develops based on the factors that have already been built into it. Dr. Harlan replied that such new tests could not be incorporated once the trial is fully under way.

Dr. Broder stated that prevention is an extremely important obligation of NCI, but acknowledged that certain realities concerning prevention must be accommodated. He said that researchers who propose valid and important prevention trials must remember that the length of time required for prevention trials is such that paradigm shifts should be expected.

Dr. Harlan reminded the Board that it is not possible to insert an element of new information into a large-scale clinical trial without first gaining important experience through small-scale studies. He cited the hormone replacement study as an example of this process.

Asked by Dr. Broder whether he considers the tamoxifen chemoprevention trial a small-scale study, Dr. Harlan said that it is not, adding that tamoxifen had been used as an adjunct and with contralateral breast cancer before this trial was started. Dr. Broder asked what would happen if the tamoxifen study showed a positive effect in 5 to 6 years, while the WHI is still under way. Dr. Harlan replied that the WHI would not be changed, but that women defined as high risk in the tamoxifen study would be offered the opportunity to take tamoxifen. The only way to accommodate the new findings, he asserted, would be to provide information to the women to enable them to make a choice.

Dr. Greenwald observed that none of the current trials with human cancer incidence endpoints can be concluded early enough to consider modification of the WHI based on their findings. He cited as examples the tamoxifen trial and the beta carotene component of the Women's Health Initiative, which will not produce answers until the late 1990s at the earliest. Dr. Greenwald also expressed his opinion that the factors being addressed in the WHI are of major importance to understanding the leading causes of death and disease among women.

If the United States had the same breast cancer death rate as Japan, Dr. Greenwald stated, we would have 11,000 deaths per year instead of 46,000. He cited an article by Ziegler

et al., in the most recent issue of the *Journal of the National Cancer Institute*, which shows that a third-generation Asian American woman has the same risk as the White population. This, Dr. Greenwald concluded, demonstrates that the difference in death rates is based on lifestyle differences. He suggested that this will hold true even if BRCA or other genetic factors are also proven to be involved. Issues related to dietary fat and hormones, he observed, have been discussed for the past two decades and will not be resolved without a major trial. He stressed that the multiple disease endpoints of the WHI have the potential for substantial public health impact, related not only to cancer, but to other diseases as well.

Dr. Calabresi returned to the question of tamoxifen. If it proves to be protective against breast cancer and other diseases, he suggested, all of the women will choose to take it and will drop out of the WHI. Dr. Harlan answered that women who chose to take tamoxifen would not be dropouts but, rather, participants confounded by taking another treatment during the study.

Dr. Chabner asked whether the study design complies with authorization language requiring that Phase III studies include a valid analysis of gender and racial subgroups. Dr. Harlan, noting that the WHI was designed prior to drafting of the guidelines referred to by Dr. Chabner, stated that the WHI is intended to include a minority representation somewhat greater than in the general population. Four of the 16 initial clinical centers, he said, are located in catchment areas focusing on recruitment of minorities using culturally appropriate strategies. Dr. Harlan added that race/ethnicity is not expected to produce major differences in response to treatment and, therefore, a full sample size for each racial/ethnic group should not be necessary. Too little information is now available, he acknowledged, to determine whether such differences do exist. The observational study, he added, will include among its sample of 100,000 women approximately 20,000 minority women, the largest such sample ever studied.

Dr. Chabner stated that there is some reason to believe that change will differ among some groups. Results from the Women's Health Trial feasibility study show that adherence to diet modification is about the same across most racial/ethnic groups, while their initial levels of fat intake vary. This is not a real problem, Dr. Chabner suggested, because even with highs and lows for certain groups, their change is likely to be in the same direction as the main effect for the entire study population.

Dr. Hugh McKinnon, ex officio NCAB member representing the Environmental Protection Agency, asked what response was made to the Institute of Medicine comment on the possibility that lifestyle changes among older persons may not have as marked an effect as among younger persons. Dr. Harlan cited migration studies showing that women who move from a low-fat-intake environment to an environment where fat intake is higher assume the risk of the new environment within 10 to 20 years. This suggests, he said, that the lifestyle effect is not limited to early life. Another critical question related to age, Dr. Harlan said, is whether estrogen plays an intermediate role in the development of breast cancer, since estrogen metabolism differs in premenopausal and postmenopausal women. Another practical point, he noted, is that a study of very young women does not allow for a sufficient number of endpoints to adequately test a hypothesis.

Dr. Becker pointed out that increased risk among migrant populations is caused not only by adopting a high-fat diet but also by giving up their native diets. Asians who migrate to