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

Summary of Meeting
December 14 & 15, 1992

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]
December 14 & 15, 1992

The National Cancer Advisory Board (NCAB) convened for its 83rd regular meeting at 8:00 a.m. December 14, 1992, in Building 31, C Wing, 6th Floor, Conference Room 10, National Institutes of Health (NIH).

NCAB Members

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

President's Cancer Panel

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

Alternate Ex-Officio NCAB Members

Captain Bimal C. Ghosh, DOD
Dr. John Johnson FDA
Dr. Brian C. Lee, CPSC
Dr. Theodore Lorei, DVA
Dr. Hugh McKinnon, EPA
Dr. Raymond Sphar, DVA
Dr. Kevin Tonat, NIEHS
Dr. John C. Wooley, DOE
Dr. Ralph Yodaiken, DOL

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. Werner Kirsten, Associate Director, Frederick Cancer Research and Development Center
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. The procedure does not apply to en bloc actions.

Liaison Representatives

Dr. Eve Barak, Associate Director for Cell Biology, Division of Cellular Biosciences of the National Science Foundation, representing the National Science Foundation, Washington, D.C.

Dr. R. Davilene Carter, representing the American Association for Cancer Education

Ms. Carol Curtiss, representing the Oncology Nursing Society

Dr. Robert W. Frelick, Past President, Delaware State Tumor Registry, representing the Association of Community Cancer Centers.

Dr. Edward P. Gelmann, Chief, Division of Medical Oncology of the Vincent Lombardi Caner Research Center, representing the American Society of Clinical Oncology

Dr. Elaine Locke, representing the American College of Obstetricians and Gynecologists

Dr. Thomas King, representing the American Association for Cancer Research

Dr. Edwin A. Mirand, Associate Director and Dean, representing the Association of American Cancer Institutes

Mrs. Yvonne Soghomonian, representing the Candlelighters Childhood Cancer Foundation.

In addition to NCI staff members, meeting participants, and guests, a total of 45 registered members of the public attended the meeting.

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

After calling the meeting to order, Dr. Calabresi introduced five new members of the National Cancer Advisory Board (NCAB)—Ms. Zora Brown, Dr. Robert Day, Dr. Pelayo Correa, Ms. Barbara Gimbel, and Dr. Ellen Sigal—and introduced several guests representing medical, research, and professional organizations. He welcomed the 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. He then called for approval of the previous meeting's minutes, which were unanimously approved without change.

Dr. Calabresi announced the times and locations for meetings of the Subcommittee on Interaction with Voluntary Organizations and the Subcommittee on Cancer Centers. Future NCAB meeting dates were confirmed as stated on the agenda. Dr. Calabresi noted that the current meeting would be the annual review of National Cancer Institute (NCI) programs and would feature overviews of the Division of Cancer Etiology (DCE), the Division of Cancer Prevention and Control (DCPC), and the Frederick Cancer Research and Development Center (FCRDC).

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

Dr. Freeman, Chairman of the President's Cancer Panel, stated that the Panel had held five major meetings since the last meeting of the NCAB. Two meetings of the Panel itself focused on prostate cancer and on voluntary organizations. The latter meeting was attended by representatives of eight organizations involved in the fight against cancer. The President's Cancer Panel is planning a major meeting on psychosocial aspects of cancer for the summer of 1993, to be held in conjunction with the meeting of the American Cancer Society. Dr. Freeman added that a meeting on research progress in the past 10 years is in the early stages of planning.

In addition, three meetings of the Special Commission on Breast Cancer were convened by its Chair, Mrs. Nancy Brinker; these meetings focused on nutrition, radiation, and toxic substances, on patient advocacy, and on hormonal factors in cancer. Dr. Freeman noted that a meeting of this special commission is planned for January 1993 on treatment, quality of life, and rehabilitation of breast cancer.

In closing, Dr. Freeman expressed the President's Cancer Panel's concern regarding the formation of a committee at the National Institutes of Health (NIH) on what is called "alternative medicine." He stated that members of the Panel are writing to Dr. Bernadine Healy, NIH Director, to express their concern about possible confusion between proven and unproved therapies.

III. REPORT OF THE DIRECTOR, NCI—DR. SAMUEL BRODER

Announcements

Before yielding the floor, Dr. Calabresi announced that on January 15th Dr. Broder, NCI Director, would be presented in Paris with the Griffuel Cancer Research Prize by the French Association for Research on Cancer. The fourth NCI scientist to receive this award, Dr. Broder is being honored for his work on the relationship between cancer and immunodeficiency and on retroviral therapy.

Dr. Broder welcomed the new members of the NCAB and explained that during this program review meeting the Board would not perform its usual grant review function. He called the Board's attention to a handout listing a number of awards and honors received by NCI staff and congratulated the recipients.

On December 7th, Dr. Broder announced, scientists at the National Institute of Neurologic Diseases and Stroke (NINDS) initiated the first clinical trial to test whether gene therapy can play a major role in the treatment of malignant brain tumors. The protocol's principal investigator, Dr. Edward Oldfield, and other NINDS scientists are collaborating with NCI gene therapy researchers headed by Dr. Michael Blaese and with a former NCI staff member, Dr. Kenneth Culver of Clinical Research and Genetic Therapy, Inc.

In this new strategy, Dr. Broder explained, a gene borrowed from the herpes virus is inserted into the proximity of brain tumor cells via cells that have been transduced using a retroviral vector to produce thymidine kinase. The drug ganciclovir is then administered. Dr. Broder added that the mechanisms by which tumor cells are altered and killed through contact with genetically altered cells are still under study. He described this trial as an important example of the role of the intramural research program in "pushing the outer envelope" of new approaches to cancer prevention and treatment.

Dr. Broder announced the 55th anniversary of the NCI's Extramural Grants Program. The first award of the National Advisory Cancer Council, predecessor to the NCAB, was a November 1937 grant of $27,000 to Dr. Lewis Fieger of Howard University for a study of carcinogen synthesis. Dr. Broder observed that it was fitting that this early award focused on issues related to environmental and chemical carcinogenesis.

Dr. Broder stated that a major challenge for the NCI this year was presented by the Congress, which asked the Institute to facilitate an outside review of the National Cancer Program. The 1993 Senate Appropriations Report directed the Institute to establish an independent panel to evaluate the Program's achievements relative to the investment that has been made; the President's Cancer Panel was asked to convene an ad hoc group to assist in this process. The Senate specified that the panel should include representatives from the fields of prevention and control, molecular biology, vaccine development, epidemiology, clinical investigation, environmental carcinogenesis, virology, drug development, and rehabilitation; in addition, it should include members from outside the scientific community, including cancer survivors, parents of children with cancer, public health experts, and representatives of the insurance and pharmaceutical industries. In addition, the 1993 House Appropriations Report

encouraged the NCI Director to reach beyond the "current cancer establishment" as part of a fundamental review of the research program.

While these requests do not have a specific timetable, Dr. Broder noted, this issue will require the attention of the NCI and the NCAB in the coming fiscal year. He stated that the Institute is developing a plan to coordinate an overall evaluation of the National Cancer Program, for which the final format will be open to discussion. As part of this general commitment to measuring progress and, potentially, in response to the Congressional requests, the NCI has identified six topical areas and launched panels of scientists, chaired by members of NCI Boards of Scientific Counselors, to examine the past 10 years and identify advances in prevention, mechanisms of carcinogenesis, molecular medicine, and a number of other issues. The panel on treatment met in October 1992 and the other five panels are scheduled to meet in January and February. Dr. Broder suggested that summaries of the formal reports of these panels could be presented during future NCAB meetings.

Dr. Broder expanded upon the discussion of the President's Cancer Panel's activities briefly summarized earlier by Dr. Freeman. The October 5th meeting on voluntary organizations, he said, illustrated the richness and variety of interest in cancer research, treatment, and education. Presentations were made by the American Cancer Society, Cancer Care, the Damon Runyon-Walter Winchell Cancer Research Fund, the Leukemia Society of America, CAN ACT, Stop Cancer, the Candlelighters Foundation, and the National Coalition for Cancer Survivorship. At the November Panel meeting on prostate cancer, participants discussed the need for further research on the disproportionate impact of this disease on African American men. Dr. Broder added that NCI funded the initial development of the prostate-specific antigen (PSA) test, now being widely used, in Dr. Mingchu's lab at Roswell Park.

He continued by reviewing recent meetings of the Panel's Special Commission on Breast Cancer: on September 23rd, the Commission addressed the topics of nutrition, etiology, and implications for prevention; on October 23rd, the Commission heard testimony from patient advocates and voluntary organizations; and on November 12th, the topic was hormonal factors in breast cancer. On January 11-12, 1993, the Commission will discuss treatment and rehabilitation. Dr. Broder emphasized that these meetings are open to the public and suggested that those interested in discussing future Commission meetings should contact Ms. Iris Schneider, Executive Secretary for the President's Cancer Panel. Additionally, on January 28-29, 1993, NCI will hold a special multidisciplinary symposium on breast cancer among young women that will result in an NCI publication.

Dr. Broder described the second NCI workshop on taxol and taxus, held on September 23rd, as a great success. He noted that the Oncologic Drugs Advisory Committee of the Food and Drug Administration (FDA) recently recommended approval of taxol, at least for use in the treatment of refractory ovarian cancer. The concerted efforts of the NCI, the Department of Health and Human Services, the Department of Agriculture, and the Department of the Interior, in cooperation with the Bristol-Myers-Squibb Corporation under the provisions of the Federal Technology Transfer Act, have resolved the issue of taxol supply so that no woman who needs the drug will be denied access to it.

Turning to future activities, Dr. Broder stated that the NCI's Division of Cancer Etiology is planning a conference on *Women's Health, Occupation, and Cancer* to be held in November 1993. Topics will include gender-specific differences in cancer risks and methodological issues associated with occupational cancer risks. He invited suggestions on additional topics for this meeting.

Budget Report

Dr. Broder explained that he would not be able to present a detailed breakdown of figures for research project grants, cooperative groups, and other budget mechanisms because these figures had not yet been approved by NIH. Instead, he briefly presented a comparison between final "bottom line" figures for fiscal years 1992 and 1993. The 1992 estimate for NIH was approximately $10 billion and the 1993 appropriation is just under $10.4 billion—an increase of about 3.5 percent. For NCI, the 1992 appropriation was approximately $1.95 billion and the 1993 figure will be approximately $1.98 billion after an "across the board" reduction of about $16 million, resulting in an increase of about $34 million, or 1.7 percent. However, Dr. Broder pointed out that the existence of congressionally mandated earmarks, requiring expenditures of $105 million on specific items, means there will actually be a shortfall of about $71 million. It is not yet clear how these directives will be met.

Issues for Consideration by the Board

Dr. Broder mentioned several major areas that will need the attention of the Board in the near future, suggesting that these matters be referred by Dr. Calabresi to the appropriate subcommittees. Two issues briefly mentioned by Dr. Broder were the need to encourage the development of a larger corps of individuals who conduct investigator-initiated clinical research and the need for discussion of the philosophies and policies of the Institute regarding the mix of program project grants and traditional investigator-initiated R01 grants.

The third issue focused on the "bypass" budget for fiscal year 1995. In addition to asking for the Board's advice and assistance in developing this professional needs budget request, Dr. Broder asked for suggestions on clarifying the intended uses of the bypass budget in order to prevent discussion of sections of the budget out of the context of the entire document.

Dr. Broder suggested that issues concerning the appropriation of approximately $200 million to the Department of Defense for breast cancer research will require attention when further information becomes available. He noted that the Institute of Medicine has been asked to provide recommendations about these issues.

Finally, Dr. Broder suggested that the Board send a message of concern to Dr. Howard Temin, who was not able to attend due to illness.

Questions and Answers

Dr. Salmon expressed his opinion that the main problem is the earmarking of activities based on the bypass budget without provision of adequate funding. Dr. Broder said that this is an issue the Board must address. He added that the bypass serves multiple functions; his own philosophy, he stated, is that the bypass budget is primarily a scholarly document as well as a strategic planning document that should be interpreted and defended as an interactive whole.

Dr. Day asked whether the NCI's spending plan had been submitted to NIH. Dr. Broder replied that it had been submitted about a month previously but had not yet been approved. He suggested that, based on the projected percentage of increase, one could estimate that most programs will be held flat and that a few may show a slight decrease. He concluded that 1993 will be a fiscal year in which resources are restricted.

Dr. Calabresi commended Dr. Broder and the Institute for bringing the brain tumor studies of thymidine kinase to clinical trial so quickly. He asked how many patients were being treated and suggested that a presentation be made at the February Board meeting. Dr. Broder, consulting with Dr. Rabson, answered that approximately five patients had been approved by the Recombinant Advisory Committee and agreed that a presentation would be appropriate. He stressed the significance of this research not only because primary brain tumors are a critical problem in their own right, but also because metastatic disease of the brain is sometimes a cause of death in cases of lung cancer, breast cancer, and other tumors. Noting that this research is critically important in that it will stimulate new avenues of research into the process of tumor regulation with implications beyond this specific protocol, Dr. Broder said that the Institute hopes to have further information on this topic in the coming year.

It is also expected, he added, that Dr. Schlom's recombinant CEA vaccinia vector-produced vaccine research may move into clinical trials within the next year. A number of cancers express CEA, including about 50 percent of breast cancers, and this, by copresentation with vaccinia, may induce immunity.

Before introducing the next speakers, Dr. Calabresi stated that during the present meeting an opportunity would be provided to discuss the formation of three task forces, conceived as the result of work done by the agenda subcommittee during the past year, on the topics of budgetary issues, the R01 versus P01 issue, and the problem of encouraging young people to enter the field of clinical investigation. Other areas he identified for further discussion during the meeting were the Department of Defense appropriation for breast cancer research and issues concerning the ASSIST Program.

IV. MISSION OF THE NATIONAL BREAST CANCER COALITION

Dr. Calabresi introduced Susan M. Love, M.D., Associate Professor of Clinical Surgery at the University of California, Los Angeles, and Chairperson of the Research Task Force of the National Breast Cancer Coalition, and Ms. Frances M. Visco, partner in the law firm of Cohen, Shapiro, Polisher, Shiekman, and Cohen and President of the National Breast Cancer Coalition.

Presentation by Ms. Visco

Ms. Visco explained that she would describe the National Breast Cancer Coalition and that Dr. Love would explain what the Coalition wants. She stated that the Coalition serves as a voice and grassroots advocacy organization for the estimated 2.6 million American women with breast cancer, including the 1 million, according to NCI estimates, who do not yet know they have the disease.

Ms. Visco outlined the history of the Coalition, which began in the spring of 1991 when, on behalf of the Faulkner Breast Center, Dr. Love brought together representatives of five other groups—NABCO, Why Me, the Mary Helen Mattner Project for Lesbians with Cancer, the Greater Washington Area Coalition for Cancer Survivorship, and Cancer Care. Their invitation to women's and breast cancer groups throughout the country attracted more than 150 women to the Coalition's first meeting and resulted in a membership of more than 100 organizations.

Ms. Visco's local organization, the Linda Creed Breast Cancer Foundation of Philadelphia, became part of a working board composed of 20 members. Membership now totals more than 165 organizations, ranging from the American Cancer Society to a group of three women in St. Louis, and thousands of women and men have joined the Coalition's National Action Network. The Coalition has members in every State and expects to double membership within the next 6 months.

Ms. Visco highlighted the Coalition's primary goals: to promote research through improved availability and coordination of funding and through the recruitment and training of scientists; to improve access to high-quality breast cancer screening and care for all women, especially the underserved and underinsured, through legislative action and improved health care delivery; and to increase the involvement and influence of women living with breast cancer in the legislative and regulatory processes and in the design of breast cancer clinical trials.

The Coalition's first effort was its "Do the Right Thing" campaign; its goal was to collect letters supporting funds for breast cancer research from 175,000 women, representing the estimated number who would be diagnosed with breast cancer in 1991, but in less than 6 weeks 600,000 letters were collected and sent to the Congress and the White House. As a result, Ms. Visco stated, the Congress appropriated an additional $40 million for breast cancer research, for a total of $132 million, in fiscal year 1992.

The Coalition sponsored hearings in February 1992 to determine the amount of money needed for research on curing and preventing breast cancer. Ms. Visco said that her remarks would be accompanied by a summary of the testimony of 15 renowned scientists who spoke at that hearing on promising research areas that merit additional funding. The Coalition's Research Task Force, cochaired by Dr. Love and Dr. Kaye Dickerson, used findings from this hearing to develop recommendations for the appropriation of an additional $300 million for breast cancer research, for a total of $433 million, in 1993. "300 Million More" became the rallying cry of a National Action Network effort to communicate the Coalition's

recommendations to the Congress through cards, mailgrams, telephone calls, and personal visits.

The goal was to increase breast cancer research appropriations to NCI, and the NCI allocation for fiscal year 1993 did increase to $195 million. While the Coalition's efforts to transfer money from the Department of Defense to the domestic budget were not successful, these efforts did result in the reallocation of funds within Defense for breast cancer research. As a result, the Department of the Army will administer $210 million for breast cancer research. Ms. Visco asserted that the Coalition did not lobby to keep this money out of the NCI budget, "even though," she stated, "NCI testified against our request." The Coalition, Ms. Visco observed, had not expected to be sitting down with General Travis to plan how to spend money on breast cancer research within the Department of the Army, but she said that, to date, they are pleased by the Army's response.

In addition to working to increase research funding, Ms. Visco cited the Coalition's activities during the past year in helping pass the Mammography Quality Standards Act and the Cancer Registries Act; a new goal will be to ensure adequate funding for these programs. She added that the Coalition plans to increase its attention to issues of access; too many women die, she said, because they do not have the means or information necessary to obtain screening or treatment services.

At the State level, the Coalition coordinated 39 events in 31 States, centering around Mother's Day. The Massachusetts Breast Cancer Coalition worked to have the disease declared an epidemic in that State and worked to pass a State quality assurance bill. California member organizations caused the State legislature to amend personal income tax laws to permit taxpayers to contribute amounts in excess of their tax liability to the newly created California Breast Cancer Research Fund. The Coalition sponsored a rally at the Pennsylvania State House in support of a Mammography Quality Standards Act that was subsequently passed.

Ms. Visco concluded by observing that a fundamental change has taken place in breast cancer during the past year because women with breast cancer have taken matters into their own hands. She stressed that the Coalition wants to forge a partnership with scientists, physicians, and the agencies that have a profound effect on the lives of women with breast cancer.

Presentation by Dr. Love

Dr. Love began her presentation by listing three objectives of the National Breast Cancer Coalition—accountability, representation, and a shift in emphasis. While the Coalition has worked hard to increase funding, she said, it is still difficult to obtain a full picture of how monies have been spent in the past. The Coalition wants to see the establishment of mechanisms to monitor the disbursement of current and future funds to ensure that taxpayers' money is well spent.

Dr. Love suggested that representation by women with breast cancer in decision-making bodies, oversight committees, and monitoring panels would be a step toward improved

accountability, in addition to providing a means to influence the future direction of breast cancer research. She said that opportunities for such representation should include:

- An additional seat on the NCAB and a permanent breast cancer NCAB subcommittee to oversee breast cancer issues, help set the research agenda, and advise on the allocation of resources. Dr. Love acknowledged the important role of the NCAB in setting the breast cancer research agenda and noted that Ms. Zora Brown was recently appointed to the Board as a representative of women with breast cancer. She added, however, that the Coalition would like to see an additional woman with breast cancer, preferably one with access to a large national network of constituents, appointed to the Board.
- Permanent breast cancer study sections with consumer representation to allow appropriate peer review and provide data for assessing the demand for future funding, as well as a mechanism for reporting the number of breast cancer grants submitted, approved, and actually funded.
- A formal structure for exchanging ideas with NCI (including collaboration on the development of the bypass budget). Dr. Love mentioned that the Coalition had had several substantive meetings with Dr. Broder and expressed the view that the sharing of concerns should be formalized between the Coalition, the NCI Director, and the various NCI Divisions. She noted that such linkages would enable the Coalition not only to bring grassroots concerns to the Institute but also to bring back to the women of the Nation an accurate representation of NCI's activities.
- Requirement by NCI that the planning and oversight of all projects, such as SPORES, cooperative groups, cancer centers, advisory boards, and clinical trial subcommittees, include consumer participation.

The National Breast Cancer Coalition, Dr. Love noted, has a large pool of qualified experts and breast cancer survivors who are available to serve as consumer representatives, and is in the process of surveying the membership to enlarge this pool at the local and national levels. She added that the Coalition is open to input from the NCAB on possible avenues to achieve representation and accountability.

Dr. Love emphasized the Coalition's belief that a change in the direction and pace of breast cancer research is needed. She said that women living with the disease are demanding increased funding for research on the prevention and cure of breast cancer. Recently, she added, members of the Coalition met with Hilary Clinton and expressed unanimously that their

request was not for research into treatments to prolong their lives but for research to prevent breast cancer among their daughters.

Mechanisms suggested by the Coalition to achieve this shift in emphasis include: breast cancer study sections; expedited review of breast cancer proposals and full funding of all meritorious proposals; identification and elimination of barriers to innovative investigator-initiated research; attraction of new researchers into the field; and encouragement of all NIH Institutes to become involved, as outlined in the *Trans-NIH Breast Cancer Initiative* proposed by Dr. Broder in the 1994 bypass budget.

Dr. Love urged that multiple clinical prevention trials be conducted simultaneously and that intermediate markers be developed in order to expedite the discovery of the cause of breast cancer. The biology of the disease must be exploited, she said, to develop more subtle treatments before surgery, radiation, or chemotherapy is needed. This new approach must be communicated to the scientific community to encourage development of creative ideas and to attract new researchers. The peer review system must be reevaluated to ensure that basic scientists are assisted by epidemiologists, psychosocial experts, women with breast cancer, and others to ensure that all aspects of proposals are being addressed.

For example, Dr. Love said, the identification of a familial breast cancer gene must be accompanied by appropriate research into psychosocial and quality of life aspects so that women who have the gene are appropriately treated. Another example of an issue that may not seem significant from a scientific point of view but is of major concern to women is the use of post-menopausal hormone replacement after breast cancer treatment.

Dr. Love remarked that the Coalition has been encouraged by the broad-ranging approach taken by NCI in its 1994 bypass budget. The *Trans-NIH Breast Cancer Initiative*, she stated, represents the kind of integrative program that is necessary. She concluded by presenting the Coalition's recommendation of the establishment of an office for breast cancer coordination to oversee all Federal activities in this area. This office would be able to coordinate the breast cancer research agenda across all Federal agencies, including HCFA, CDC, DoD, as well as NIH, to eliminate redundancy and foster an integrative approach. She declared that accountability, representation, and a shift in emphasis are obtainable goals, and asked for the NCAB's assistance in fulfilling the Coalition's mission.

Questions and Answers

Dr. Calabresi suggested that programs already in place within the NCI are working on some of the issues mentioned by Dr. Love, such as research on prevention and etiology. He noted that research on the p53 gene is relevant to breast cancer but is not included among projects described as breast cancer research. He asked whether the Coalition had evaluated monies being spent on general or basic science that have an impact on breast cancer. Dr. Love acknowledged that basic science research, as well as research on other types of cancer, have shed light on the breast cancer problem, but maintained that special study sections are needed to get a better understanding of what is happening in the field of breast cancer research.

Dr. Brown thanked Dr. Love and Ms. Visco for appearing and expressed her approval of their emphasis on the issue of women's lack of access to treatment. Dr. Love said that the Coalition hoped to make access a greater priority in its activities.

Dr. Sigal expressed her concern that new mechanisms for accountability might add expensive and duplicative layers of bureaucracy. Dr. Love stated that the Coalition is open to exploring efficient ways to increase representation and accountability. Ms. Visco emphasized that the Coalition feels strongly about the need for change, but added that the form in which change takes place is subject to further discussion. She stressed the need for change not only in the focus of cancer research but also in the "power base," so that women affected by this disease have a greater impact on decision making.

Dr. Salmon asked whether the Coalition's objectives in its talks with the Army are the same as those described in its presentation to the NCAB. Dr. Love stated that the objectives are exactly the same, and added that the Coalition has also made contact with the Institute of Medicine.

Dr. Calabresi expressed his approval of the fact that additional money had been made available for breast cancer research but also expressed concern that it had been given to the Army because of questions regarding the existence of a peer review mechanism for the project. Dr. Love said that the Coalition has the same concerns, especially in light of the fact that the Army had recently spent $25 million in breast cancer funds on the purchase of mammography equipment. She stated that the Coalition will remind the Army that this is a high profile appropriation, and expressed the belief that the Army understands its significance.

Ms. Visco repeated her assurance that it had not been the Coalition's intention to get the money appropriated to the Army; the group, she stated, had tried to get the money appropriated to NCI "despite the fact that NCI was opposing this." Dr. Broder objected, pointing out that NCI had never given testimony in opposition to this funding and, in fact, had testified in support of the appropriation. Ms. Visco apologized, noting that NIH, not NCI, had opposed the money. She added that the Coalition had been unaware of NCI's testimony in favor of the appropriation, observing that this is a good indication of the need for better communication between the two organizations, replacing tension with partnership.

Dr. Freeman expressed appreciation for the presentation and support for the Coalition's goals. He expressed concern, however, that any efforts to focus on one particular cancer might have the effect of reducing the availability of resources for fighting other cancers—lung and prostate cancers, he mentioned, are very prevalent in poor communities. He urged that efforts stressing breast cancer research focus on raising additional funds rather than redistributing available funds for all cancers. Dr. Love stated that the Coalition agrees with Dr. Freeman, noting that in its testimony the group points out that it wants a "bigger pie," not just a "bigger piece of the pie."

Dr. Freeman also asked about the implications of setting up committees to oversee research on specific cancers, suggesting instead a broader approach to consumer involvement in the spectrum of cancer research. Dr. Love highlighted the need to achieve consumer representation at all levels of NIH and NCI, suggesting that breast cancer could serve as a

model for other cancers. AIDS, she added, had already provided a model for consumer involvement, resulting in a shift in approaches to problems—for example, in making clinical trials more accessible. Dr. Love observed that before starting to meet with NCI, the Coalition had not been aware of all of the activities related to breast cancer research; she suggested that consumer representation would be useful in letting the public know more about what is going on.

Dr. Broder thanked Dr. Love and Ms. Visco for taking the time to come to the meeting, noting that there had been a number of suggestions for the NCI and the Board to consider and try to bring to reality. He added that there are ways in which the Coalition and its member organizations can help the Institute by demonstrating that new models and approaches can work in their own communities. Dr. Broder expressed hope that among the options it considers, the Coalition would work to encourage the development of such models through the existing and exploratory SPORES projects, noting that Dr. Love's institution, UCLA, has one of the exploratory SPORES. He said that nothing is more successful in allowing a governmental authority to build on ideas than empirical evidence that the ideas have succeeded at the grassroots level. Dr. Love agreed, and added that it needs to go both ways. She said the Coalition is working to set up a mechanism within the Southwest Oncology Group as well as the NSABP.

Dr. Becker observed that one of the most positive goals expressed during the presentation was to avoid competition between disease states. He argued that it is not necessarily true that certain advances could have been achieved more quickly if more research had been focused on breast cancer, pointing out that two substantive advances that will benefit breast cancer, as well as other cancers, came from studies of two very rare diseases, retinoblastoma in children and Li-Fraumeni syndrome. Dr. Becker suggested that there is a danger that a "tidal wave of advocacy" could unintentionally damage the "bulwarks" of basic science, which has been the greatest contributor towards cancer prevention over the past three decades; he warned that, in order to obtain funding, scientists might have to divert their efforts toward those diseases that have strong advocacy groups. He urged such groups to remember where past advances came from and argued that medical research has never worked well on a directed basis. Acknowledging that diversion of funds from basic research is not the intent of the Coalition, Dr. Becker noted that the best intentions in political action do not always work out very well. Dr. Love reiterated the Coalition's intent to develop additional funds for breast cancer, not to take resources away from basic science. She pointed out that the Army money is an example of new funds that were not previously devoted to cancer research.

Recognizing that special study sections on breast cancer may have a partial role, Dr. Salmon added to Dr. Becker's comments by recommending that efforts to develop new resources should not only avoid reducing resources for basic research but should give some of the additional resources to nontargeted basic research. He gave two further examples of discoveries of importance to breast cancer that were not targeted—recombinant DNA techniques and the monoclonal antibody technique.

Dr. Freeman asked Dr. Broder about the amount of money currently being spent on breast cancer research versus other targeted cancers. Dr. Broder began by stating that no level of commitment to breast cancer will be adequate until prevention and cure are achieved. He

reported that $196 million have been committed for breast cancer research in fiscal year 1993, noting that in the past 4 years this allocation has increased by 177 percent while the Institute's overall increase has been 35 percent. Referring to the Coalition's expressed goal of developing a tracking mechanism for advances in breast cancer research, Dr. Broder urged that such a system be designed to acknowledge the fact that much work fundamental to the understanding of breast cancer is not targeted research. Explaining that science traditionally focuses on models that are amenable to studies applicable to a range of topics, such as yeast models and drosophila, Dr. Broder stated that numerous advances benefiting breast cancer could not have been targeted for breast cancer in any credible definition.

Some changes, Dr. Broder suggested, that appear to be feasible administratively might actually go against the core of the scientific method and force cancer research into a period of incremental increase in knowledge without significant breakthroughs. In closing, Dr. Broder maintained that cancer research would benefit from broad support for the entire NIH budget, suggesting that NCI is hindered if other Institutes are hindered. The communality of function across NIH, he stated, requires the support of bodies such as the NCAB for a vigorous, healthy biomedical research program.

Dr. Love responded that increased representation of women with breast cancer, as well as other consumers, would help NIH and NCI get across the message that basic research creates advances in all kinds of cancers. She suggested that an increased public understanding of existing programs and decision-making processes would result in wider support for the traditional scientific approach to cancer research.

Dr. Correa asked for further information on the intended benefit of representation of patient advocates in study sections. Dr. Love noted that there are scientists who have breast cancer. She also suggested that the involvement of women with breast cancer in the design of clinical trials would improve the accessibility of the trials and provide input on psychosocial ramifications of the disease.

Ms. Visco thanked the Board for the opportunity to speak. She acknowledged that change is difficult and assured the Board that the Coalition is not suggesting a reduction in basic research. However, she concluded, the Coalition feels that some decisions made in the past have not been in the best interest of women with breast cancer and believes that consumer representation in the decision-making process and a shift in the focus of breast cancer research are needed.

Dr. Calabresi again thanked the speakers and assured them that everyone on the Board is very interested in the subject of breast cancer. He asked to correct one point for the record. In discussing the Coalition's recommendations, Dr. Love had suggested that the NCAB did not have a subcommittee on breast cancer; in fact, Dr. Calabresi stated, one of his first actions as Chairman was the appointment of the Subcommittee on Women and Cancer, Chaired by Ms. Brenda Johnson and composed of Dr. Fred Becker, Dr. David Bragg, Ms. Zora Brown, and Ms. Malek.

Dr. Salmon, in response to the suggestion that women were underrepresented in breast cancer clinical trials, noted that an article by Dr. Michael Friedman in last year's *Journal of the*

National Cancer Institute showed that breast cancer, in proportion to other clinical trials, was extremely well represented. Dr. Love replied that her statement referred to the fact that less than 5 percent of women with breast cancer were involved in trials; she was not, she said, referring to the number of clinical trials.

V. DIFFERENTIATION THERAPY—A NEW APPROACH TO CANCER TREATMENT—DR. SAMUEL WAXMAN

Dr. Calabresi introduced Dr. Samuel Waxman, Clinical Professor of Medicine and head of the Cancer Chemotherapy Foundation Laboratory at the Mt. Sinai School of Medicine in New York. Dr. Waxman defined differentiation therapy as a biological concept with molecular biological underpinnings that has produced extraordinary new results in the clinic, particularly in leukemia. He displayed a slide depicting two sets of cells. One test tube contained untreated mouse erythroleukemia cells, which were proliferating and undifferentiated. The second test tube contained cells treated with dimethylsulfoxide (DMSO). As a result of this treatment, the cells had changed to a differentiated state in which they produced hemoglobin, and they had stopped growing. If this conversion could be accomplished without much toxicity, it would represent a new strategy, differentiation therapy, for the treatment of cancer.

Dr. Waxman observed that during the process of differentiation through exposure to DMSO, the cells grow just as well as the untreated cells, indicating a lack of toxicity of the chemical. The agent, then, does not kill the malignant cells but programs them to become differentiated. When exposure to the chemical is removed, the cells die as part of a normal life cycle. This indicates that a malignant cell still contains the information to respond to messages to mature, differentiate, and stop growing. Dr. Waxman explained that a number of unrelated compounds have been found to act as differentiation inducers when added to test tubes with mouse erythroleukemia cells.

Dr. Waxman noted that the science behind this process involves molecular biology in addition to cell biology. There are changes at the membrane, target genes are regulated, and oncogenes or growth-related genes undergo changes. While this process may be specific to leukemia, he explained, a similar analysis with variations on this theme of multiple changes can be done with other cancers. Other differentiation inducers mentioned by Dr. Waxman included acetamides, retinoids, a compound called hemin, and fatty acid analogs. Only a few of these, he explained, have been used in the clinic, while others have been limited to laboratory experiments, but their potential for clinical application is great. Multiple agents can be used together to create synergy—smaller amounts of the compounds used together can induce more cells to differentiate, suggesting a pharmacological approach using combinations of these agents.

Dr. Waxman presented, as a model of the process from test tube observation to clinical application, slides of cells from patients with acute promyelocytic leukemia. When exposed to retinoic acid, derived from vitamin A, these cells stop growing and undergo differentiation into morphologically white cells, granulocytes, that can engulf bacteria.

Dr. Waxman reviewed basic research in molecular biology and molecular genetics during the past several years that have made this process a model for differentiation therapy. It has been known for some time, he said, that this leukemia is associated with a translocation in two chromosomes, 15 and 17. It was found that on chromosome 17, there is a gene site for an important protein in vitamin A metabolism—the nuclear receptor called retinoic acid receptor alpha (RARα). The translocation disrupts this receptor and fuses to a new gene called PML—the promyelocytic leukemia gene. The presence of this chimeric gene in virtually all patients with this disease explains why these cells respond to all trans-retinoic acid (ATRA).

In about 1988, a group in China began using ATRA in pill form to treat acute promyelocytic leukemia patients outside the hospital. Dr. Waxman presented data on 32 of these patients, spanning a wide range of ages, some of whom had been treated with chemotherapy and had experienced relapses. All cases experienced complete remission in which the bone marrow was not wiped out—instead, it became diminished and then repopulated. The leukemic blast, Dr. Waxman explained, had been converted to a leukemic differentiated cell. This work has been corroborated in Paris, and the NCI has been providing ATRA to anyone in the United States with this leukemia. This is a satisfying way to treat leukemia, Dr. Waxman noted, because the bone marrow is not destroyed and 90 percent of patients respond. The excitement of this approach is spreading to other areas within the cancer field.

Through studies in molecular biology and molecular genetics, Dr. Waxman reported, researchers are now finding chimeric genes associated with translocations in other, more common forms of leukemia. The opportunity exists to identify the proteins in these cases and develop targeted differentiation therapy. Meanwhile, it has been observed that retinoic acid works in the test tube with other cell lines, suggesting that it not only has an effect on a specific disruptor gene, but also a wider biological effect on the entire differentiation program.

Dr. Waxman briefly described another compound that has been examined in various hematologic malignancies. Hexamethylene bisacetamide (HMBA), related to DMSO but used in smaller amounts, has been used in acute myelogenous leukemia in combination with chemotherapy. Interferon, he noted, seems to be important in the treatment of chronic myelogenous leukemia, which may be related to a differentiation program. Differentiation therapy in other forms of hematologic dysplasia is also being studied.

Dr. Waxman added that some of the more common solid tumor cell lines may be induced to differentiate, although it is not as clearly understood as in leukemias. Looking at monoclonal antibodies that identify differentiation, he explained, researchers have seen changes in neuroblastoma, lung cancer, colon cancer, breast cancer, and others. Clinical implications of this research includes chemoprevention. Studies in China and the United States have resulted in the reversal of precancer conditions using new generations of retinoic acids, either alone or in combination with interferon. ATRA has been used in France in patients with Kaposi's sarcoma with high response rates. Clinical trials are now being matched with laboratory predictions in neuroblastomas and pediatric tumors.

Dr. Waxman presented data from a study at the M. D. Anderson Hospital by Dr. Scott Lippmann using retinoic acid and interferon to treat patients with locally advanced cervical

cancer, a disease generally not responsive to chemotherapy. There were definite responses, even in patients in advanced stages of disease. The mechanisms are not entirely clear, but it is possible that differentiation plays a role. Dr. Waxman added that the treatment does not involve debilitating toxicities.

The same group, Dr. Waxman continued, had an experience treating advanced squamous carcinoma of the skin. Cell biology and molecular biology predicted that these cells would respond to a form of retinoic acid, perhaps synergized with interferon. The study achieved an 85 percent response rate in patients with local and regional disease. Dr. Waxman noted that though this is a rare, difficult-to-treat disease, the study may provide information on working with lung and upper airway cancers. He stressed the fact that treatment with retinoic acid is not a cure; relapse in patients maintained on ATRA is predictable, indicating that a relative resistance to the compound develops. Early studies have had successful long-term results in following ATRA-induced remission with chemotherapy.

Dr. Waxman also discussed the use of differentiation following chemotherapy. The traditional approach to treating manifest disease is attempting to eradicate the cancer cell population through antiproliferative, cytotoxic agents. During the period of time when the body is recovering from the toxicities of this treatment, the cancer cell population also has an opportunity to recover. This is an ideal time to develop a strategy for using differentiation inducers, which could be synergistically activated by a pretreatment of chemotherapy. In some cases a cascade of terminal cell division is provoked by the differentiation inducer, resulting in more cell death. In some situations, cancer cells get new antigens on their surface and can then be treated with monoclonal antibodies and hormones when the cell population is lower.

Dr. Waxman summarized by stressing the need for the National Cancer Program to acknowledge this exciting new approach to cancer treatment that can both enhance and be enhanced by chemotherapy. It is important, he said, to keep in mind that chemotherapy causes toxicities that tend to result in cell sensitivity or resistance, and that the differentiation agents work just as well regardless of these factors. Therefore, he concluded, differentiation therapy should be viewed as an important new partner to chemotherapy.

Questions and Answers

Dr. Enrico Mihich, a former Board member, asked whether the customary high-dose chemotherapy is compatible with the follow-up differentiation therapy. Dr. Waxman answered that this has not been tested clinically. He noted that every high dose has a tail of a low dose, which would be there prior to the differentiation inducer, and added that the synergism of traditional chemotherapy and differentiation therapy can achieve high levels of cell death with lower dosages of chemotherapeutic agents that, used alone, do not cause cell death.

Dr. Wilson asked how universal the effect of retinoic acid is on a wide range of tumors. Dr. Waxman indicated that this is an evolving story in which molecular biology is still identifying new targets for retinoic acid. He predicted that the biological possibilities related to new retinoids will have a profound effect in all growing cells.

Dr. Calabresi asked Dr. Becker to comment briefly on retinoic studies at the M. D. Anderson clinic with carcinoma of the cervix and with retinoic acid interperitoneally. Dr. Becker first addressed Dr. Wilson's question, observing that the presence of a retinoic acid receptor is not commensurate with conviction that a tumor will differentiate. He said that the studies on leukemias at the clinic have shown that remission invariably occurs and then invariably fails. A number of agents are being tried at the point of return of the tumor, including metamide, and prolonged survivals are being seen. Dr. Becker briefly described high remission rates among difficult cases of head and neck squamous cell carcinomas using a combination of retinoic acid and interferon.

Dr. Becker stated that in addition to its broad-based program with cervical carcinoma, the clinic's most exciting development relates to prevention. Dr. Kee Hong has been able to reduce the recurrence of head and neck tumors in the first 2 years from 28 percent to 4 percent using oral treatment of retinoic acid, and believes this can be improved with combined interferon. He added that there is some evidence that this regimen can significantly reduce the appearance of a second primary cancer in patients who have had a single lung cancer. Dr. Becker concluded by saying that these types of responses to a relatively benign therapy in patients with cancers that have not responded to chemotherapy is very exciting, but he noted that there are many promising agents that are not yet understood, and cautioned that retinoic acid is not the whole answer.

Dr. Broder suggested that it might be desirable to focus on patients with, for example, bronchial metaplasia or other conditions in which it might be possible to move into primary prevention of neoplasms. Dr. Becker said that the studies done so far have been limited to patients who have already demonstrated a tumor because the potential benefit versus risk is significant, and that there are always concerns with patients who have never had a tumor that the process could be accelerated. He agreed, however, that this is one area in which research in cancer treatment and prevention could "leap frog" over some steps toward prevention efforts because the therapy is well understood and controlled.

Dr. Bettinghaus addressed a question to Dr. Waxman on the data from China, asking what happens to the resistant cell after treatment that makes it not amenable the next time. Dr. Waxman said that it is a complicated question, explaining that the pharmacology changes the binding proteins to sequester the compound developed, so that it is not a true resistance of the leukemia to the treatment, although that may partially be the case. There is still much to learn about dosages, he stated, noting that an increased dose does not predictably result in a response because it tends to cause more problems with metabolism.

Dr. Waxman made a further comment on the use of differentiation agents in the clinic. He said it would be impossible to evaluate the effect of these agents in a clinical trial in bronchial metaplasia without having the laboratory technology in place to show that differentiation is actually taking place. Dr. Waxman also stressed the need for drug screening programs that can predict the ability of agents to cause the loss of proliferation associated with differentiation. Until these are available, he said, the research will continue with clinical observations in other forms of cancer.

VI. DIVISION OF CANCER ETIOLOGY PROGRAM REVIEW—DR. RICHARD ADAMSON

Dr. Adamson explained that the Division of Cancer Etiology is responsible for planning and conducting the Institute's program of coordinated research on cancer causation and its basic research on cancer prevention. The DCE supports both intramural laboratories and extramural programs that seek to elucidate the mechanisms of cancer induction at each step of the cellular process, from initiation to transformation of normal cells to malignant ones.

Investigators pursue studies on chemical, physical, and viral agents using the disciplines of cellular and molecular biology, biochemistry, chemistry, pharmacology, microbiology, and immunology. Epidemiologic studies are also done to identify risk factors predisposing people to various cancers. The overall purpose is to provide information for preventing, interrupting, or reversing the initial or transformed cell prior to the development of clinical disease.

Dr. Adamson presented a slide illustrating the organizational structure of the DCE. He explained that the Deputy Director, Dr. Susan Sieber, chairs the DCE Promotion and Review Committee and Animal Care and Use Subcommittee and serves as the Division's representative to the NCI Planning and Program Committee. The Director, Dr. Adamson continued, is the NCI representative on a Department of Health and Human Services (DHHS) committee whose acronym is CCEHRP, which coordinates environmental health and related programs, as well as on the National Toxicology Program Executive Committee. Mark Kochevar, head of the Administrative Branch, handles financial and personnel matters.

Dr. Adamson identified the Division's three major programs—the Biological Carcinogenesis Program (Dr. Edward Tabor, Director), the Chemical and Physical Carcinogenesis Program (Dr. Adamson, Acting Director), and the Epidemiology and Biostatistics Program (Dr. Joseph Fraumeni, Director). He reported that there were no organizational changes in the Biological Carcinogenesis Program or the Chemical and Physical Carcinogenesis Program. In the former, the Biological Carcinogenesis Branch is responsible for managing grants and contracts for biological products. In the latter, there are two branches managing extramural programs: the Chemical and Physical Carcinogenesis Branch administers the grant program and contracts for providing chemical carcinogens and metabolites and compounds used in chemoprevention studies; the Radiation Effects Branch administers an extramural grant and contract program focusing on biological and health effects of exposure to radiation.

The Epidemiology and Biostatistics Program's Extramural Programs Branch is responsible for administering grants in epidemiology and related activities. During fiscal year 1992, Dr. Adamson announced, organizational changes for this program's intramural activities were planned, and early in fiscal year 1993 these changes were approved. Two new branches were created—the Genetic Epidemiology Branch (Dr. Margaret Tucker, Chief) and the Viral Epidemiology Branch (Dr. William Blattner, Chief). The Genetic Epidemiology Branch will undertake interdisciplinary studies with clinicians and laboratory investigators to clarify mechanisms of genetic susceptibility and will cooperate with intramural programs, extramural investigators, and various organizations in research on genetic determinants of cancer.

The Viral Epidemiology Branch, created from a section within the Environmental Epidemiology Branch, focuses on epidemiologic studies designed to identify the role of RNA and DNA viruses and other infectious agents in the etiology of cancer. The branch will also perform studies on HIV and related viruses to define their role in the etiology of cancer and other diseases.

Dr. Adamson added that both of these new branches will help develop educational materials related to their missions. The creation of these branches, he noted, will allow for better management of the program and easier review of the Environmental Epidemiology Branch, since they were created from existing resources (including full-time equivalents, space, and monies) from within that branch. Their creation is also in accord with the NIH Strategic Plan in the areas of molecular medicine, vaccine development, population-based studies, and international research.

Dr. Adamson explained that, in the interest of time, he planned to briefly review a few scientific highlights and then introduce an outside speaker to discuss another area in more detail. He mentioned, however, that he would answer any questions from Board members about the other scientific highlights.

Beginning with a study of the tumor suppressor p53 gene in the Biological Carcinogenesis Program, Dr. Adamson explained that hepatocellular carcinoma is a liver cancer that kills about a quarter of a million people annually throughout the world, about 14 to 15 thousand of whom live in the United States. Previous studies have shown that a specific mutation of p53, codon 249, is found in about 17 percent of tumors from four countries in southern Africa and also along the southeast coast of Asia. No similar mutations were found in specimens from other locations.

Initially, Dr. Adamson continued, these mutations were correlated with exposure to aflatoxin, a contaminant produced by food molds. Recently, the mutations were found more frequently in individuals exposed to aflatoxin and infected with hepatitis B and also in hepatitis B-positive subjects with a low rate of aflatoxin exposure. While the precise roles of these agents remain unclear, research during the past year indicates that a loss of function of the p53 suppressor gene is important in the alteration of liver cells to cancer cells, and that both aflatoxin and the hepatitis B virus synergistically interact in the etiology of human liver cancer.

Dr. Adamson moved on to describe studies of food-derived heterocyclic aromatic amines in the Chemical and Physical Carcinogenesis Program. It has been thoroughly documented, he said, that during the normal cooking of fish, poultry, and meat, various mutagenic and carcinogenic heterocyclic aromatic amines are formed and have been detected in body fluids of persons who have consumed cooked beef.

During the past year, fried bacon was found to contain amounts of heterocyclic aromatic amines 10 times higher than cooked beef. Microwaved bacon did not contain any of these compounds. Dr. Adamson suggested that it would be prudent to recommend to the public that any bacon they eat should be cooked in microwave ovens. He added that some of

the population, particularly the African American population in the South, eat foods seasoned with bacon grease, which is also likely to be high in heterocyclic aromatic amines.

In a bioassay, Dr. Adamson continued, one heterocyclic aromatic amine was found to cause only two types of tumors in rats. Most of the heterocyclic aromatic amines cause a wide range of tumors in rats, but one compound—PhIP (2-amino-1-methyl-6-phenylimidazo [4,5-b] pryridine) caused only colon and breast tumors in a high proportion of the rats.

Dr. Adamson reported that Dr. Felton, at the Lawrence Livermore Laboratory, recently found mutagenic activity associated with certain bread products, particularly those containing wheat gluten, when cooked at normal temperatures but for a period of time 50 percent longer than normal. Also, in intramural studies and in studies by Dr. Dashwood at the University of Hawaii, chlorophyll was found to have a protective effect in *in vitro* mutagenicity assays of the heterocyclic aromatic amines, in inhibiting DNA adduct formation in rats, and in inhibiting absorption of various heterocyclic aromatic amines from ligated sections of the intestine *in situ.*

Moving to the Epidemiology and Biostatistics Program, Dr. Adamson announced findings of a multicenter study—involving the University of Southern California, the Northern California Cancer Center, the University of Hawaii, and intramural investigators—that have not yet been published. The study found that Asian American women whose grandparents were born in the United States had a fivefold higher risk of breast cancer than recent migrants from rural portions of Asia who had been in the United States less than 7 years. Exposure to western lifestyles had a relatively rapid impact on migrants living here 10 years or more, who had an 80 percent higher risk than recent migrants.

Dr. Adamson next reviewed interactions between the Division of Cancer Etiology and the Division of Cancer Prevention and Control. The Division's Directors have made presentations to each other's Boards of Scientific Counselors. Interactions between Division staffs included development of the risk model for the tamoxifen study, a joint etiology and prevention study on esophageal cancer, and a multivitamin study. Several other joint projects are ongoing in which both prevention and etiology are being studied in the same populations, including a breast cancer demonstration project following up on approximately 58,000 women.

The DCE, Dr. Adamson added, has also provided DCPC and other agencies, including regulatory agencies, with advice regarding the formulation of prevention strategies. The Division performed epidemiological studies on tobacco that, along with carcinogenesis studies performed by an NCI grantee, were brought to the attention of the DCPC and the Office of Smoking and Health, resulting in legislation and alerts to the public. Other intramural and extramural studies on environmental tobacco smoke have been supported by the Division, including a recent study by Drs. Fontham and Correa showing that environmental tobacco smoke is responsible for a large portion of the adenocarcinoma cases among nonsmoking women.

Dr. Adamson listed several other areas of cooperation between DCE and DCPC. He highlighted epidemiological studies on dietary risk, such as those showing that some vegetables reduce risk for stomach cancer and that beta carotene affects risk for lung cancer,

which have also provided strategies for chemoprevention trials; studies on ionizing radiation that have led to reductions in recommended medical exposures; and studies on dysplastic Nevus syndrome by Dr. Clark at the University of Pennsylvania and Dr. Tucker and colleagues that have led to public and professional education on this syndrome and its linkage to malignant melanoma.

Dr. Adamson also listed DCE interactions with the National Institute of Environmental Health Sciences (NIEHS), including participation in each other's advisory boards. The DCE and NIEHS Directors are both members of the Executive Committee of the National Toxicology Program (NTP) and the Departmental committee that coordinates environmental health and related programs within the Public Health Service. The DCE and NIEHS have also sponsored workshops together on topics such as the long-term effects of diethylstilbestrol exposure, and both will be involved in the upcoming international conference on women's health focusing on occupational cancer risk. The Division is also a major contributor of nominations to the NTP/NIEHS Bioassay Program.

Dr. Adamson reviewed several managerial initiatives during DCE's fiscal year 1992. A computerized financial tracking system was installed that enables administrators to download daily, weekly, or monthly transactions from the NIH Central Accounting System to personal computers to create customized reports for monitoring and projecting expenses. Dr. Adamson emphasized progress regarding affirmative action and equal opportunity employment. During the summer, the Student Research Training Program hired 63 college, graduate, and medical students, of whom 29 were members of racial/ethnic minorities; the group included 17 minority and 16 nonminority women. During the last two fiscal years, 43 percent of staff conversions and promotions were women.

Dr. Adamson next reported that the overall budget for DCE was $334 million in 1991 and $371 million in 1992, an increase of $36.3 million. Intramural programs, grants, and contracts were all increased; the increase for contracts was the first in several years. Dr. Adamson also reviewed the role of the Board of Scientific Counselors, which performs concept review of contracts, RFAs, cooperative agreements, and interagency agreements; provides evaluation of the scientific performance of staff scientists by site visits to intramural laboratories; and convenes several ad hoc subcommittees on areas of importance. Dr. Adamson stated that members of the Board have expertise in viral oncology, chemical carcinogenesis, radiation carcinogenesis, molecular biology, epidemiology, biostatistics, and genetics. He noted that the loss of Dr. Correa from the Board is mitigated by gaining his participation on the NCAB.

Dr. Adamson explained that at least two members of the Board of Scientific Counselors, one of whom serves as the chairperson, participate in each site visit. Dr. Adamson stated that site visits sometimes result in reallocations of resources and organizational changes; site visit teams report back to the full Board in closed session and reports on implementation of their recommendations are made within a year of the visit.

In October 1991, Dr. Adamson stated, 12 concepts were presented to the Board for a total of $27 million over the life of the concepts. All of the concepts were approved. Dr. Adamson highlighted two of these concepts—interagency agreements with the Environmental

Protection Agency (EPA) for a collaborative program on environmental cancer and with the National Institute for Occupational Safety and Health (NIOSH) for research on occupational carcinogenesis. Each project within each of these collaborative agreements is brought to the Board for its approval. Among the other concepts approved in October, Dr. Adamson highlighted a study of cancer risk in women with augmentation mammoplasty.

At the March 1992 meeting, 10 concepts were proposed and approved for a total lifetime cost of $17 million. Dr. Adamson highlighted three of these: a contract for inter- and intraspecies identification of cell cultures; an interagency agreement with Oak Ridge National Laboratory for the collection, separation, and elucidation of environmental carcinogens, looking particularly at combustion and smoke-related exposures; and a prospective study of cancer among men and women in agriculture, which Dr. Adamson said would be described later during this meeting by Dr. Aaron Blair.

At the most recent meeting in May 1992, 12 concepts were presented and approved. There were two interagency agreements among these: a study of human health consequences of polybrominated biphenyls, a continuation of a cohort being done in collaboration with the Centers for Disease Control and Prevention, NIEHS, and other agencies; and an agreement with the EPA to look at small fish carcinogenesis models. There were also several RFAs of interest, including an epidemiological study of ovarian cancer and a transfer of theoretical biostatistical methodology to epidemiologic studies of cancer. Another important concept was to conduct a case-control study of osteosarcoma that has both retrospective and prospective components.

VII. NOVEL STRATEGIES IN CHEMICAL PROTECTION AGAINST CANCER—DR. PAUL TALALAY

Dr. Talalay began by noting that chemoprotection against cancer was probably little more than a footnote in the cancer plan enacted by the Nixon administration in 1971. Since then, chemoprevention has taken its place with three other strategies—early diagnosis, improved treatment, and avoidance of carcinogens—as one of the four major strategies for cancer control and prevention.

Chemoprotection can be defined as the establishment of a state of decreased susceptibility to carcinogens by the administration of chemicals, many of which are already present in the human diet. When chemoprotection is achieved, it is usually not specific for a carcinogen or a target organ, but protects against a variety of cancers. It is highly cost effective and is prescriptive, empowering individuals with the means to control their health. Several considerations make the pursuit of chemoprotection against cancer a compelling goal: the lack of significant overall progress in the treatment of the most common cancers; epidemiological evidence that most human cancers are associated with extrinsic factors that are avoidable; and experiments demonstrating that a variety of chemical agents can protect animals against chemical carcinogens.

In 1951, Richardson and Cunningham studied an azo dye carcinogen, the butter yellow derivative, 3-methyl-4-dimethylamino-azobenzene. When this dye was fed to rats for a

prolonged period of time, 100 percent liver cancers resulted and a large percentage of animals had metastases. In the hope of accelerating this process, these researchers coadministered 60 micrograms of 3-methylcholanthrene, a potent carcinogen, once a week to these animals. Surprisingly, after an even longer period of time, only 17 percent of the animals had liver cancer and there were no metastases.

Analysis of this phenomenon by James and Elizabeth Miller at the University of Wisconsin showed that the 3-methylcholanthrene reduced the incidence of tumors by stimulating hepatic activities of the enzymes that destroyed the carcinogen by cleaving the azo linkage, hydroxylating the rings, and demethylating the nitrogen group. It was also demonstrated that the binding of the azo dye to liver proteins was reduced and that the enzyme elevations required protein synthesis. It is now known, Dr. Talalay explained, that this is an incomplete explanation, since 3-methylcholanthrene also induces many other enzymes, including those responsible for conjugation of carcinogens with glutathione and glucuronic acid.

Dr. Talalay described what he called the "reverse Richardson experiment" in which the polycyclic aromatic hydrocarbon, dimethylbenzanthracene—a compound that causes mammary tumors in Sprague rats—was used by Dr. Charles Huggins a few years later to show that the administration of small doses of the azo dye Sudan III protected against mammary tumors, adrenal haemorrhage, leukemia, and chromosomal breakages. None of these experiments attracted much attention because it was believed that the models were not relevant to human cancer.

The work of Lee Wattenberg, a pathologist at the University of Minnesota, was a milestone in chemical protection against cancer. He showed that two phenolic antioxidants, BHA and BHT (widely used as additives to preserve packaged foods), are anticarcinogenic. Wattenberg demonstrated that the administration of BHA and BHT markedly reduced tumor incidence and multiplicity in rodents that were given benzopyrene. Similar experiments with a variety of other carcinogens also showed that these antioxidants were inhibitors of tumor formation.

Dr. Talalay explained that the majority of carcinogens are themselves innocuous because they are carcinogen precursors. The presence of Phase I enzymes, a family of cytochromes P-450, converts these procarcinogens to either highly reactive electrophiles (positively charged compounds that are ultimate carcinogens) or nonelectrophilic metabolites. The electrophilic and nonelectrophilic metabolites are substrates for Phase II enzymes, such as glutathione transferase, glucuronosyl transferases, and quinone reductase, which conjugate or modify these metabolic products to create detoxification products that can be excreted.

Examining the enzymatic activities of animals treated with BHA or BHT, Dr. Talalay and his colleagues found that BHA elevated the activities of Phase II enzymes, as a result of enhanced transcription, without significant effects on Phase I enzymes. The inductions occurred in the liver and in many peripheral tissues as well as in cultured cells. These findings led to the conclusion that Phase II enzymes and glutathionine elevations are a major protective mechanism against cancer and electrophile toxicity. Dr. Talalay added that monitoring of

enzyme induction by several researchers has led to the recognition or isolation of chemoprotectors, such as dithiolthiones, isothiocyanates, and terpenoids.

Dr. Talalay proposed that the susceptibility to chemical carcinogens is controlled, in part, by the balance between enzymes that activate carcinogens and those that inactivate them. The corollary to this proposition, he continued, is that it should be possible to reduce the susceptibility to carcinogens by manipulation of the profiles of these two enzymes. It has been shown that many compounds belonging to different classes are chemoprotectors with little in common. All of these compounds alter the metabolism of carcinogens and elevate Phase II detoxification enzymes.

Dr. Talalay said that for purposes of analysis, a simple experimental system was needed to identify the potency of these enzyme inducers and their mechanism of enzyme induction. A murine hepatoma cell line responded to all the chemoprotective inducers. The marker enzyme, quinone reductase, was selected for monitoring this induction. Dr. Talalay and his colleagues developed a simple and precise enzyme assay involving microtiter cell culture systems.

The microtiter plates used in this experiment contain 96 wells. Two duplicate plates are seeded with a number of the hepatoma cells and are then treated with different concentrations of inducer. One plate is used to measure the enzyme (quinone reductase) activity. A duplicate plate measures toxicity. A computerized optical reader provides a ratio of activity from which the potency index can be determined.

Dr. Talalay described how his team attempted to address the question of chemical specificity among chemoprotective inducers. They investigated why the position of the hydroxyl groups was important for induction and found that compounds with adjacent or opposite hydroxyl groups (1,2-diphenols and 1,4-diphenols) are inducers, whereas the 1,3-diphenols are not. A fundamental difference between these compounds is that catechols and hydroquinones can undergo oxidation to quinones. It was concluded that the ability to undergo oxidation—redoxlability for diphenols and phenylenediamines—is essential for induction.

This experiment did not answer the question of whether the reduction/oxidation process itself, or the quinone product, was essential for the induction process. Experiments with a series of compounds, however, did answer the question. Dr. Talalay started with coumarin chemoprotectors and then examined partial structures and related structures. Many alpha, beta unsaturated ketones were inducers. At least one large group of inducers were Michael reaction acceptors. Dr. Talalay explained that the Michael reaction was first described in 1877 by Arthur Michael, a chemistry professor at Harvard, who showed that a double bond attached to an electron-withdrawing group could react well with a nucleophile to make a condensation product that reversed reaction in organic chemistry. Dr. Talalay reported that the information his team learned about the chemistry of the substances that raised toxification enzymes led them to the conclusion that they could predict what types of compounds are inducers and suggest them for anticarcinogen testing. He noted that anticarcinogen testing is a very slow process.

Several epidemiological studies have shown that high consumption of vegetables is associated with decreased risk of certain cancers. Several experiments have also shown that the feeding of vegetables to rodents protects them against chemical carcinogenesis, and other studies have shown that they elevate Phase II enzymes. Dr. Talalay applied the microtiter plate test to an examination of a wide variety of vegetables. Results with broccoli indicated a high concentration of quinone reductase inducer activity and little toxicity. Dr. Talalay and his team surveyed five families of vegetables: Cruciferae, Liliacae, Umbelliferae, Chenopodiacae, and Solinacae. They selected a variety of broccoli for further study because it was high on the scale of inducer activity and because its consumption was increasing.

Dr. Talalay and his colleagues analyzed organic solvent extracts of broccoli by reverse phase high pressure liquid chromatography. The inducer compound they found was an isothiocyanate known as sulforaphane. Isothiocyanates exist very widely in plants, normally as precursors. Isothiocyanates, also known as mustard oil, are responsible for the sharp taste of mustard, horseradish, watercress, and other foods.

Dr. Talalay stated that sulforaphane is the most potent naturally-occurring inducer of protective enzymes discovered thus far. Sulforaphane was previously isolated from a weed known as hoary cress, *Candaria draba*, in the 1950s in Czechoslovakia. Many other isothiocyanates have been shown to be anticarcinogenic, and Dr. Talalay expects that sulforaphane will also be found to be anticarcinogenic.

Dr. Talalay concluded by repeating that the susceptibility of carcinogens is controlled by a delicate balance between enzymes that activate carcinogens to their ultimate reactive form and enzymes that inactivate them. This balance can be tilted toward protection by many substances that elevate the enzymes of detoxification. Some of these enzyme inducers are present in human diets as natural constituents or additives. Dr. Talalay expressed hope that dietary modifications to include foods rich in chemoprotective activities will become a major strategy for cancer prevention. He thanked his collaborators and the NCI and American Cancer Society for their support of his research.

Questions and Answers

Dr. Salmon asked if Dr. Talalay has put sulforaphane into *in vivo* preclinical studies of mice to investigate whether it will also inactivate carcinogens and prevent cancer formation. Dr. Talalay explained that he did not intend to imply that sulforaphane is the only answer to the problem. While sulforaphane has been tested in animals for enzyme induction, enough sulforaphane is not available to conduct full-scale carcinogenesis testing. Tests that require modest amounts of carcinogens, however, are currently underway.

Dr. Chan asked for a clarification of the terms "chemoprevention" and "chemoprotection." Dr. Talalay answered that, from his point of view, chemoprotection specifies an active interventive process in which the biochemical means raise or lower the susceptibility of cells to cancer. The term "prevention" implies a public health measure in which one avoids carcinogenic practices. Nevertheless, "chemoprevention" is a widely used term.

Dr. Calabresi took this opportunity to thank Dr. Paulette Gray of the NCI Division of Extramural Activities for organizing a summary publication of the twentieth anniversary symposium of the signing of the National Cancer Act. He then adjourned the meeting for a luncheon recess.

VIII. HORMONES AND CANCER—DR. BRIAN E. HENDERSON

Dr. Henderson began by noting that he would present the collective work of a number of researchers—a summary of 20 years of work on the relationship between hormones and cancer, with the specific intention of using hormonal intervention in preventing cancer. He named the four major hormone-related cancers as breast, endometrial, ovarian, and prostate cancer. This group of cancers accounts for approximately one of every three cancers. The hypothesis maintained over the years, Dr. Henderson said, is that the hormone that drives the normal growth, development, and function of a gland is the same hormone that is responsible for the cancer in that gland.

These cancers develop from prolonged cell proliferation that is driven by steroid and polypeptide hormones. This hormone is a testosterone derivative, dihydrotestosterone, in prostate cancer, estrogen in endometrial cancer, and estrogen and progesterone in breast cancer. In this model of hormone-induced cancer, it is cell proliferation itself, Dr. Henderson said, that is the mutagenic event. In the course of cell division, errors are made, these errors accumulate, and a malignant phenotype eventually emerges. The cells that divide are driven by hormones, removal of which at any stage should stop the process from proceeding—the basis of hormonal chemoprevention. Dr. Henderson stated that this carcinogenic process is nongenotoxic carcinogenesis, or carcinogenesis resulting from cell proliferation when cellular DNA damage occurs in the process of cell division.

Endometrial Cancer

Dr. Henderson then presented evidence that hormones cause particular cancers. He started with endometrial cancer, noting that this is the simplest model. When estrogen is present alone, endometrial cells proliferate; when progesterone is present they do not. There are several situations that can lead to elevated levels of circulating estrogen in the absence of progesterone, including obesity, certain ovarian tumors, and exogenously administered estrogen in the absence of progesterone.

Dr. Henderson then presented data on White, postmenopausal females. Beginning in 1961 through the late 1960s, the incidence of endometrial cancer was fairly flat, he said. In the early to mid-1960s, conjugated equine estrogen first became widely available in the form of Premarin and was widely distributed. Five years later, an epidemic of endometrial cancer occurred in many places, and incidence tripled in under 10 years. Fortunately, Dr. Henderson noted, there was not much change in the mortality rate because most of these cases were treatable and curable.

Presenting data from a prospective study on the relationship between endometrial cancer and estrogen replacement therapy, Dr. Henderson said that current long-term estrogen users are at 12 times higher risk than nonusers. When estrogen therapy is stopped, the risk goes down. Dr. Henderson said this represents a clear dose-response relationship between estrogen and endometrial cancer. It is a cause-and-effect relationship much like that of cigarette smoking and lung cancer.

Dr. Henderson then discussed the normal menstrual cycle, noting the midovulatory surge in estrogen and the surge of progesterone in the luteal phase. There is proliferation of endometrial cells in the estrogen-only phase and cessation of that activity when progesterone is present. When progesterone is given together with estrogen, as in the use of combined oral contraceptives, the risk of endometrial cancer is reduced to approximately one-half that of nonusers. Dr. Henderson added that when progesterone is added to estrogen replacement therapy, the risk of endometrial cancer is lowered.

Ovarian Cancer

Combined oral contraceptives also protect against carcinoma of the ovary, Dr. Henderson said. In this case, the oral contraceptive, by ablating the effect of luteinizing and follicular stimulating hormone secretion, is stopping ovulation, thus reducing ovarian cancer risk. The annual change in the risk of these cancers per year of oral contraceptive use can be calculated to show a rather profound effect—a 10 percent reduction in the risk of getting these two cancers for each year of use of oral contraceptives. The data show that this is a lifelong effect that is never reversed.

Dr. Henderson then presented data published by the National Cancer Institute on the average rates of ovarian and endometrial cancer in 1973 to 1974 compared to 1986 to 1987. The data showed incidence and mortality for women less than 50 years of age. Sixty percent of the women in the 1986 to 1987 group had used oral contraceptives for an average of 5 years. Dr. Henderson noted that the change in incidence of ovarian and endometrial cancer over this 15-year period is exactly the magnitude of change one would expect given the pattern of oral contraceptive use. These two cancers, he stated, are being prevented in large numbers because of oral contraceptive use.

Breast Cancer

Clearly, continued Dr. Henderson, oral contraceptives haven't done much to protect against breast cancer. Mortality is down slightly, he said, probably because of adjuvant therapy, but incidence is up in the same group of women because combined oral contraceptives do not protect against breast cancer.

Dr. Henderson then presented the risk factors for breast cancer. He explained that breast cancer, like endometrial cancer, is due to increased exposure to estrogen, but that progesterone, an antiestrogen in other parts of the body, acts like estrogen in the breast. This is one of the reasons that oral contraceptives don't protect against breast cancer. If not for menopause, he added, breast cancer would affect half the female population by age 70.

Age of menarche and, particularly, the age at which a woman starts to cycle regularly is a major risk factor. Women who experience an early menarche and begin to cycle immediately have a risk of breast cancer almost four times that of women who are late to start and late to be regular. Therefore, early onset of regular ovulation is a major risk factor for this disease.

Early menarche, Dr. Henderson said, is a characteristic of a sedentary, organized Western society, and Americans have more breast cancer because of it. Not enough is known about the dietary and nondietary factors that affect the onset and quality of puberty and, if breast cancer is to be prevented, he stated, we are going to have to know more in these areas.

Another important risk factor for breast cancer is age of first birth. The younger the age at first birth, the lower the risk. One effect of parity is to lower the amount of circulating estrogen. The number of pregnancies has an independent effect on risk, lowering it, as does lactation. Menopause is also an important event. The earlier it is, the lower the risk; the later it is, the higher the risk.

Reiterating, Dr. Henderson stated that everything that is known about breast cancer points to ovarian steroid hormones, particularly estrogen, as the major cause of the disease. He explained that there are milestones in a woman's menstrual and reproductive life that set her lifetime risk. The first of these is menarche, when the breast begins to grow and develop. Breast cancer risk grows the fastest from the time of menarche to the first full-term pregnancy, and grows the slowest after menopause. The importance of this, Dr. Henderson stressed, is that the earlier the intervention, the greater the impact on lifetime risk.

Dr. Henderson then showed data comparing age-specific incidence of breast cancer in women experiencing menopause at age 50, at age 45, and with a bilateral oophorectomy at age 35. The data showed that women undergoing the bilateral oophorectomy had a much more substantial lifetime benefit than women experiencing menopause later in life.

Dr. Henderson noted that researchers are working to develop an approach to contraception that will prevent breast cancer, as well as endometrial and ovarian cancer, using a GnRH agent that produces a medical oophorectomy and includes enough estrogen to prevent bone loss and to protect against cardiovascular disease risk. The approach also uses progesterone to try to reverse any endometrial hyperplasia. He said this would be an add-back hormone replacement therapy in a person who has had a reversible medical oophorectomy.

This regimen has been tried on approximately 20 women and has been well tolerated and reversible. The effect of this treatment on a woman's risk of breast cancer, if used for 10 years from ages 30 to 40, could be to reduce lifetime risk by one-half.

Dr. Henderson then described another approach based on the use of tamoxifen to block estrogen's ability to bind to breast tissue. The tamoxifen trial in healthy women is based on studies that show an average 38 or 39 percent reduction in contralateral breast cancer. This data led to the idea of using tamoxifen to prospectively prevent breast cancer. Since estrogen is the cause of breast cancer, the use of tamoxifen to prevent it makes a lot of sense, he said.

Dr. Henderson stressed the importance of age in relation to tamoxifen treatment. Tamoxifen therapy at age 50 for 5 years would have some effect on the lifetime risk of breast cancer, but it would not be very great. If used earlier, it can have a huge effect, reducing the risk by approximately 50 percent. Dr. Henderson stated that the tamoxifen trial is very well designed because it includes younger women at high risk as well as older women, which will allow validation of what is thought to be an important age-dependent difference in the degree of protection women will receive.

Dr. Henderson then noted that the effect of progesterone in breast cancer is becoming an increasingly difficult problem. Unlike endometrial cancer, in which most of the mitotic activity occurs in the first half of the menstrual cycle, in breast cancer it occurs in the second half of the cycle. This is what originally led researchers to believe that progesterone is a breast cancer mitogen, not an antiestrogen. A Swedish study published in the *New England Journal of Medicine* then showed that combination estrogen and progesterone therapy appeared to increase the risk of breast cancer substantially above estrogen use alone. This study was recently updated and a substantial, though not as large as first published, increase in breast cancer risk was seen over use of estrogen alone. Dr. Henderson said that combination therapy appears to approximately double the risk that occurs with estrogen alone. These findings are important, he said, because progesterone therapy added to estrogen is widely used.

Prostate Cancer

Turning to a discussion of prostate cancer, Dr. Henderson said that 5-alpha reductase converts testosterone to dihydrotestosterone, which is the relevant hormone driving mitotic activity in the prostate cell. Japanese men of the same age as their White counterparts circulate the same amount of testosterone, but less of the metabolites of 5-α-reductase, suggesting that a relative deficiency in the amount of this enzyme may be the reason for the apparent protection of Japanese men compared to Whites.

Noting the age-specific incidence of prostate cancer, Dr. Henderson said that finesteride taken for 5 years at age 50 to 55 could reduce the risk of prostate cancer by about 50 percent.

Dr. Henderson concluded that this is an exciting time for the field of hormone intervention. He reiterated that work is already being done in hormonal intervention with oral contraceptives, a trial is currently underway with tamoxifen, pilot studies are being conducted with new approaches to contraception, and, possibly, a national trial of finesteride will be undertaken.

Questions and Answers

Dr. Bettinghaus asked if anything had been done in regards to postmenopausal hormonal therapy to try to plot the presumed savings of cardiovascular disease versus the increased risk of breast cancer to provide advice to women on this particular issue.

In response, Dr. Henderson said that a woman clearly benefits if she takes estrogen alone because of the cardiovascular disease benefit. The use of progesterone is a bit more confusing because it is thought that breast cancer risk will increase and it is uncertain what will happen to the cardiovascular disease benefit derived from estrogen.

Dr. Bragg asked whether studies have been done on the relative impact of different doses of estrogen replacement therapy on cancer and other protective effects. Dr. Henderson responded that there are some data comparing 1.25 milligrams with .625 milligrams of Premarin and also some data comparing conjugated equine estrogens with estradiol valerate, which is used in Europe. He said it appears that a higher dose means a higher risk of breast cancer, and it is not clear that there is more cardiovascular benefit.

Dr. Wilson asked whether there is any evidence of hormonal factors that are active in breast cancer in men. Dr. Henderson answered by saying that there is little data on men. The data that are available suggest that estrogen is probably the relevant hormone in men as well.

Dr. Freeman, noting that contralateral breast cancer is diminished in women on tamoxifen, asked if the estrogen receptor status of the groups who are protected is known. Dr. Henderson responded that the only study he is aware of is one that included only estrogen receptor-positive women.

Dr. Becker asked about potential causes of early menarche and whether there is evidence that it is caused by a sedentary lifestyle. Dr. Henderson said that the age of menarche in rural Chinese, Japanese, and other Asian populations is late, usually 16 or 17 years. It is known from anthropologic studies, he said, that there is some relationship between accumulation of body fat and onset of menarche. Little else is known about how these events affect the onset of puberty.

Dr. Salmon asked whether any data exist on flavone, an antiestrogen, in the oriental diet in the form of bean curd. Dr. Henderson stated that there is not enough known to answer the question.

Dr. Chan then asked about data on vegetarians and the development of these types of cancers. Dr. Henderson answered that the Seventh Day Adventist population, which is not a meat-eating population, but is a milk and dairy product-consuming population, appears not to have the protection against breast cancer that was originally thought. Hormone levels in vegetarian women in their teenage years have been studied, he added, and have been found to be no different than those of their meat-eating counterparts.

IX. A MECHANISTIC ROLE FOR THE PAPILLOMAVIRUSES IN HUMAN CERVICAL CANCER—DR. PETER M. HOWLEY

Dr. Howley said that he would briefly present the evidence that associates the human papillomaviruses (HPVs) with certain human cancers, most notably cervical cancer, and review data that provide a mechanistic role for these viruses in the progression of benign, preneoplastic cervical dysplasia to cervical cancer.

Papillomaviruses are small DNA tumor viruses that are the causative agents of warts or papillomas in humans and other higher vertebrates. The first papillomavirus was described by Shope in 1933 as the causative agent of cutaneous horns in the cottontail rabbit—this was the first virus shown to be associated with epithelial cancers. Investigators, including Peyton Rous, established a role for cofactors in carcinogenic progression with this animal papillomavirus.

Dr. Howley stated that there are more than 60 distinct types of HPVs; each tends to be associated with specific clinical entities—HPV-1 with plantar warts, HPV-2 with common warts, etc. Approximately 25 HPVs are associated with genital tract lesions; they are usually divided into high-risk and low-risk groups, depending on whether the lesions they cause are likely to progress to malignancy.

Dr. Howley noted that interest in the HPVs was spurred in the 1980s by their association with cervical cancer. Cervical cancer is responsible for about 500,000 deaths worldwide; in the United States, there are about 13,000 new cases and 5,000 deaths per year. Dr. Howley suggested that these deaths in the United States are probably preventable, since most occur among women who do not participate in pap smear screening. Risk factors include early age of onset of sexual activity and number of sexual partners. A venereally transmitted agent has long been suspected as the cause of cervical cancer; in the 1960s and early 1970s, the herpes simplex virus was thought to be this agent. However, molecular and seroepidemiologic studies failed to find convincing associations between the herpes simplex virus and cervical cancer. Dr. Howley noted, however, that studies have not ruled out the possibility that the herpes simplex virus may be a cofactor in cervical cancer, perhaps augmenting the effects of HPVs.

The first evidence of the association between HPVs and cervical cancer came in the mid-1970s, when an abnormality, called koilocytosis, seen on pap smears in cases of mild cervical dysplasia was identified as the cytopathic effect of an HPV infection. Investigators were able to identify actual HPV antigens and particles in some of these cells. Dr. Howley explained that this research linking HPVs with lesions that are considered preneoplastic spurred molecular studies to identify the HPV.

The first studies to identify specific HPVs were done using venereal warts, or condyloma acuminata. Two new HPVs, Type 6 and Type 11, were found in condyloma acuminata cells but could not be associated with cervical cancer. Dr. Harald zwi Hausen then examined invasive squamous cell carcinomas of the cervix and was able to isolate two additional new HPVs, Type 16 and Type 18, from such lesions. Approximately 70 percent of cervical cancers studied were shown to contain one of these two HPVs. Additional HPV types have been identified in cervical cancers and preneoplastic lesions; altogether, an HPV can be identified in 85 to 90 percent of human cervical cancers. These same HPVs have also been found in some penile, vaginal, perianal, and upper airway carcinomas. Dr. Howley summarized that HPV-6 and HPV-11, associated with condyloma acuminata, represent the low-risk end of the spectrum; at the other end of the spectrum are HPV-16, HPV-18, HPV-31, HPV-33, and a few others, which are associated with cervical dysplasia or intraepithelial neoplasia—lesions at risk for progression to malignancy.

Laboratory observations, Dr. Howley reported, have shown that these high-risk HPVs can efficiently immortalize primary human keratinocytes, which are the target cells of the HPVs, in tissue culture, whereas the low-risk HPVs cannot. This immortalization assay has been valuable in identifying the HPV genes involved in this function and in examining the mechanisms by which the viral gene products contribute to carcinogenic progression.

Displaying a slide with a schematic representation of the circular genome of HPV-16, Dr. Howley explained that the E1 and E2 genes are important regulatory genes that are involved in DNA replication and in the regulation of the transcriptional promotor that drives the E6 and E7 genes, which participate directly in carcinogenic progression and immortalization. He highlighted the E1 and E2 genes because of an important change that occurs in the progression of benign preneoplastic lesions to cancer. In preneoplastic lesions, the DNA is generally extrachromosomal; in its normal circular form, all of the genes are intact. In HPV-associated cancer, however, the DNA is integrated. Integration appears to be random in that it can occur on a variety of chromosomes; however, the viral genome is usually disrupted within the E1 and E2 genes in the course of integration.

The integration event that disrupts E1 and E2 leads, in turn, to the deregulated expression of the promotor of E6 and E7 and, therefore, the deregulated expression of the viral oncoproteins they encode. Dr. Howley noted that, since E6 and E7 are expressed in the benign precursor lesions as well as in cancers, they necessarily play a role in the normal life cycle of the virus. E7 has transcriptional modulatory properties and cellular transformation properties similar to E1A, a well-studied transforming gene of adenovirus. This similarity puts the extensive literature on studies of E1A and its mechanisms at the disposal of those studying E7. Dr. Howley's laboratory has identified structural similarities between E7 and E1A and shown that E7, like E1A, is able to complex and functionally inactivate the retinoblastoma protein (Rb), a product of the retinoblastoma tumor suppressor gene, which is located on the human chromosome 13.

Dr. Howley noted that there is a strong predisposition for the development of retinoblastomas in children when both alleles of the Rb gene are mutated or deleted. Mutations or deletions of this gene have also been detected in many other human cancers, including small-cell carcinomas of the lung, breast cancer, and prostate cancer. The Rb protein is phosphorylated and dephosphorylated in a cell cycle-dependent manner, and its function in regulating cell cycle progression is controlled by its state of phosphorylation. Dr. Howley added that the function of Rb is still being studied in a number of laboratories; it is clearly involved in the transcriptional regulation of certain key cellular proteins that are involved in DNA synthesis. DNA tumor virus oncoproteins, including HPV E7, work in part by complexing with the Rb protein and inactivating its function in normal cell cycle regulation.

Dr. Howley moved on to discuss the E6 protein, which, like E7, is expressed in HPV-positive cancers. His laboratory, in collaboration with Dr. Arnold Levine of Princeton, hypothesized that E6 might target a second tumor suppressor gene product called p53, based on an analogy with other DNA tumor viruses, such as the adenoviruses and SV40, that have been extensively studied. Adenovirus type 5 encodes a second transforming gene, E1B, and the 55 kilodalton it encodes is capable of binding and inactivating p53. Similarly, the large T antigen of SV40 also binds and inactivates p53.

HPV E6 was tested for p53 binding based on the hypothesis that a common feature of all of these tumor viruses is a need to target and inactivate tumor suppressor gene products to support their progression into the S phase of the cell cycle in order to replicate the viral DNA. p53, Dr. Howley noted, is mutated in a high percentage of human cancers. It is considered to be a "cellular policeman" that plays a role in protecting the genome from damage. When the cell senses damage from radiation, viral infection, or other agents, the level of p53 is increased, leading to an arrest in cell cycle progression until the damage can be corrected.

Dr. Howley stated that the adenovirus E1B and SV40 T antigen oncoproteins inactivate p53 by stabilizing it in an inactive complex; E6 actually promotes the degradation of p53. The ability of E6 proteins to target the degradation of p53, he added, correlates well with the cancer-associated properties of these viruses. The E6 proteins of the high-risk HPVs bind and degrade p53, whereas the E6 proteins of the low-risk HPVs do not. The degradation process requires the energy of ATP hydrolysis. Thus, the presence *in vitro* of inhibitors of ATP hydrolysis, such as AMP or ATP gamma S, inhibits the degradation process. These inhibitors also give rise to intermediates in the degradation process, which are larger molecular weight complexes in which p53 has been ubiquinated. Dr. Howley stated that his laboratory has shown that E6 targets the ubiquination of p53.

Dr. Howley observed that this selected degradation of important cellular negative regulatory proteins such as p53 is a new mechanism by which dominant acting oncoproteins may function; it underlines, he stated, an important mechanism of regulation within the cell. Not only the synthesis of proteins, but also the regulation of the half lives of proteins, can have a profound impact on important regulatory proteins such as p53.

Dr. Howley reviewed two important differences between the oncoproteins encoded by HPVs. The E7 proteins encoded by the high-risk HPVs actually complex Rb with a much higher affinity than E7 proteins encoded by the low-risk HPVs; it has been shown that the transforming properties of the high-risk E7 proteins in rodent cells are due to this high affinity. The E6 proteins of the high-risk viruses are able to complex with p53 and target its degradation *in vitro*, whereas the E6 proteins of the low-risk viruses do not have this function.

To address the relevance of these biochemical observations to human cervical cancer, Dr. Howley's laboratory studied a series of human cervical carcinoma lines. It was predicted that in HPV-positive cell lines, there may be no selective advantage for mutations in the Rb or p53 genes, since E6 and E7 function by the inactivation of the gene suppressor products Rb and p53 at the protein level. It was also predicted that if the inactivation of Rb and p53 is important in cervical carcinogenesis, the functions of these tumor suppressor gene products would be abrogated by some other mechanism in the HPV-negative cell lines.

In other words, one could predict that these genes would be wild type or not mutated in the HPV-positive cells, and mutated in the HPV-negative cells, if the model were correct. Dr. Howley reported and demonstrated with slides that these predictions are, indeed, supported by experimental data. These studies, he added, are being extended in several laboratories to examine primary cancers; a London study of p53 in genital carcinoma has shown that mutations of p53 in HPV-positive carcinomas are rare.

To summarize the data associating HPVs with human cervical carcinoma, Dr. Howley stated that the high-risk HPVs are transcriptionally active in a high percentage of cervical cancers. These high-risk HPVs contain transforming genes, E6 and E7, as well as regulatory genes, E1 and E2, which control the expression of the transforming genes. Integration of the viral genomes in cervical cancers disrupts the expression of the E1 and E2 genes, resulting in deregulation or derepressed expression of the viral transforming genes. The E6 and E7 oncogenes encoded by these high-risk HPVs target important cellular regulatory proteins, including Rb and p53, providing a molecular basis for the role of these viruses in human cancers.

Dr. Howley pointed out that carcinogenic progression is a rare consequence of infection by a high-risk HPV; it has been estimated that a woman who is infected with HPV-16 has a chance of about 1 in 30 of developing cervical cancer in her lifetime. The progression to cancer takes an average of 20 to 25 years. This suggests that while the virus may be a necessary component in most human cervical carcinoma, it is not sufficient—other genomic mutations probably must occur.

Dr. Howley asked, in closing, "What is the advantage to the virus to evolve these mechanisms to knock out the tumor suppressor gene products?" He explained that the virus normally divides and replicates its DNA only in the terminally differentiated cells of the squamous epithelium. These cells are no longer cycling and are not replicating their DNA. In order to replicate its DNA, however, HPV must use the host cell's enzymatic machinery. Since it depends on the host cell for DNA polymerase and other enzymes involved in DNA synthesis that are only expressed during the S phase of the cell cycle, it must create a signal for the cell to progress into the S phase. It does this by complexing and inactivating Rb. The "cellular policeman" p53, however, can also prevent the cell from progressing into S and it too must be functionally inactivated; in the case of the high-risk HPVs, this occurs through its targeted degradation.

Questions and Answers

Dr. Salmon asked whether sufficient information is available to begin developing a vaccine for HPV-16 and HPV-18. Dr. Howley replied that enough information exists to associate HPVs with cervical cancer, which should be enough to prompt the development of such vaccines. One approach could be to prevent infections with a vaccine—based on the capsid proteins of the viruses—that would neutralize incoming infections; another approach could be to take advantage of the fact that E6 and E7 are expressed in the preneoplastic cells as well as the cancers—targets for the vaccine could be provided by the fact that peptides from the viruses are presented on the cell surface through the major histocompatibility antigens.

Dr. Kirsten asked whether the nature of the interaction of E6 and E7 with the p53 and the Rb proteins is known. Dr. Howley stated that the interaction between E7 and Rb is a direct one involving a region of about 10 amino acids on the E7 protein. The interaction of E6 and p53 is more complex; another cellular protein called the E6-associated protein is involved in mediating this binding.

Dr. Calabresi asked whether having warts on the fingers or plantar warts offers protection or indicates added risk. Dr. Howley said he has not seen any studies on that question, but added that he thinks protection in such a case would be unlikely.

Dr. Wells asked whether nonpapillomavirus tumors are biologically different from the HPV-related tumors and whether he has any insights into the mechanisms involved in the HPV-negative cancers if E6 and E7 are not involved. Dr. Howley cited a *Lancet* article from about 2 years ago suggesting that HPV-negative cancers are much more aggressive than the HPV-positive cancers. In response to the second question, he stated that in HPV-negative cancers the genes are *de novo* mutations and, at least in some cases, involve the p53 and Rb genes.

Dr. Wells asked how many cancers have the papillomavirus. Dr. Howley stated that about 90 percent of human cervical cancers are HPV-positive. He added that one important question is whether the HPV-negative cancers were negative from the start or whether a selection took place along the way; he suggested a scenario in which there could be immunologic selection against the expression of E6 and E7, which would select for HPV-negative cancer cells. It is not possible to tell the history of an HPV-negative cancer cell, he noted, and in some cases it certainly may have been HPV-positive at some point.

Dr. Becker observed that cervical carcinoma is manifested at early ages in certain populations and at much later ages in other populations; he asked whether Dr. Howley knows of any factors associated with these age differences. Dr. Howley said he has no explanation, noting that in current studies of young women with rapid progression from dysplasia to cancer, the question of whether there are differences in the HPVs involved is being asked. Dr. Becker suggested that additional genetic events and differences in promotional factors might be involved. Dr. Howley agreed that this will be a very important area for investigation, noting that several recently published studies have suggested that the expression of E6 in the "knockout" of p53 function contributes to genomic instability.

X. PROSPECTIVE STUDY OF CANCER AMONG MEN AND WOMEN IN AGRICULTURE—DR. AARON BLAIR

Dr. Blair, Chief of the Occupational Study Section, began by describing a new project in the Epidemiology and Biostatistics Program of the Division of Cancer Etiology, which is a collaborative effort between the NCI, the Environmental Protection Agency (EPA), and the National Institute of Environmental Health Sciences (NIEHS). This project is a long-term (10 years or more) prospective study of health among farmers, their families, and pesticide applicators. The study will evaluate rural lifestyle factors that possibly contribute to the origin of cancer and other diseases.

NCI investigations during the past decade indicate high rates for certain cancers among farmers. Cancer maps developed by the NCI in the 1970s revealed that there was a high rate of leukemia in the central region of the U.S. related to agriculture and a rural lifestyle. Other studies conducted in the U.S. and abroad indicate that farmers tend to experience excesses for several tumors, including non-Hodgkins lymphoma, multiple myeloma, leukemia, soft-tissue

sarcoma, and cancers of the skin, lips, stomach, brain, and prostate. This study, Dr. Blair explained, could provide insight into the etiology of these tumors and, possibly, explanations for their rising rates.

Dr. Blair noted that one specific factor that may contribute to the relationship between cancer and the rural environment is contact with hazardous materials, particularly pesticides. Studies have shown pesticides to be carcinogenic in laboratory animals, he said, and those pesticides that are carcinogenic come from several different chemical classes. The strongest link found in epidemiologic studies of cancer and pesticides is between the phenoxy acetic acid herbicide 2,4-D and non-Hodgkin's lymphoma. This finding is supported by studies in Kansas, Nebraska, Sweden, Canada, and Italy, as well as a study associating lymphoma in dogs with their owners' use of 2,4-D on their lawns. Other associations have been found between non-Hodgkins lymphoma and grain fumigants, leukemia and soft-tissue sarcoma with insecticides, ovarian cancer with triazine herbicides, and lung and pancreatic cancer with DDT and DDE.

Research in this area is especially important, Dr. Blair continued, because the use of pesticides is becoming more common in urban areas. Methods of pesticide application vary widely, from the use of large equipment to manual application. The collaborative group decided to initiate a long-term prospective study to arrive at a more accurate assessment of pesticide exposure. Previous epidemiologic studies have based their evaluations entirely upon information gained from interviews. This is a productive approach, since family farmers function as both management and labor, thus enhancing their knowledge of the use of chemicals. Errors in recall can occur, however, and weaken the power of a study. Some advantages of the long-term prospective study include periodic collection of information on exposures, monitoring to relate measured levels to interview data, and the opportunity for evaluation of many disease outcomes.

The Division of Cancer Etiology Board of Scientific Counselors recently visited the Environmental Epidemiology Branch and encouraged the Branch to develop long-term prospective studies dealing with issues in occupational and environmental cancer. With regard to this new study, experienced investigators have provided advice and guidance and several internal and external advisory groups have been organized. Dr. Correa serves as the chair of an advisory panel composed of members of the Board of Scientific Counselors and experts in the fields of epidemiology, biostatistics, biomarkers, and exposure monitoring. This panel will continue to provide counsel and oversight throughout the conduct of the study.

Participants in the study will be identified when they apply for the required pesticide licenses. A cohort of approximately 80,000—56,000 farmers and 24,000 other pesticide applicators—will be assembled. Additionally, about 40,000 spouses and 80,000 children of the farmers will be included in the study. Family members will be assessed for their involvement in farm activities, special risk associated with early age, and indirect exposures to agricultural chemicals.

Dr. Blair explained that the study will include four components: 1) questionnaires to all individuals seeking pesticide licenses and spouses of farmers; 2) detailed environmental and occupational exposure monitoring on a sample of approximately 200 farmers and their

families; 3) biologic marker studies; and 4) cohort tracing through disease registries. From interviews, information will be collected on agricultural exposures as well as diet, tobacco and alcohol use, medications, family history of cancer, and pregnancy. The monitoring component will include analyses of occupational exposure to pesticides by inhalation and skin contact; environmental exposure from air, water, food, and soil; and delivered dose through analyses of blood and urine.

Biomarker analyses, he continued, will include indicators of early biologic effects. For example, in a study of grain handlers to evaluate chromosomal aberrations, Dr. Ilan Kirsch, NCI, found a correlation between an increased frequency of recombination of immune receptor loci and pesticide use. In a previous study, he also had found a high frequency of recombination among ataxia telangiectasia patients, among whom there is a high incidence of non-Hodgkin's lymphoma. These data suggest that pesticides may cause genomic instability, which may increase the risk of lymphoma.

The EPA and the NIEHS will focus their investigation on the potential effects of agricultural chemicals on nonmalignant conditions. One strength of the prospective design, Dr. Blair noted, is that once exposures are characterized, other outcomes can be examined relatively inexpensively. He added that the two States in which the study will be conducted have not yet been selected, but this is expected to be accomplished later this month. NCI staff are working with EPA and NIEHS to develop study materials, which will be reviewed by the advisory panel within the next few months. Staff plan to begin enrollment by December of 1993.

Dr. Blair concluded by recognizing Dr. Michael Alavanja, Project Officer for NCI, Dr. Elaine Gross, EPA, and Dale Sander, NIEHS, for their work on the investigation.

Questions and Answers

Dr. Becker asked what would happen if a population of farmers began to accumulate chromosomal aberrations with a given product—would the product be proscribed and would the farmers be told? Dr. Blair explained that both subjects and certain regulatory agencies would be apprised of the findings.

Regarding the map showing leukemia incidence, Dr. Wilson commented that, perhaps, the lack of incidence in the central valley of California is due to the fact that migrant workers do much of the farming in that area. Dr. Blair agreed and added that the central valley of California is more urban, overall, than areas such as Kansas.

Dr. Day asked how the study will handle the issues of prior dosage and the damaging effects of certain materials over time. Dr. Blair explained that subjects will be interviewed about their entire farming careers and that the combination of interview information and monitoring will help indicate past exposures.

Dr. Salmon asked whether the study team has considered using a control group of organic farmers. Dr. Blair answered that this issue has been discussed, but no decision has

been made. He added that practicality and cost are the main considerations and are being investigated.

Dr. Chan asked if the research team has any data to compare the incidence of cancers in the U.S. with other countries. Dr. Blair stated that farmers in most developed countries tend to experience excesses for certain tumors.

Dr. Bettinghaus asked if the study will be able to sort out the use of different pesticides by different kinds of people. Dr. Blair answered that the study cannot look at every pesticide, but can focus on the major ones. He explained that the use of pesticides depends on the type of commodity and agricultural practice being conducted, and that most farming operations use only a few products year after year. It should be possible, therefore, to sort out the information on the major pesticides.

Dr. Calabresi thanked Dr. Adamson for presenting a wonderful program and providing a terrific overview. He then announced the locations for the Subcommittee on Interactions With Voluntary Organizations and the Subcommittee on Cancer Centers and invited new members to attend both meetings and to consider joining one of the subcommittees. He then adjourned the meeting for the day.

XI. DIVISION OF CANCER PREVENTION AND CONTROL PROGRAM REVIEW

Overview of the DCPC Cancer Prevention and Control Program—Dr. Peter Greenwald

Dr. Greenwald explained that his presentation would provide an overview of the Diet and Cancer Early Detection Program administered by the Division of Cancer Prevention and Control, after which Dr. Alfred Haynes, Chairman of the Division's Board of Scientific Counselors, would speak about the Division's applied programs, particularly on smoking prevention research activities. The program review, he added, would continue with presentations by Dr. Otis Brawley, a Program Director with the Community Oncology Branch, on chemoprevention of prostate cancer and by Dr. James Phang, Chief of the Laboratory of Nutritional and Molecular Regulation in Frederick, on nutritional studies.

Before discussing the Diet and Cancer Program, Dr. Greenwald offered some observations about the chemoprevention program, which has developed nine "second generation" agents that are being examined in small human studies but are not yet in Phase III clinical trials. Examples include DFMO, an ornithine decarboxylase inhibitor that has demonstrated chemopreventive activity against rat mammary and colon tumors; oltipraz, a schistosomiasis drug that has demonstrated *in vivo* chemopreventive activity; and several nonsteroidal anti-inflammatory drugs that inhibit prostaglandin synthesis.

A major concern in chemoprevention is the limited number of possible Phase III trials because of their size, the time required, and high costs. These issues have been discussed in

the Executive Committee and will be discussed further with the Board of Scientific Counselors.

Presenting a slide depicting schematically the strategic plan of the Diet and Cancer Program, Dr. Greenwald noted that, as with much of NCI-sponsored research, the program begins with basic research. A subcommittee of the Board of Scientific Counselors recently emphasized the need for basic research on metabolic effectors of dietary origin and for studies of the interaction between diet and drugs, hormones, and metabolites.

The next part of the scheme, Dr. Greenwald continued, is preclinical research. The Division has funded three clinical nutrition research units, which are essentially P01 grants that work both in the preclinical and clinical areas, at UCLA, the University of Alabama, and Memorial Sloan-Kettering. The program has also issued several Requests for Applications, including one now in its third year on blood and tissue micronutrient levels; an RFA on biomarkers of dietary fat for which applications are due on January 26th, 1993; and a new RFA approved in October 1992 on diet and steroid hormone metabolism.

Dr. Greenwald presented two examples of epidemiologic studies relevant to clinical trials that have been started. The first is a study of vitamin E, an antioxident that is active in the lipid phase, and breast diseases recently published by researchers at Harvard University. Results of this study suggest that vitamin E received from foods protects against breast cancer among postmenopausal women, while data on vitamin E from supplements were not clear. Dr. Greenwald added that the recommended dietary allowance of vitamin E is about 8 to 10 milligrams per day.

Dr. Greenwald's second example was a Swedish study to be published soon in the *Journal of the National Cancer Institute*, which collected data on dietary fat at the time of diagnosis in 50- to 65-year-old women with breast cancer who were estrogen receptor-positive. Those who had no treatment failure had the lowest levels of fat intake. The data suggest that diet following diagnosis for postmenopausal women may affect therapy outcome.

Moving on to clinical metabolic and marker studies on the schematic slide, Dr. Greenwald said that in addition to clinical nutrition research units working in this area, the Division has a new concept for interactive R01s for nutrition and cancer prevention; he suggested that because these are done as an RFA with a set-aside and a single review group, they will, in a way, be similar to P01 projects. Applications for these projects, he noted, are due January 19th, 1993.

Moving to clinical trials with cancer endpoints, Dr. Greenwald reviewed several trials relating to diet in women. These trials, he observed, have similar names and are sometimes confused with each other. The Harvard Women's Health Study is a clinical trial involving more than 40,000 nurses aged 45 and over. The sample, Dr. Greenwald noted, includes licensed vocational nurses, which provides a broader representation of minority women. The factorial design allows for analysis of three agents—beta-carotene, aspirin, and vitamin E—as well as the interaction among the three. The endpoints include overall epithelial cancers; breast, lung, and colon cancers; and a number of cardiovascular events.

Dr. Greenwald next described a minorities feasibility study that will later be incorporated into the NIH Women's Health Initiative. This trial, being conducted in Atlanta, Birmingham, and Miami, involves about 2,250 women who are randomized to a regular diet or to a low-fat diet that includes increased fruit, vegetables, and whole grains. The endpoints are efficacy of recruitment and adherence to the low-fat eating pattern.

This led to a description of the clinical trial part of the NIH Women's Health Initiative itself. Dr. Greenwald reported that a coordinating center in Seattle has been selected and the process of selecting 45 clinical units is underway. Enrollment is expected to begin in June 1993. In this study, which Dr. Greenwald identified as a partial factorial design, subjects will be 50- to 70-year-old women. One randomization in the trial is based on hormone regimens: estrogen replacement therapy; progesterone and estrogen; and a control group. Another randomization will be to a low-fat eating pattern or a control. There will be a group randomized to both regimens, a group randomized only to the hormones, and a group randomized only to the diet. A third randomization will involve calcium and vitamin D versus a placebo. The reason for the complexity of this design, Dr. Greenwald explained, is that "you get a lot more for your money," but the complexity makes it a difficult trial to implement.

Dr. Greenwald reported that the pilot study for the Women's Intervention/Nutrition Study (WINS) was completed and an application has been submitted to scale up the study. Postmenopausal women with early-stage breast cancer were randomized to a regular medical therapy, usually tamoxifen, or therapy plus a low-fat diet. Early results showed that the women on tamoxifen alone gained about 7 pounds, while the women on therapy and diet lost about 2 pounds. The study's objective was to determine whether this affects rates of cancer recurrence and survival.

Dr. Greenwald announced that, although these nutritional studies are still in progress, the Division feels that enough data have been collected to support the development of public recommendations. He described one such program, the *5 a Day—For Better Health* program, which started as a local program in California and has been expanded into a national effort. Its aim is to increase the consumption of fruits and vegetables to five to nine servings per day, based on epidemiologic data suggesting benefits of this diet. Within NCI, the effort is coordinated by Kay Loughrey in the Office of Cancer Communications and Jerianne Heimendinger in the DCPC. The program is a partnership with industry in which NIH is working with the Produce for Better Health Foundation, a group of more than 400 food suppliers (e.g., Sunkist, Green Giant, Ocean Spray, del Monte, Campbell's, etc.) and retailers (e.g., Safeway, Giant, Kroger, Winn-Dixie, etc.).

The program was initiated last July 1st in a ceremony attended by Dr. Louis Sullivan, Dr. Bernadine Healy, and Bruce Obend of the Produce for Better Health Foundation. In the month following this event, Dr. Greenwald reported, media messages about the program were seen 122 million times. The food industry itself spent more than $1 million during that month on advertising of fruits and vegetables. The program has been featured on major television network programs and in newspapers and magazines across the country.

Dr. Greenwald mentioned another direction within the food industry that is likely to have major long-term implications for cancer incidence—genetic modification of plants. As

an example, he showed a slide depicting a tomato, bearing the brand name "Flavr Savr," that has been genetically altered to slow down the softening process while the tomato is ripening. In a process using technology developed by the biomedical field, antisense RNA binds messenger RNA to decrease information transmitted to DNA for the protein-making ribosomes in the cells; this results in "turning down" the production of the softening enzyme called polygalacturonase. These tomatoes can thus be allowed to ripen on the vine, producing a flavor more favorable to the consumer.

Dr. Greenwald observed that most of the research on genetic alteration is aimed at making plants more resistant to disease and drought, reduce reliance on pesticides and fertilizer, and extend shelf life. He suggested the possibility that increased biomedical research in this area would generate information about health that might motivate the food industry to incorporate factors relating to good health into their genetically altered products.

As another example of developments in the food industry, Dr. Greenwald said that several years ago, as the Institute was beginning to do beta-carotene studies, he visited a citrus fruit chemistry lab in Pasadena. When he asked whether changes in the food supply could be made if beta-carotene is found to reduce cancer risk, he was told that much is already known about the chemistry of citrus fruits. The initial interest of the industry has been to alter the color of grapefruit and make other changes to influence the consumer, but as a result, Dr. Greenwald observed, knowledge is being expanded. Researchers in this lab have also discovered a way to grow lemon sections that contain juice *in vitro*.

Dr. Greenwald reminded the Board of a compound developed by the food industry called limonene, an oil from the skin of the orange that is used in soft drink flavorings. In large amounts, he stated, this compound reduces mammary tumors in rats. This kind of phenomenon underscores the importance of understanding food chemistry as well as conducting studies to determine what can be done with the information.

Dr. Greenwald reported that another important food trend is a significant rise in the production of soybeans. A number of food products are made from soybeans, including pizza toppings, hot dogs, and hamburger additives that reduce the formation of heterocyclic amines. There are also a number of compounds derived from soybeans that are of interest in cancer prevention research, including protease inhibitors such as the Bowman-Burke inhibitor that will soon be tested in chemoprevention trials; phytosterols—structures similar to cholesterol that affect bile steroid metabolism in the colon, possibly in a way that may be associated with lowered colon cancer risk; inositols—phytates that chelate ion-generated free radicals; saponins, which inhibit lipid peroxidation; and isoflavones—plant estrogens, some of which may have actions much like tamoxifen.

As a final example of changes in the food industry, Dr. Greenwald mentioned the development of fat substitutes—actually, nonabsorbable fats—such as the compound called Olestra for which Proctor and Gamble is seeking FDA approval. The structure of the fat molecule developed by Proctor and Gamble, based on a sugar molecule, prevents the hydrolization of the fatty acids, thus preventing the absorption of calories from fat. Cooking oils, baked goods, and other products could be produced containing fats that would not be absorbed.

Dr. Greenwald speculated that in the next 20 or 30 years, major changes in cancer incidence rates, in diseases such as breast, colorectal, and prostate cancers, will take place as a result of changes in the food supply. Many of the changes are driven by demographic trends that have increased reliance on precooked foods. Dr. Greenwald suggested, however, that the national level of effort in understanding the health effects of diet is very small. The fields of food science and agriculture, he stated, are not focused on health issues; more linkage is needed between leading biomedical research institutions, including NIH and NCI, to provide leadership in this area.

Dr. Greenwald turned his attention to a brief review of the Early Detection Program. Many of the leads for early detection, he said, come from broad basic research; often, the first use that is made of an advance in biology is a diagnostic or early detection test. In the DCPC, early detection work is separated into preclinical and early clinical pilot studies, early detection trials, and demonstration and application programs. Preclinical research helps bridge the gap between basic science and human applications. The key field of study in the Early Detection Program is research on biomarkers.

Dr. Greenwald reported that the Division is considering the possibility of doing early detection substudies in conjunction with large prevention trials, suggesting that the early detection substudy's value would be independent of the success or failure of the prevention study. He recalled that Dr. Becker had earlier raised the idea of merging the early detection trials of biomarkers of lung cancer with studies on the prevention of secondary lung cancers.

Dr. Greenwald described a major trial that is in its early stages—the Prostate, Lung, Colorectal, and Ovary (PLCO) Cancer Screening Trial. The aim is to randomize 148,000 men and women aged 60 to 74 into either early detection or usual care. The patient accrual phase, expected to involve 4,500 men and 4,500 women, begins in April. After 2 years the Board of Scientific Counselors will review the evaluation of the first phase and discuss whether to scale up the study and whether to modify its design. The ultimate design is to screen 37,000 for prostate cancer, with 37,000 controls, using the prostate-specific antigen (PSA) test and digital rectal examinations, with disparities resolved by transrectal ultrasound and, possibly, biopsies. Similar strategies will be used for lung, colon, and ovarian cancers.

Within a few years, Dr. Greenwald stated, the Division expects to have useful information on the specificity, sensitivity, and predictive value of the PSA test for prostate cancer and, perhaps, a better idea of how to use the test more effectively. Mortality endpoints, however, will take longer—past the year 2000—because of the timing from diagnosis to death in these cancers. Dr. Greenwald asserted that this is expected to be a very useful study.

In the demonstration and application area, Dr. Greenwald reported that NCI has recently added early detection guidelines to the Physician Data Query (PDQ) system. This is an interactive online system available through a toll-free number. Dr. Greenwald explained that the guidelines are not limited to "do it" or "don't do it," but include levels of evidence for each guideline. For example, level one includes randomized trial evidence, such as that suggesting mammography for women over the age of 50. The lowest level of evidence is the opinion of respected authorities in the absence of study data.

Questions and Answers

Dr. Calabresi, observing that the Board should "practice what we preach," suggested that fruit be served at NCAB meeting coffee breaks.

Dr. Lawrence asked how long it would take to determine whether any mortality reduction results from the intervention in the PLCO trial. Dr. Greenwald replied that the estimate is 10 to 16 years, explaining that a data monitoring committee will determine the earliest possible statistically valid mortality endpoint.

Dr. Sigal asked whether the DCPC plans to work with the FDA on developing its new initiatives in food labeling and in promoting awareness of the labeling program. Dr. Greenwald stated that the NCI has worked closely with the FDA over a long period of time and has written comments on the guidelines. He speculated that the FDA has plans for consumer education on the labeling program that will begin after the program is in place. Dr. Greenwald added that NCI has also worked closely with the Department of Agriculture on its new food pyramid, predicting that there will be broad efforts across HHS to promote it.

Dr. Enrico Mihich (a former NCAB member) referred back to a slide Dr. Greenwald used to present information on the Swedish study on dietary fat and breast cancer, calling attention to the fact that there were small differences in fat intake (36, 37, and 40 percent) among the study groups. He asked how large the sample would have to be to attribute significance to these kinds of differences. Dr. Greenwald answered that for the Women's Intervention/Nutrition Study (WINS), which is designed to test that question, the sample size is 2,000.

Presentation on the DCPC Cancer Control Science Program (CCSP)—Dr. Albert Haynes

Dr. Haynes, Chairman of the DCPC Board of Scientific Counselors, began by observing that the highest priority in cancer prevention research is finding efficacious methods of preventing the occurrence of the major forms of cancer and finding methods of detecting disease early enough to make a significant difference in outcome. The real benefit accrues to the public, he added, only when these advances are successfully applied in the general population. This is the challenge of cancer control science.

The goal of the Cancer Control Science Program, Dr. Haynes continued, is to find the most effective ways to apply scientifically proven strategies to the reduction of cancer risk, incidence, morbidity, and mortality. Its research concern is not efficacy but effectiveness. On one hand, cancer control science must resist pressure to promote unproved strategies; on the other hand, it must try to close the gap between what scientists have proven to be effective and what the public practices. Cancer control research is conducted not under ideal conditions but in the real world of public health agencies, public and private providers, community coalitions, and both general and special populations.

Dr. Haynes stated that the largest effort of the Cancer Control Science Program has been focused on smoking and tobacco control, because it is known that many cancer deaths

could be prevented if smoking could be reduced—smoking cessation and prevention offer the single greatest potential for the reduction of cancer mortality. The COMMIT program, the largest smoking intervention trial in the world, directly involves about 2 million people. This program is testing whether a community-based intervention protocol can help meet the Institute's year 2000 goal of reducing the prevalence of smoking. The trial will end in 1994.

The follow-up demonstration project—the American Stop Smoking Intervention Study (ASSIST)—is being planned; its intervention phase is expected to begin later next year. This program, which is expected to reach 90 million Americans, is a collaborative effort among the NCI, the American Cancer Society, State and local health departments, and other organizations. Its objective is to develop comprehensive tobacco control programs in 17 States.

Dr. Haynes noted that at the last meeting of the DCPC Board of Scientific Counselors, a member expressed concern about future funding for the ASSIST program. The Board passed a motion recommending that the ASSIST program not be subjected to a disproportionate adjustment from its projected budget requirements. Dr. Haynes stated that this motion reflected concerns about the credibility of NCI in relationship to its collaborators and a desire to avoid any slowing of the ASSIST effort.

The Cancer Control Science Program, Dr. Haynes continued, also works with State and local health departments to support application research to ensure that strategies that have been shown to be efficacious become the standard of practice. To capitalize on the many contacts the general public has with physicians and dentists, for example, the program has supported smoking cessation research by these practitioners and focused on training them in the most effective strategies.

The program has supported several research activities in underserved populations, specifically the African American, Hispanic, and Native American groups. These studies have focused on primary and secondary prevention of cancers of the lung, breast, and cervix. Dr. Haynes added that there are three major leadership initiatives seeking the involvement of these communities in the effort to increase awareness and use known strategies to reduce cancer in their respective populations. The initiative in the African American community, he noted, was developed by the NCAB to involve business, civic, religious, and lay leaders in the development of cancer prevention coalitions. The success of this effort has led to similar initiatives in the Hispanic and Appalachian communities.

Dr. Haynes mentioned the Science Enrichment Program, which was begun by the DCPC and this year was expanded and decentralized through the participation of other Institutes. This program is expected to be a stimulus to disadvantaged youth to pursue scientific careers.

Introducing a brief discussion of program results, Dr. Haynes expressed his belief that the Division should make much greater efforts to make the results of its funded research more widely available to the public. He suggested that some of the frustration expressed by the National Breast Cancer Coalition during this meeting reflects inadequate communication of the research being conducted.

In the case of tobacco control, Dr. Haynes stated that the Institute is fortunate to have a set of indicators defined by the national plan for the year 2000, including several specific objectives: reducing smoking; reducing the initiation of smoking by children and youth; increasing the proportion of smokers who stop smoking; reducing smoking during pregnancy; slowing the increase in lung cancer deaths; promoting nonsmoking workplace policies; and increasing State plans to reduce tobacco use. In some cases progress has been made, Dr. Haynes reported, but data are not always available to determine whether targets will be met by the year 2000.

The prevalence of cigarette smoking has declined in most segments of the population from 29 to 26 percent between 1987 and 1990. This trend indicates that the rate will be reduced to between 20 and 22 percent by the year 2000. The aim of the ASSIST program is to lower the target to 15 percent. Dr. Haynes pointed out the interesting fact that daily smoking among African American youth in high school is significantly lower than among Whites. He also noted that the rate of increase in lung cancer deaths has slowed—the male mortality rate declined in 1989 but the female rate continues to rise—but is not likely to meet the year 2000 target.

Dr. Haynes observed that the ASSIST program is often misinterpreted as an initiative that, by itself, will reduce smoking by 43 percent in the target States. The 43 percent reduction, he explained, is the reduction required to meet the year 2000 target, and is expected to be the result of both the ASSIST program and the declines during the past several years. While there has been some concern that the program cannot be implemented in all 50 States, Dr. Haynes said that it is reasonable to expect that many public and private agencies will participate in this effort once the effectiveness of the variety of approaches involved has been demonstrated.

Dr. Haynes closed by acknowledging that DCPC cannot assume total responsibility nor total credit for the reduction in smoking prevalence but must always remain in the forefront of cancer control science.

Questions and Answers

Before opening the floor to questions, Dr. Greenwald said that because of a number of questions that have been raised about the ASSIST program, he would make some comments about the budget. He also suggested that, later, Ms. Brown might want to comment on the issue of minority accrual to the breast cancer prevention trial.

Dr. Greenwald stated that the fiscal year 1992 budget for cancer control was $107 million. The figure for 1993, which has not been confirmed by NIH, is $105 million. This represents a $2 million reduction in the line item that covers the ASSIST program. During this period of change, the largest increase in any prevention and control effort was in the ASSIST program, which was increased by about $11 million.

Dr. Greenwald declared that there is no disproportionate reduction in the ASSIST budget. He explained that the actual budget for all NCI activities, including prevention and control, is lower than the amount that was requested in the professional needs, or bypass,

budget. He also noted that, with the exception of the large prevention trials, the largest single priority in the prevention and control effort is smoking prevention, which accounts for $20.7 million of the prevention and control budget; he added that the ASSIST program accounts for $18.2 million of that allocation.

Dr. Calabresi asked whether a commitment was made to a higher level for ASSIST and then reduced. Dr. Greenwald replied that there was not a commitment but, rather, an aim to fund the program at a higher level; he said that, in meetings and in their contracts, the participants had been made aware that the level of funding would depend on the availability of funds. When concepts are brought before the Board of Scientific Counselors, he explained, the Division asks for authority to use the entire estimated budget for the project if that amount is available. In this case, budget projections were made through 1997, although the Division did not actually know its fiscal year 1993 appropriations yet. He repeated that the NCI did not promise a specific level, but asked for that level in its budget request and clearly told the investigators how the budgeting process works.

The initial proposal for ASSIST, Dr. Greenwald continued, was based on findings from a number of specific intervention trials, but findings from the COMMIT trial, which is a community intervention trial, were not available. In that trial, 22 communities are randomized to examine the effects of an intensive smoking prevention and cessation effort. It was assumed that the evaluation from that trial would be complete this spring and would be instrumental in making a judgment about the level of funding for ASSIST. Dr. Greenwald said that the evaluation results will not be available until a year from January.

Although COMMIT and ASSIST are different programs with different aims, Dr. Greenwald stated that there is some linkage between the two that might affect expectations about how successful ASSIST will be. He said that information from the evaluation of COMMIT may influence decisions on whether to scale up the ASSIST program later, and added that there are options for extending ASSIST in 1997 or 1998 rather than building it up at this time.

Dr. Greenwald concluded that he considers the ASSIST program to be a high-priority project with a good budget and feels that the process was conducted with clear communication with the participants. He cautioned, however, that if the projected budget of $105 million for cancer control in fiscal year 1993 is further reduced, the distribution of the budget will have to be reexamined, including ASSIST.

Dr. Bettinghaus called the attention of the Board to a letter sent to Dr. Broder by the advisory committee, which he chairs, that oversees the ASSIST program. He stated that Dr. Greenwald's account of the budget process is not understood by all members of the ASSIST program, particularly the coordination committee. Part of the concern, he said, is how the money is being spent within the trial itself. The planning of the program was based on a total budget of $22 million, of which about $18 million was to be spent on the intervention and the remainder on the coordinating center and on evaluation. The actual budget represents a reduction for the intervention sites alone, since the coordinating center's allocation was not reduced. The reduction of funds for the intervention from $18.5 million to $14.5 million, Dr. Bettinghaus noted, is a 22 percent reduction, although at the coordinating committee meeting

there was no proposal to reduce the overall goal of the program—that is, trying to achieve a 43 percent reduction in smoking.

Dr. Bettinghaus suggested that the increase in ASSIST cited by Dr. Greenwald is misleading, since the current phase is a planning phase with a budget of $7.6 million with no intervention activity other than the formation of coalitions. A dramatic increase, he said, is expected in any trial that is moving into patient accrual. States involved in ASSIST are now faced with the problem of how to cut their budgets; they are forced to make difficult decisions on whether to reduce direct intervention services, limit media expenses, postpone hiring specialists to work in minority communities, or curtail other activities. The fact that the original funding level for ASSIST was announced by Secretary Sullivan, Dr. Bettinghaus commented, solidified the belief on the part of the States that the final budget was not a failure to upscale as far as desired but an actual downscaling of what had been planned.

Dr. Bettinghaus suggested that the combined political efforts of State public health departments, the American Cancer Society, and other groups, especially in the context of the transition to a new administration, may result in the restoration of this budget. Acknowledging the difficulty of Dr. Greenwald's position, he said that the ideal solution would be to find several million dollars between now and October 1, 1993. Other options might include allowing some carry-over of funds by States if they are able to reduce their planning efforts and the extension of the program by 1 or 2 years as suggested by Dr. Greenwald, although this might be difficult to justify in light of the goal to meet a year 2000 target.

Dr. Bettinghaus emphasized the fact that the investigators involved in the ASSIST program, as well as the scientific advisory committee, feel that this is a significant reduction that will have a major impact on the trial itself. He added a concern that, in spite of the large amount of money being put into tobacco research, there are only three mentions of tobacco in the executive summary of the bypass budget.

Dr. Greenwald offered two comments. He stated that the $20.7 million tobacco research figure he had mentioned was within the cancer control budget; there are other NCI resources, he said, going towards tobacco research, such as carcinogenesis work. He said that the Division would be willing to have the scientific advisory committee look at all the details of the distribution of the $18.5 million allocation for the ASSIST program; he stressed the need for a rigorous evaluation, but stated that the exact allocation of funds within the program is not fixed. He said that the idea of carry-overs and extensions is something to consider, but added that the Institute's experience suggests that each grantee must be looked at individually to see what they have accomplished and how the funds would be used.

Dr. Bettinghaus suggested that the scientific advisory committee would agree, but expressed understanding for the problem faced by the States that are being asked to do the planned level of effort with significantly fewer dollars. He suggested that it would not be possible to reach the program's goal under these circumstances.

Dr. Lawrence, speaking on behalf of the American Cancer Society (ACS), stated that the perception of the ACS and its representatives in outlying units was that Dr. Sullivan had made a commitment to this program; he said that Dr. Greenwald's factual explanation is

perceived by those in the field as "sleight of hand"; the participants in the program, he added, feel that they have been let down. Dr. Lawrence also observed that this program, as a demonstration project designed to translate research into practice, looks like a public relations failure. He urged, for the sake of the Institute's image, that the budget be readjusted.

Dr. Greenwald suggested that it might be necessary to work with other Public Health Service agencies, the ACS, and others to consider ways to increase the involvement of the public health community as a whole. He noted that the biggest single player in the effort to reduce tobacco use has been the NCI; others such as the ACS have been involved, he acknowledged, but he suggested that the partnership has not been equal. The program, he said, is not a demonstration of scientific efficacy but a public health action, and this type of effort requires a broader coalition.

Dr. Broder agreed but noted that the Institute did make a commitment at the time of approval in 1988 for at least a tentative amount of money. Dr. Greenwald responded that there are many examples of concepts that are approved with budgets based on need so that the Institute has the authority to spend the money if it is able to get the funding.

Dr. Broder observed that this is a very complicated area and asserted that the NCI is receptive to all of the options that have been suggested. He advised against placing too much emphasis on artificial criteria such as meeting year 2000 targets; these are important goals, he acknowledged, but other initiatives have to be undertaken both on scientific grounds and to meet the expectations of the public.

Dr. Broder emphasized the fact that "the budget is everything." Affirming that the Institute has a strong commitment to the prevention and control line, Dr. Broder stated that it is important not to fragment these resources. The President's budget for prevention and control for fiscal year 1993 is $91 million, he said, which is a dramatic $15 million reduction from 1992. Dr. Broder pointed out that there are many important priorities that must be addressed within that budget.

The Institute understands the importance of tobacco-related issues and places a high priority on them, he said; however, there are some crucial cancers for which smoking plays no apparent role, including breast cancer and prostate cancer, and there are very specific Congressional mandates as well as public expectations to find new approaches to combating these diseases. Dr. Broder urged the Board to continue focusing on the National Cancer Program as a whole. He suggested that this is not the last year in which the Institute will be faced with a difficult fiscal reality.

There are several areas, Dr. Broder speculated, in which cuts could be made to provide more resources for the ASSIST program, including R01s and P01s, leadership initiatives, or the Cancer Information Service. However, he warned against reorganizing the Institute or sacrificing long-range plans based on political momentum. From a fiscal point of view, he said, it would be preferable to plan for an extension of the ASSIST program, and this would also avoid delaying other studies. He said he would find it unacceptable to delay a major study solely for the purpose of meeting a year 2000 goal.

Ms. Brown raised a question about the public relations budget and the budget for the Office of Cancer Communications. She observed that she has not seen much media attention paid to the cancer issue as it relates to minority communities. In current issues of major magazines aimed at Black audiences, she said, there is an advertisement from the tobacco companies offering a free year's supply of cigarettes to readers over the age of 21. She found this to be deplorable and added that there is no information in these magazines about the National Cancer Program or the Institute's programs that target the Black community.

Dr. Bettinghaus suggested that because the revenues from these ads is important to the publishers, it is unlikely that any information on cancer and tobacco will ever appear in their pages. Dr. Broder confirmed that a number of magazines have said that advertisers would pull their support if such stories were published. Ms. Brown suggested that the Institute could counter this through other media that are not allowed to use tobacco advertising.

Dr. Broder noted that, unlike the situation with other preventive approaches, there is no longer any scientific ambiguity about the fact that smoking causes multiple cancers as well as a number of other diseases. The public health issues are clear. He agreed that more could be done to reach out to the African American community, but suggested that the financial interests arrayed in favor of smoking are formidable and reach to all levels of government.

Dr. Haynes called attention to efforts by the National Black Leadership Initiative on Cancer (NBLIC). Ms. Brown reported that she has visited every NBLIC region this year and discovered a lack of support and resources. She argued that the Institute cannot rely on the resources of the National Black Leadership Initiative to take on the challenge of reaching the Black community alone. The Institute, she urged, must find a way to include the African American community in all of its outreach activities. Ms. Brown also highlighted the lack of minority representation in the public relations firms that do most of the Institute's outreach work.

Dr. Wilson asked for Dr. Greenwald's comment on the idea that the effect of large expenditures on smoking cessation among the educated component of the population might be trivial compared with the substantial effect that could be achieved through prevention efforts aimed at young people. Dr. Bettinghaus pointed out that ASSIST is a prevention, not a cessation, trial. Dr. Greenwald stated that there is a lot of effort targeting people at high risk for smoking, including minorities and underserved populations. He continued by suggesting that the appointment of a new Surgeon General who has served as health commissioner in the State of Arkansas, Dr. Jocelyn Elders, might help in communication with the new administration.

Dr. Van Nevel said that Ms. Brown raised an important problem, and stated that the Office of Cancer Communication has made efforts to link its programs with those of the NBLIC. He said he could not report the total amount spent on minority programs because it is found in different portions of the budget; in support contracts it is approximately $350,000. He added that the Cancer Information Service has several special outreach efforts aimed at African Americans, as well as targeted publications. Many of the program's efforts in the past have centered around National Minority Cancer Awareness Week in April; in the future, the approach will be a more continuous, year-long effort. Many of the programs targeting African

Americans, Dr. Van Nevel said, have focused on breast cancer rather than smoking. He expressed interest in meeting with Ms. Brown to discuss better coordination between NCI and the NBLIC.

Dr. Salmon suggested that if cuts in the ASSIST have to be made, some effort should be made to coordinate the cuts across all elements of the program. It does not look good from the perspective of those in the field, he said, if any elements, such as the coordinating center, are not reduced. He also asked whether the National Heart, Lung, and Blood Institute (NHLBI) is making any contribution to the tobacco problem.

Dr. Broder stated that the NCI is proud of its role as the lead agency on this issue and pointed out that the Institute has played an historic role in initiating antismoking programs. He said that other NIH Institutes do not play a large role in these efforts, but noted that the Office of Smoking and Health in the Centers for Disease Control could possibly play such a role. Dr. Salmon asked whether other agencies have been formally asked to participate, and Dr. Greenwald replied that other agencies have been invited.

Dr. Salmon suggested that the Board consider making a recommendation to the Congress that a significant increase be made in the tax on cigarettes and that revenues from this increase should be used to help resolve issues related to tobacco and health, including the ASSIST program. Dr. Calabresi interjected that Mrs. Bynum said that such a resolution was passed 5 years ago. Dr. Salmon asked that a resolution be drafted immediately so that it can be presented in a timely manner to the new Congress. Dr. Bettinghaus seconded the motion and noted that the timing will appropriately coincide with the requests for the second round of funding for ASSIST.

Dr. Lawrence reemphasized his earlier point that ASSIST participants in the field have not been receptive to the claim that there was not really a reduction in the budget. He said that they would rather hear a more practical response to their concerns. Dr. Greenwald repeated that the budget is less than the amount in the bypass budget, but not disproportionately less.

Dr. Broder asked for comments on the proposal to let ASSIST go into 1998 with a prorated extension, recognizing that there is no promissory note offered today. Dr. Bettinghaus said that an extension, among other things, could be appropriate. He observed that something that happens 5 years away may seem like forever to those working in the field. He added that some of the grantees were not able to spend all of their planning funds, in part because contracts were awarded at the last minute. Some may have assumed that the funds would carry over as with block grants, but because they were NCI contract funds they did not, and thus some planning funds were lost. He suggested that they could make some savings in planning activities this year if they could be assured that planning funds could be carried over into the next year. This, along with an extension of a year, might make it possible to meet the program's goals.

Dr. Bettinghaus said that guidance from staff will be needed on what kinds of target audiences should be retained and which should be cut in light of the 22 percent reduction. He suggested that it might be advisable to place much of the program's emphasis on working with

high-risk audiences. Dr. Bettinghaus closed by suggesting that meetings be held with the ACS to try to recover the credibility of this partnership.

Dr. Adamson said that Dr. Salmon's resolution on the cigarette tax is very important; a number of studies, he noted, have shown that the price of cigarettes affects both initiation and cessation of smoking. He suggested getting voluntary organizations involved in the effort to increase the tax on cigarettes; it could be used, he added, both for deficit reduction and for research on tobacco-related health problems.

Dr. Lawrence observed that a tax increase is one way to reach populations, including the underprivileged and the young, for whom education is not effective.

Dr. Sigal also commended Dr. Salmon's proposal. She said that Congress can be receptive to ideas on how to pay for needed assistance, but added that there would be a great deal of opposition from the tobacco lobby and legislators from certain States. She also urged that in lobbying for funds, it is important to make sure that the funds are earmarked for the specific issues for which they are intended.

Dr. Calabresi announced that there would be a brief break before proceeding.

XII. PROSTATE CANCER PREVENTION TRIAL—DR. OTIS BRAWLEY

Dr. Greenwald introduced Dr. Otis Brawley to discuss the background of the prostate cancer prevention trial at NCI. Dr. Brawley has been in charge of planning this large prevention trial during the past year and a half.

Dr. Brawley began his presentation by explaining that, although the Institute supports research on prostate cancer therapy, there is currently no cure for metastatic prostate cancer. Screening through digital rectal examination and PSA provides reliable diagnosis, but the NCI has not established that this type of screening decreases mortality relative to prostate cancer. The Division's prostate, lung, colon, and ovarian cancer trial is examining the question of whether PSA screening and digital rectal examinations actually decrease mortality.

The other option, Dr. Brawley stated, is primary prevention. He reported that both the Surveillance, Epidemiology, and End Results (SEER) program and the American Cancer Society estimate that 130,000 men will be diagnosed with prostate cancer in 1993. Dr. Brawley pointed out that prostate cancer is the second leading diagnosed lethal cancer in men, the fourth leading cause of cancer-related mortality overall, and the second leading cause of cancer-related deaths among men in the United States—35,000 deaths are estimated for this year.

Dr. Brawley noted that little is known about prostate cancer etiology. It was first thought that the prostate cancer prevention project should be modeled after the breast cancer prevention trial that utilized the GALE model, which looks at epidemiology and risk factors. However, too little information is available on prostate cancer to construct a GALE model for

prostate cancer risk at this time. Dr. Brawley mentioned that the prevalence of incidentally diagnosed prostate cancer in men who die of other causes is at least 30 percent.

Dr. Brawley reported that recent data from Wayne State University point to evidence that prostate cancer starts at an early age. As a result of close sectioning of the prostate, it was found that approximately 40 percent of men in their 40s who died from trauma had evidence of small prostatic cancerous tumors. Other pathologies such as adenomatous atypical hyperplasia and prostatic intraepithelial neoplasia were also found.

The incidence of clinically diagnosed prostate cancer increases dramatically with age—in fact, the greatest risk factor for the diagnosis of prostate cancer in the U.S. is increasing age. Other risk factors include Black race and heredity. The risk of diagnosis among Black men is 9.6 percent, compared with 5.2 percent risk among White men. There is some evidence that men whose brothers or fathers had prostate cancer have a two to three times greater risk than the general population, and men who have multiple relatives with prostate cancer may have up to six times the average risk.

Dr. Brawley next addressed the role of androgens in prostate cancer and prostate cancer etiology. One of the key tenets of the prostate cancer prevention trial is the fact that prolonged stimulation of the prostate with androgen leads to prostate cancer. If this stimulation can be decreased over time, Dr. Brawley noted, the incidence of prostate cancer can be decreased. Prostate cancer is very rare among men who are castrated and men who have congenital deficiencies of androgen synthesis. Serum androgen levels or activity, called androgenic power, correlate among populations in terms of prostate cancer risk. In the 1940s, Huggins and Hodges found that removal of the testes frequently led to tumor progression in men who had frank prostate cancer.

Dr. Brawley specified that androgens promote prostate cell proliferation, promote prostate cancer cell proliferation, and inhibit prostate cancer cell death in the normal prostate. Dihydrotestosterone (DHT) is the predominant androgen within the prostate. Testosterone secretes into the prostate and is converted to DHT—10 times more powerful an androgen than testosterone—by an enzyme called 5-alpha reductase, which acts as a biologic amplifier. People who have clinical 5-alpha reductase deficiencies generally do not develop prostates; if they receive DHT injections, however, they develop prostates. Since DHT exists only in the skin and the prostate, it is possible to block the synthesis of DHT and cause little or no systemic toxicity. Men who are treated for prostate cancer with orchiectomy or androgen blocking drugs often develop gynecomastia, impotence, and problems with bone mineralization. Individuals who undergo 5-alpha reductase blockade do not have these problems. Dr. Brawley reported that three 5-alpha reductase inhibitors will enter clinical trials and at least 12 additional 5-alpha reductase inhibitors have been used in laboratory tests.

Prostate cancer is an androgen-dependent disease, but prostate cancer cells lose their androgenic sensitivities as the disease progresses from a normal to more cancerous state. Dr. Brawley emphasized that there is only one androgen receptor, responsive to both DHT and testosterone, in the prostate cancer cell. He described how finasteride, a drug that can block DHT, looks chemically similar to testosterone and works as a competitive inhibitor. 5-alpha reductase binds to finasteride, so it cannot convert testosterone to DHT. This drug causes a

slight rise in the level of testosterone, but elicits an overall decrease in androgenic stimulation in both animals and humans.

Dr. Brawley added that a drug does not need to kill cells to be an effective cancer preventative agent, but must inhibit cancer initiation or promotion. 5-alpha reductase inhibitors do kill off cancer in the laboratory and show mild activity in metastatic undifferentiated prostate cancer.

Dr. Brawley presented slides of *in vitro* growth curves using PC3, one of the few human prostate cancer cell lines available in the laboratory. He related that PC3 is a mildly androgen-responsive cell line, and its growth rate decreases with increased doses of finasteride.

Currently, Smith, Kline, and French have a drug called Epristeride, also a 5-alpha reductase inhibitor, in Phase II testing. Dr. Brawley presented a slide of PC82, the other human cancer cell line, being tested in castrated mice and mice treated with Epristeride. This drug also had some activity against prostate cancer cell lines.

Dr. Brawley reported that finasteride has been approved by the U.S. Food and Drug Administration as treatment for benign prostatic hyperplasia (BPH). He presented data gathered during the past 5 years from studies of more than 4,000 men who were given either finasteride or finasteride and a placebo. Dr. Brawley noted that finasteride causes a 70 to 80 percent decrease in serum DHT and a 95 percent decrease in intraprostatic DHT. It causes a 10 percent increase in serum testosterone and a 40 to 50 percent decrease in serum PSA. Most importantly, it causes a decrease in prostate volume and an increase in urinary flow among men with benign prostatic hyperplasia.

In randomized clinical trials in which 555 men received a placebo and 543 men received 5 milligrams of finasteride, the number of adverse experiences was equal. Patient-reported side effects were less than 1 percent. Statistically significant patient-reported problems in sexual function were decreased ejaculate volume and impotence. Dr. Brawley remarked that finasteride is a safe drug that is tolerated well with prolonged use and decreases androgenic stimulation of prostate cells and, therefore, shows evidence of being a successful prostate cancer prevention drug.

The hypothesis of the prostate cancer prevention trial is that DHT is an important promoter of malignant prostatic growth. Pharmacologic inhibition of 5-alpha reductase will result in a decrease in promoter influences, and prolonged DHT reduction will result in a decreased incidence of prostate cancer. All possible clinical trials have been conducted to test this hypothesis, except for a large randomized trial. A large randomized trial is needed to identify intermediate markers and intermediate endpoints and to determine whether finasteride will prevent prostate cancer. The trial would involve 18,000 men in their 50s, 60s, and, perhaps, early 70s. Such a broad sample of histories and biopsies would provide the opportunity to learn about BPH and the treatment power of finasteride. It would also be an opportunity to test for additional side effects of 5-alpha reductase inhibitors in a controlled clinical setting. The drugs have proven to be safe when administered to 4,000 men over a period of 3 to 4 years.

A randomized clinical trial, Dr. Brawley continued, would reveal information about prostate biology and epidemiology. At this time, oncologists have the ability to diagnose prostate cancer, but they cannot determine the significance of many prostate cancers or predict whether the patient should or should not be treated. The trial has a prostate cancer screening component, which will provide insight into PSA delta.

Dr. Brawley concluded his presentation by stating that the randomized clinical trial would encourage several ancillary studies and foster research regarding quality of life issues in the aging male.

Questions and Answers

Dr. Becker asked how many men are taking the agent prescribed for the presence of BPH and whether they will continue to take the drug. Dr. Brawley did not have an exact number, but explained that the drug was approved in the United States in July of 1992, and has since been approved in 23 countries in Western Europe and the Middle East. The current FDA insert suggests that a patient be treated for 6 to 12 months, after which time the patient and physician should determine whether there has been improvement. If improvement has occurred, the patient should continue to take the drug indefinitely.

Dr. Becker questioned whether a controlled trial is necessary, suggesting that it might be possible, instead, to follow large numbers of men who continue to maintain prostate reduction with finasteride. Dr. Brawley answered that a controlled randomized trial is needed to ascertain the sorts of differences that the Institute wants to study. Dr. Greenwald expressed agreement with Dr. Brawley on the need for a controlled clinical trial. He reminded the Board that widespread use of hormonal replacement therapy was adopted in the early 1960s without a clinical trial. As a result, no one knows who the best candidates are for this treatment, during what interval, and at what age. Dr. Greenwald added that a window period of about 4 or 5 years now exists in which to study the best design for prostate cancer prevention.

Dr. Correa shared Dr. Greenwald's support of a controlled trial and asked about the age and race breakdown of the trial and whether DHT in the drug will be measured. Dr. Brawley answered that cooperative groups are constructing the proposal, so exact age groups are unknown, but he expressed hope that men aged 55 to late 60s or early 70s will be included. He said that approximately 15 to 20 percent of patients will be Black, representing the proportion of Blacks in the U.S. population. Dr. Correa stressed that the sample should include a majority of Blacks because prostate cancer rates are higher in this population. Dr. Greenwald said that an effort will be made, but it will be difficult to achieve logistically. Dr. Brawley stated that he has no objection to overrepresentation of Blacks in the trial, but added that he feels a Black majority would be a problem.

Dr. Bragg followed up Dr. Becker's concern that pharmaceutical companies' financial participation should be encouraged in the trial. Dr. Brawley explained that Merck has agreed to provide enough drug and placebo for a trial of up to 20,000 men, provide this drug to the participants for up to 10 years, and pay for the distribution of the drug.

Dr. Bragg asked whether, perhaps, Proscar is targeted at the wrong age groups, in light of Dr. Henderson's analogy that hormonal stimulation responsible for breast cancer is triggered at an early age. Dr. Brawley answered that Dr. Bragg is correct theoretically. Many individuals think of the drug as a chemoretardive agent rather than a chemopreventive agent. Dr. Brawley affirmed that the ideal trial would include men in their 20s and 30s, who would be followed up until later life; however, this type of trial would be expensive and take about 50 years to complete. Dr. Greenwald commented that although he agrees with Dr. Henderson's discussion on lifelong breast cancer risk, many factors occurring later in life also affect risk. He also stressed that a rise in incidence relative to age begins much earlier in breast cancer than in prostate cancer.

Ms. Brown expressed her concern about obtaining a representative sample of Black men in the trial. She stated that it will be difficult to attract the desired number of subjects for the same reasons it was difficult to reach Black women for inclusion in the tamoxifen trial—frightening information provided during initial outreach and myths about side effects. In order to increase participation, Ms. Brown recommended disseminating information prior to the trial from a public relations perspective. Dr. Brawley asserted that there is an obligation to make clinical trials and information about them available to everyone. He added that every individual has the right to decide if he or she wants to participate in a trial and should not be overly recruited.

Dr. Salmon stated his concern that the duration of the trial's follow-up has been underestimated. He asked whether finasteride in men with metastatic prostate cancer has been studied through the Division of Cancer Treatment or elsewhere and whether finasteride has been used as an adjuvant to radiotherapy. Dr. Brawley clarified that although this is a 10-year study, cooperative groups follow patients until death. Dr. Salmon remarked that the trial will have longer-term budgetary implications. Dr. Brawley affirmed his statement and went on to explain that there is evidence of extremely mild activity for finasteride in widely metastatic cancer. The drug has not been tested as an adjuvant.

Dr. Calabresi asked if PSA still is used as a screening tool. Dr. Brawley answered that the drugs used in the randomized trial all interfere with PSA, and many people are advocating for PSA screening. It is possible that finasteride increases the sensitivity of PSA as a screening test. Finasteride drives down the PSA secreted from BPH. Individuals on both arms of the trial who have higher PSAs will be biopsied and evaluated for prostate cancer.

Dr. Becker expressed his concern that finasteride will mask elevations of PSA that would be diagnostic for the presence of cancer. Dr. Calabresi shared Dr. Becker's concern. Dr. Broder emphasized that a well-controlled randomized clinical trial is needed to resolve many of the questions raised in this meeting and to avoid the risk of changing the demographics of PSA testing. A controlled trial is a way of providing a scientific foundation for the debate. Dr. Becker suggested that since PSA and digital examination comprise the two arms of diagnosis, perhaps one arm could be substituted with ultrasound examination to provide another modality for testing.

Dr. Correa asked if there might be a lack of Black subjects because the sample is limited to CCOP. Dr. Brawley explained that the sample will not be limited to CCOP,

although a majority of patients will be recruited under CCOP. A large percentage of minority patients accrued to clinical trials come from university hospitals. There is also the question, he continued, of whether healthy minority patients will be interested in a trial to try to maintain their health. This issue will require different approaches and understanding on the part of researchers.

XIII. LABORATORY OF NUTRITIONAL AND MOLECULAR REGULATION: UPDATE—DR. JAMES MING PHANG

Dr. Phang presented an overview of the activities of the Laboratory of Nutritional and Molecular Regulation (LNMR), Division of Cancer Prevention and Control, NCI. The conjunction of high-tech methodologies, breakthroughs in basic cancer biology, and epidemiological findings in human populations, he said, presents a scientific opportunity to formulate novel paradigms linking dietary factors, nutrition, and cancer prevention.

The LNMR is composed of a multidisciplinary group of scientists, including cancer biologists, biochemists, molecular biologists, and nutritional scientists. It was determined that the LNMR would conduct research in basic science relevant to nutrition and cancer, emphasizing the basic mechanisms by which nutrients directly or indirectly augment or inhibit tumorigenesis. These studies may lead to an understanding of the molecular mechanisms underlying known associations between diet and cancer by elucidating complex interactions between various nutrients and dietary factors.

The strategy, Dr. Phang emphasized, is to take the leads from epidemiology, clinical nutrition, endocrinology, metabolism, clinical oncology, and animal studies, and to translate them into physiologic paradigms that can be attacked by studies using molecular methodologies.

Dr. Phang then presented a few examples of the LNMR's activities. He began with the study of retinoids. Retinoic acid and 4-hydroxyphenyl retinamide (4-HPR) are used in clinical trials for cancer prevention in the aeroesophageal tract and breast. The effects of these agents on the metabolism of vitamin A remains largely unknown. Therefore, retinoid metabolism in animals was studied, emphasizing the effects of nutriture and synthetic retinoids on vitamin A metabolism.

Dr. Phang said that their approach was to use biochemical assay methodologies for various tissues in combination with radioretinol kinetics. With this methodology, he said, they were able to describe vitamin A metabolism as a dynamic entity. Studies showed plasma retinol was markedly decreased with administration of 4-HPR. However, the levels of retinol and its metabolites were essentially unchanged in the kidney, lung, and liver. The reason for this, Dr. Phang said, elucidated by radioretinol kinetics, is that retinol from the plasma pool is very rapidly recycled to the tissues. The recycling rate almost quadrupled in the presence of 4-HPR. Although markedly decreased plasma retinol levels were associated with 4-HPR administration, tissue levels were not affected by 4-HPR when vitamin intake was adequate. The development of methodologies to perform kinetic studies in humans using stable isotopes may be important for clinical chemoprevention studies with retinoids, he concluded.

Moving to another topic, Dr. Phang stated that steroid sex hormones play a critical role in cancer of the breast, endometrium, and prostate. Although diet may influence hormone production and circulating hormone levels, he said, their focus was on the target tissues of these hormones and on the possibility that dietary factors may have hormone-like activity. Alternatively, dietary factors can modulate the effects of endogenous hormones at the tissue level. Therefore, a project was initiated emphasizing the identification and characterization of hormone-like factors from dietary sources using the expression of pS2, a protein which is responsive to estrogen in mammary cancer cells, as a screening assay.

Dr. Phang continued, saying that lignans, a dietary fiber, are broken down to enterodiol and enterolactone. Dr. Phang then said the question they asked themselves was, do enterolactone and nordihydroguaiaretic acid, another dietary factor, have hormone-like effects? The expression of pS2 is markedly increased when cells are treated with estradiol, nordihydroguaiaretic acid, and enterolactone. Therefore, expression of pS2 may be a useful assay to screen for hormone-like factors from dietary sources. He added that the interaction of these dietary sources with endogenous hormones is also of interest. Diet can be a source of factors with hormone-like effects, and dietary factors can alter the metabolism of hormones.

As an example, Dr. Phang stated that testosterone can be metabolized to dihydrotestosterone, the most potent androgen found in prostate cancer. These androgens can be conjugated, forming aqueous metabolites. One of the main conjugates is glucuronides catalyzed by UDP glucuronyl transferase. This enzyme can be upregulated by dietary factors.

This led, Dr. Phang said, to the question: Do prostate cancer cells metabolize testosterone and dihydrotestosterone to glucuronides? Using human prostate cancer cells, LnCAP, PC-3, and DU-145, only Ln-CAP retained androgen responsiveness. Ln-CAP and PC-3 readily metabolized testosterone. When these cells were incubated with testosterone, only Ln-CAP produced aqueous metabolites or conjugates, especially glucuronide. PC-3 produced primarily organic metabolites. Further examination revealed that only the Ln-CAP had intracellular accumulation of androgens. There was no detectable accumulation of androgens in either PC-3s or DU-145s.

Further tests showed that Ln-CAP had marked activity of UDP glucuronyl transferase, whereas, PC-3 and DU-145 did not. Ln-CAP, which are androgen-responsive cells, retained androgens intracellularly, mostly in the form of glucuronides, whereas PC-3 and DU-145, androgen-unresponsive cells, had no detectable intracellular androgens. "What are the UDP glucuronyl transferase isotypes that can be upregulated by dietary factors?" Dr. Phang asked.

Dr. Phang said they studied biological defense mechanisms versus carcinogens, emphasizing cellular resistance and membrane efflux pumps. Certain foods may contain factors that activate defense mechanisms to mitigate cellular damage or, perhaps more importantly, to decrease the cellular burden of carcinogens, Dr. Phang postulated. They hypothesized that the processing of carcinogens is in many ways parallel to that of chemotherapy drugs where there is activation, possible DNA damage, and detoxification. Tumor cells soon become resistant. It has been shown, Dr. Phang said, that there is an active efflux pump which is the main mechanism responsible for the resistance. This efflux mechanism is mediated by Pgp-170. Pgp expression, however, is also found in cells and

tissues that have not been exposed to chemotherapy drugs. Therefore, they considered that carcinogens are substrate for Pgp efflux, and that dietary factors and nutrients may be modulators of this mechanism.

The first question is, Dr. Phang said, "Does Pgp serve as a mechanism for cellular defense against chemical carcinogens." To answer this question, they used MDR cells derived from human breast cancer MCF-7 that were developed by exposure to adriamycin. Resistance to adriamycin was accompanied by increased expression of Pgp. These MDR cells also showed cross-resistance to benzopyrene and, furthermore, benzopyrene inhibited azidopine binding to Pgp. Though benzopyrene is a widely acknowledged environmental carcinogen, it generally is not considered to be a carcinogen for mammary tissue. Therefore, dimethylbenzanthracene (DMBA), a related compound that is known to be very active against breast tissue, was tested.

It was shown that DMBA is a substrate for Pgp. The efflux of DMBA was completely blocked by verapamil and quinine, two known inhibitors of Pgp function. Dr. Phang then said the next question they asked was, "Are there dietary factors that enhance cellular defense against carcinogens by augmenting the function of the Pgp-mediated efflux pump?" A wide variety of agents were screened and flavonoids, compounds found in fruits and vegetables, were shown to augment Pgp activity. As an example, Dr. Phang said that kaempferol, a flavonol widely distributed in fruits and vegetables, was very active with Pgp.

When MDR cells were incubated with DMBA, they showed accumulation. However, when 100 micromolar kaempferol was added in conjunction, there was marked reduction in the accumulation of DMBA. Kaempferol also had an effect on DMBA efflux. Thus, said Dr. Phang, certain chemical carcinogens, benzopyrene and dimethylbenzanthracene, for example, are substrates for Pgp. Pgp serves as a cellular defense mechanism against carcinogens, Dr. Phang proposed, and flavonoids are examples of dietary factors that enhance the function of Pgp.

Dr. Phang then briefly listed some other projects in the laboratory: the study of post-translational modification mechanisms of *ras* oncoproteins and its effects on translocation, regulation of farnesylation and palmitoylation by dietary factors, modulation of p53 accumulation and function by dietary factors and the role of phosphorylation, the effects of caloric restriction on carcinogenesis in p53 knockout mice, changes in cell membrane phospholipids and effects on receptor-dependent activation of phospholipase-D, effector functions and specific fatty acid effects on phospholipids; imidodipeptides, proline, and pyrroline-5-carboxlyate are being studied as diet-dependent messengers mediated by the transfer of oxidizing potential, and their interactions with collagen and matrix proteins are being studied.

Questions and Answers

Dr. Mihich asked about the effect of dietary factors on signal transduction, particularly in relation to PKC. Dr. Phang responded that those collaborative studies are being carried out, and that MDR cells have been shown to have very different levels of phospholipase-D.

XIV. WORKING GROUP ON PROGRAM PROJECT GRANTS—MRS. BARBARA BYNUM

Mrs. Bynum announced that Dr. Broder coauthored a paper on program project grant funding with Mrs. Mary Cushing, NCI Budget Officer. She explained to the Board that this paper augments some topics discussed in Dr. Broder's address at the last meeting. To see that research grant resources are used effectively and prudently, Dr. Calabresi will impanel a task force on program projects. Dr. Sam Wells will chair this panel, with other NCAB members to be named. Mrs. Bynum will serve as principal staff support to the task force, assisted by Drs. Marvin Kalt and Robert Browning. A substantial amount of preliminary data on the P01 portfolio will be available to support the task force, including an extensive written report. This report is a result of a preliminary evaluation conducted during the past year and a program project working group consisting of senior program review and grants management staff members, chaired by Dr. Kalt. The task force on program projects will address review of program project applications, ranking P01s, funding paradigms for P01s, policy issues concerning budget considerations, translational basic balance, and structuring guidelines for presentation of the instrument to the extramural community.

Mrs. Bynum next apprised the Board of an experimental interim P01 ranking procedure intended to help manage the large P01 workload. Current peer review of applications for awards in fiscal year 1992 utilize scoring procedures designed to counteract priority score compression. To avoid distinctions between the May 1993 round of P01s and fiscal year 1992 rounds of funding and to allow the P01 task force a period to brainstorm recommendations, the interim procedure introduces factors that define the program project grant in the context of overall goals of NCI, the incremental value of an application in its own field of science, the degree to which an application offers the opportunity to introduce innovative research procedures, and the anticipated cost/benefit value of a program project grant.

This experimental procedure, conducted in a "bicameral arrangement" with a balanced representation from the four divisional Boards of Scientific Counselors, will produce a rank order without modifying the score of record voted by the original Initial Review Group (IRG). Mrs. Bynum stressed that this should not be construed as a replacement for peer review. Information will be documented and resultant rankings will be provided to the Board and the Executive Committee to assist the Executive Committee and program staff in developing a funding plan for the remainder of fiscal year 1992.

Mrs. Bynum added that this is an experiment out of which individual ranking factors might be incorporated into peer review evaluation criteria in a final IRG structure. She stated that this procedure will begin with applications assigned to the May 1993 review, with the Board's approval.

Questions and Answers

Dr. Bettinghaus agreed that such a plan is necessary, but he expressed concern that there will be P01s that cut across Divisions or represent only a small operational area, such as the Frederick facility. Representation from the four divisions but not from those outside areas could likely shortchange an application that is innovative but not directly relevant to a

Division's goals. Mrs. Bynum replied that this action will happen after the peer review, thus allowing sufficient time to consider membership of the review panel. The Board will be apprised of its membership and solicited for suggestions if the needs of a particular group of P01s are not served.

Dr. Salmon proposed that a stable peer group be established to review applications, as opposed to an ad hoc group based on applications. Mrs. Bynum explained that these concerns are the reason for the "bicameral arrangement," in which the nuclear group will be representative of all the divisional programs.

Dr. Broder commented that, for the most part, the NIH system of peer review works and has a substantial amount of flexibility and creativity built into it. He continued that peer review is most successful when people are forced to prioritize among a given set of options, but problems often occur when they must give priority scores while looking at only one proposal at a time. In the latter setting, Dr. Broder contended, it is possible for peer review, unintentionally, to become a matter of making individualized funding decisions. When peer reviewers are forced to prioritize among a set of proposals, their true feelings about each proposal are more likely to surface.

Dr. Mihich reminded Dr. Broder that the NCAB endorsed ad hoc review for program planning as an experiment when he served on the Board. Perhaps, he said, the panel being proposed as an interim model will do, in a different way, what the program project grant review committee did as a second-tier review in the past—normalize the individual reports to a more compatible prioritization.

Dr. Broder asked the Board to approve this temporary interim measure to facilitate the review process, while a subcommittee of the NCAB works on a report of the larger issues of program projects. The Board unanimously approved the proposed interim measure.

Mrs. Bynum cautioned that, although this task force will consider a return to a two-tier system of parent committees, the experiment should not be considered a substitute for peer review.

XV. FREDERICK CANCER RESEARCH AND DEVELOPMENT CENTER PROGRAM REVIEW—DR. WERNER H. KIRSTEN

Dr. Kirsten began by noting that, due to the late hour, he would forgo a detailed program overview of the Frederick Cancer Research and Development Center. He referred Board members to their meeting notebooks for charts illustrating the FCRDC organizational structure; information on the intramural laboratories and other categorical Institutes of NIH housed in Frederick; descriptions of the contractors that operate the 700,000 square foot facility; the composition of the FCRDC advisory committee; and some scientific highlights of the basic research program and the technical and support contractors.

Dr. Kirsten related a story pertaining to the FCRDC AIDS vaccine development program. Approximately 10 years ago, he explained, Dr. Howard Temin began work on an

obscure alien retrovirus called spleen necrosis virus. He presented the first evidence of the site-directed mutagenesis of the protein called nuclear capsid in this virus. Dr. Temin showed that a mutation in this protein rendered the spleen necrosis virus noninfectious. In 1982 to 1983, he illustrated that the noninfectivity is due to the virus' incapability of packaging its own genomic RNA once it has left the cell. Later, Dr. Allen Ryan, a scientist in the FCRDC basic research program, showed that a similar nuclear capsid mutation could be induced in Maloney leukemia virus. Then, Dr. Kirsten said, when he himself joined the FCRDC 3 years ago and reviewed the AIDS vaccine development program, he decided that the program needed a new scientific approach. Knowing about Dr. Temin's and Dr. Ryan's work, he directed the contractor of the AIDS vaccine development program to attempt to mutagenize the simian and human type I immunodeficiency virus in the nuclear capsid region. Dr. Kirsten shared his belief that Dr. Temin's guidance, criticism, and encouragement contributed greatly to the success of this experiment. He then introduced Dr. George Vande Woude, Director of the FCRDC basic science program.

Introduction of ABL-Basic Research Program Scientists—Dr. George Vande Woude

Dr. Vande Woude explained that the basic research program consists of 25 independent research investigators who are grouped into seven laboratories. There are 216 employees in the program, of whom 144 are Ph.D.s or M.D.s and 108 are postdoctoral fellows or research associates. Dr. Vande Woude emphasized that the strength of science in general and the FCRDC program in particular comes from young investigators. The basic research program draws great strength from its post-doctoral fellows and working group leaders. The position of working group leader, Dr. Vande Woude explained, is similar to a tenure track assistant professorship at a university. In this position, a young investigator is given the opportunity to develop an independent research program.

Dr. Vande Woude introduced two recent appointments to this position, Dr. David Kaplan and Dr. Deborah Morrison. Drs. Kaplan and Morrison, he said, have made great contributions to research concerning signaling events driven by oncogenes and proto-oncogene products, which leads to cell division and differentiation.

Dr. Morrison joined the basic research program in 1990 as head of the cellular growth mechanism group. She received her Ph.D. from Vanderbilt in 1985 and was a research fellow at Harvard in the Dana Farber Cancer Research Center with Dr. Tom Roberts until 1988. From 1988 to 1990, Dr. Morrison was a research associate in the Howard Hughes Medical Institute Laboratory of Dr. Lewis T. Williams at UCSF. Dr. Morrison was the first to identify the *c-raf* proto-oncogene product in cells. She also discovered that *c-raf* is activated as a serine threonine kinase following mitogenic growth factor signaling. She has successfully employed vertebrate and invertebrate systems to attack the problem of *raf* in signal transduction.

Dr. Kaplan joined the basic research program in 1990 and is head of the eukaryotic signal transduction group. He received his Ph.D. from Harvard in 1987 and then was a postdoctoral fellow at UCSF with Dr. Harold Varmas until 1990. As a graduate student, Dr. Kaplan was the first to recognize the role of PIP kinase in oncogenic signaling. Shortly after

joining the FCRDC program, he and Dr. Louise Parada discovered that nerve growth factor is the ligand for the *trk* oncogene. This discovery was the first to tie nerve growth factor into the cell signaling pathway and led to the identification of several other neurotropic factors as ligands for other members of the *trk* receptor family.

Presentation by Dr. Deborah Morrison

Dr. Morrison began her presentation by stating that the laboratory in Frederick is interested in gaining a better understanding of how cells receive signals from the outside environment and how these growth signals are transmitted inside the cell to the nucleus. This information would enhance the understanding of processes involved in normal cell growth pathways so that investigators can determine how these pathways have been disrupted during uncontrolled cell growth. Dr. Morrison noted that much of the knowledge about the functioning of growth factor pathways comes from studying platelet-derived growth factor (PDGF), a factor which stimulates the growth of fibroblasts and connective tissues.

When PDGF is added to cells, it binds to a receptor found in the outside membrane of the cells, which is an enzyme capable of phosphorylating both itself and other proteins on tyrosine residues. Once the receptor molecules become activated and bind the ligand, they become associated and dimerized. When dimerization occurs, the molecules become associated with proteins located in the cytoplasm of the cell. These molecules are thought to be in proteins that are involved in relaying signals throughout the cell. There is much to learn about how the message to grow is transmitted from the receptor complex at the membrane to the nucleus. Scientific data suggest that the *raf-1* protein is involved in this pathway.

Dr. Morrison then described characteristics of the *raf-1* protein. *Raf-1* protein is a proto-oncogene product. It was first isolated as the transforming protein associated with the murine sarcoma virus. Mutant versions of the protein have been found in certain human tumors, such as small-cell lung carcinomas. *Raf-1* protein has an enzymatic activity. It is a kinase capable of phosphorylating other proteins on serine and threonine residues. It is located in the cytoplasm of the cells and has been found to be expressed in all tissues and cell types examined.

The presence of three conserved domains—a region rich in cysteine residues, a region rich in seine/threonine residues, and a kinase region comprising the catalytic domain of the protein—delineates a *raf* protein from other proteins found in a cell.

Dr. Morrison explained that a major goal of her laboratory has been to understand the normal function of this protein in transmitting cell growth signals and to determine how mutated *raf* proteins cause tumorigenesis. They do understand, she said, that when receptor tyrosine kinases or growth factor receptors are activated, the normal cellular *raf-1* protein becomes phosphorylated, it changes its mobility in protein gels, and it becomes active as an enzyme.

An analysis of various transforming *raf* proteins has shown that the most common event that occurs is a removal of the N-terminal regulatory domain, resulting in an irreversible modification or alteration of this protein. It is thought that this N-terminal domain functions to

either suppress the activity of the catalytic domain or regulate the association of the catalytic domain with its potential substrates. In this case, an irreversible alteration and an unregulatable kinase results, yielding tumorigenesis. In normal growth processes, however, the activation of the *raf-1* protein would probably involve reversible modifications and the kinase could be regulated.

Dr. Morrison stated that her laboratory has proposed a model concerning the regulation of *raf* through phosphorylation events. Support for the model comes from data suggesting that the phosphorylation resulting from growth factor treatment closely correlates with an increase in *raf's* activity. To prove this model, Dr. Morrison continued, her team had to identify residues on the *raf* protein that became phosphorylated, mutate these sites so that the residues could not become phosphorylated, and determine their effect on the biological activity of the protein.

In the past 2 years, Dr. Morrison's team has identified several sites of the *raf* protein that become phosphorylated in living cells *in vivo*. One of the sites had no effect on the activity of the protein. Two other sites serve to negatively and positively alter the activity of the *raf-1* protein and do not appear to be phosphorylated by the protein on itself *in vitro*. This would suggest that the sites are not autophosphorylation sites, but sites of phosphorylation mediated by other protein kinases within the cell.

Dr. Morrison said that her team would now like to identify the proteins in the cell that regulate this kinase. She suspects that these proteins play a role in transmitting the growth signal from the growth factor receptor complex to the *raf* protein. Dr. Morrison also would like to be able to identify the proteins with which the activated *raf* molecule interacts to promote cell growth. She is examining the fruit fly drosophila system to study these signal transduction pathways. Dr. Morrison outlined some of the advantages of studying signaling pathways in drosophila: many of the molecules critically involved in the drosophila pathways are homologous to human signaling proteins and oncoproteins; the drosophila allows for easy manipulation of the genes through genetic techniques; and the drosophila has a short developmental life cycle and, therefore, experiments can be conducted rapidly.

Dr. Morrison explained that her team has decided to focus on the development of the terminal (head and tail) structures of the drosophila embryo. These terminal structures develop within the first 24 hours after egg laying. Dr. Morrison indicated several proteins that are involved in this developmental signal transduction pathway. These proteins were identified because if they were not expressed or not functional in the embryo, the head and the tail structure did not form. One of the components is the homologue of the mammalian *raf-1* protein—drosophila *raf*. It appears that critical molecules involved in sending drosophila and mammalian growth and development pathways are similar. Dr. Morrison noted that, perhaps, their functions and roles are also similar. She emphasized that a great advantage of studying this pathway of drosophila is that it provides the opportunity to use genetic techniques to specifically determine how these proteins interact with one another and what the specific function of these proteins is. This is important because experiments, such as isolating embryos that lack a component of the signaling pathway, cannot be performed in mammalian cells since all cell types express the *raf-1* protein. Also, this system is important to the research because

mutant signaling proteins can be introduced into the embryo, which allows one to examine this effect on other components and determine the developmental phenotype.

Dr. Morrison noted that the torso receptor in drosophila is an equivalent to mammalian PDGF receptor. Possibly, she added, it can be determined whether the torso receptor functions to activate the *raf* protein as a signal transducer and whether the *raf* protein, in turn, activates proteins initiating the transcription of genes involved in terminal structure development. Experiments were performed using the torso protein and it was found that there were mutations in this receptor protein. There was a loss of function phenotype where head and tail structures did not form, and a gain of function phenotype where there was an overexpression of the head and tail structures and the normal body of the embryo did not form.

Using biochemical analysis, Dr. Morrison stated, the biological activity of this receptor was examined to determine how these mutations caused the torso protein to induce this phenotype. She explained that her team isolated the torso proteins and then detected them using antibodies that would either recognize the total population of the torso or recognize only the activated tyrosine phosphorylated receptor. In normal wild type development, the torso protein is activated at a very early and precise time. Where there was a loss of function phenotype, either the torso protein was not present or it never became activated. Therefore, it never sent the signal to develop and the head and tail never formed. Conversely, where there was a gain of function phenotype, Dr. Morrison said they found that this protein was activated prematurely and prolonged; thus, there was an aberrant expression of the receptor inducing heads and tails to form throughout the body. These results revealed that the torso activation was important in determining the proper formation of the head and tail structures.

The torso receptor cannot send the developmental signal without the drosophila *raf* protein being present, Dr. Morrison explained, and her team next sought to determine what effect activation of this receptor had on the *raf* protein—the signal inducer. Examination of the *raf* protein from extracts of embryos and protein gels revealed that at the time of torso activation, there was a change in the mobility of the *raf* protein on gels due to phosphorylation events. This activity is similar to hyperphosphorylation of the *raf* protein in mammalian cells when growth receptors are activated.

Next, the team attempted to determine the sites of drosophila *raf* phosphorylation, and identified two sites that are analogous to residues found in the mammalian *raf* protein. The terminal structure development in drosophila occurs in the absence of the receptor sending the signal, so that an activated protein exists. If this site is mutated, it has a negative effect on the protein—the kinase is no longer active and inhibits cell growth—and the terminal structure development is blocked. Dr. Morrison explained that not only are these residues conserved, but the residues surrounding these phosphorylation sites are identical, suggesting that the regulatory mechanism for both the mammalian and drosophila protein may be identical.

Dr. Morrison concluded that she and her team have identified a mechanism by which a proto-oncogene product can be regulated. Future goals relative to this research include using the drosophila system to identify the proteins that regulate the *raf* kinase, determining the downstream targets, determining what *raf* interacts with to send growth signals, identifying the homologues of these proteins in drosophila and mammalian systems, and developing reagents

to block the activity of *raf* and, therefore, block the growth-promoting potential of this protein that is critically involved in sending growth signals.

Questions and Answers

Dr. Broder asked Dr. Morrison how she would allocate this research and how she recommends this research be recorded. Dr. Vande Woude answered that the past 10 years of research have proven these genes to be important in cancer research—it is relevant at the basic cancer research level. Dr. Broder added that budgeting is a critical issue for the Institute and Dr. Morrison's presentation is an excellent example of the difficulty in characterizing research for budgetary purposes. He continued that one could argue that this research is germane to a specific type of cancer.

Presentation by Dr. David Kaplan

To begin his presentation, Dr. Kaplan explained that he would first discuss basic research on nerve growth factor and, secondly, describe efforts to develop clinical applications based on his research. Nerve growth factor is a member of the neurotrophin class of factors that regulate the survival, growth, and differentiation of neurons. This family includes four other factors—brain-derived neurotrophin factor, neurotrophin-3, neurotrophin-4, and neurotrophin-5—which are necessary to determine how the nervous system develops and survives. Dr. Kaplan explained that his laboratory uses a tumor cell (PC12 cells) to assay the activities of the neurotrophins and nerve growth factor on responsive cells. When the nerve growth factor or neurotrophins are added to the culture media, the cells stop growing and differentiate into cells resembling neurons. The differentiation process, which takes several days, is characterized by neurites, axon-like projections from the cells. These cells are now nerve cells, which secrete neurotransmitters and form synapses.

Dr. Kaplan reported that the activity of nerve growth factor has been known for approximately 30 years, but until 2 years ago, very little was known about how nerve growth factor induces and promotes the differentiation process of cells to neurons. Kaplan said that one of his first experiments with Dr. Luis Parada demonstrated that *trk* was a receptor for nerve growth factor.

Nerve growth factor interacts with at least two cell surface proteins when added to neurons. *Trk* is the protein responsible for transmitting nerve growth factor's developmental signal. The 75 kilodalton nerve growth factor receptor is a fine-tuning receptor on cell surfaces that binds nerve growth factor. If neurons lack *trk*, they will not respond to nerve growth factor. Dr. Kaplan presented a slide containing a description of *trk*, noting that it is a member of a family of genes that includes *trk*, *trk-B*, and *trk-C*, which are receptors for tyrosine kinase activity.

There is an enzymatic activity that becomes activated in response to ligand and the *trk* receptor phosphorylates proteins in the cell on tyrosine residues. Dr. Kaplan explained that these are the signals transmitted in the cell by *trk* to promote development and differentiation of nerve cells. *Trk* is exclusively expressed in the nervous system, though it was originally

identified as a proto-oncogene. When it very rarely is expressed outside the nervous system, it has an oncogenic activity. Several years ago, Dr. Mariano Barbacid identified *trk* as a potential causative agent in human colon carcinoma at the ABL-basic research program.

The outside portions of *trk* receptors bind neurotrophins, and the inside portions have the catalytic activity that phosphorylates proteins in the cell on tyrosine residues and transmits the signals. Each of the *trk* receptors binds to different neurotrophins—*trk* primarily binds nerve growth factor, *trk-B* binds brain-derived neurotrophin factor (BDNF), and *trk-C* binds neurotrophin-3 (NT3). Dr. Kaplan explained that different *trk* receptors in the nervous system play various roles. For example, Dr. Kaplan contended that *trk* and its ligand, nerve growth factor, are involved in the central nervous system maintaining the survival of nerve cells. *Trk-B* and its ligand, BDNF, are primarily involved in signaling nerve cells to develop in the embryo. Dr. Kaplan surmised that *trk* controls the timing and extent of nerve cell development, and that the more *trk* activity in the nerve cells, the faster nerve cells will develop.

Dr. Kaplan explained that it takes PC12 cells approximately 36 hours to start developing into neurons in response to nerve growth factor. He related an experiment in which he and his team overexpressed the *trk* protein 20-fold in the PC12 cells and found that neuronal development was rapidly accelerated. The neurons formed completely within 24 hours. Thus, the consequence of overexpressing *trk* in neurons is that nerve cells develop much faster. Faster development of nerve cells could have consequences to therapies for nerve injury.

Dr. Kaplan said that over the past several years, his team has attempted to identify all the proteins in cells with which the *trk* nerve growth factor receptor interacts. *Trk* not only tells cells to develop, he explained, but it tells the cells to stop growing and then to develop into neurons. Dr. Kaplan said his team has been trying to develop and isolate proteins used by *trk* to tell cells to stop growing. They have isolated one protein that might serve this function, called the 100 kilodalton protein, that interacts with cell cycle proteins. If proteins are found that are stop signals for cells, there could be potential applications to stop tumor cell growth.

Dr. Kaplan reported that his laboratory has focused on three different diseases and potential therapeutic approaches to which they can apply their research findings: Alzheimer's disease; nerve degenerative diseases and nerve injury; and neuroblastoma. One of the first populations of neurons to degenerate in Alzheimer's disease are those that contain *trk* and respond to nerve growth factor. If the amount of *trk* and *trk* activity is increased in nerve cells, the recovery, differentiation, and development of nerves can be accelerated. Dr. Kaplan's group, in conjunction with Dr. Franz Hefti's laboratory at the University of Southern California, has identified drugs that specifically act on *trk* and increase its activity and hopes to use these drugs as therapeutic agents.

To conclude his presentation, Dr. Kaplan discussed neuroblastoma, the most common extracranial solid tumor of childhood. Neuroblastoma can be divided into two classes: Stage I and Stage II tumors, which are localized and responsive to chemotherapy; and Stage III and Stage IV tumors, which tend to be disseminated and generally nonresponsive to chemotherapy. The FCRDC basic research program developed a protocol with Dr. Carol Thiele of the

pediatric branch of the Molecular Genetics Section at NIH that would enable these tumor cells to stop growing as a potential therapy for this disease. They used two agents, retinoic acid and brain-derived neurotrophin factor, to turn the Stage III and Stage IV neuroblastoma cells into neurons. Dr. Kaplan said that he and Dr. Thiele found that when they treated tumor cells with retinoic acid, the tumor cells expressed the *trk-B* receptor. When they added BDNF to these cultured neuroblastoma cells, BDNF bound to the *trk-B* receptor and promoted a differential response. The cells completely stopped growing and developed into neurons. A combination of retinoic acid and BDNF can cause fast-growing tumor cells to resemble neurons. Retinoic acid and brain-derived neurotrophic factor can now be evaluated as potential therapies for childhood neuroblastoma.

Dr. Kaplan presented a final slide showing a list of collaborators on the studies discussed, which include Drs. Luis Parada, Deborah Morrison, and Terry Copeland in the ABL-basic research program; Dr. Barbara Hempstead and her colleague Dr. Moses Chao at Cornell University Medical College in New York; and Dr. Carol Thiele in the Molecular Genetics Section at NCI.

Questions and Answers

Dr. Wells asked whether the last set of experiments dealt with Stage III tumor cells. Dr. Kaplan answered that all (8 to 10) neuroblastoma cell lines that were assayed were Stage III and Stage IV.

Dr. Wells asked whether Dr. Kaplan had examined oncogenes in those cells and if any of them amplified. Dr. Kaplan stated that they had been examined and *N-myc* is amplified in most of these cell lines. Dr. Wells asked whether this was also true at the end of the experiment. Dr. Kaplan explained that they had not checked yet, noting that the cells were no longer growing at the end of the experiment. This has now been checked by Dr. Thiele. Retinoic acid treatment of neuroblastoma cells decreases *N-myc* levels. In neuroblastoma cells that do not differentiate in response to retinoic acid, *N-myc* levels do not decrease.

Dr. Broder asked Dr. Kaplan whether he had ever examined neuroblastoma for *trk* expression to see whether he could recapitulate the activity seen in retinoic acid and BDNF. Dr. Kaplan explained that this work has been performed during the past month. At present, Dr. Kaplan said, he and his colleagues are trying to inject these compounds back *in vivo* to promote differentiation effects or perturb development, and that no other systems have yet been examined.

XVI. SUBCOMMITTEE REPORTS

Subcommittee on Cancer Centers

Dr. Salmon reported that his subcommittee received an update on the cancer centers program. The Division of Cancer Biology, Diagnosis, and Centers developed a new policy statement to support clinical trial research with Cancer Center Support Grants (CCSG) funds

and include data managers involved in pilot Phase I clinical trials. This statement is in direct response to a request from various center directors.

The subcommittee approved the minutes from the September meeting and resolved an issue relating to centers that practice outside their areas. Two additional elements were added to the guidelines for designation as NCI comprehensive cancer centers, one of which relates to conditional approval for centers that might be required to strengthen a particular program element. The revised guidelines will be distributed to the NCAB shortly.

After hearing a review of the Minority Enhancement Awards (MEA) program by Dr. Evans, the subcommittee unanimously passed a resolution recommending that it be continued and expanded, but funded by a specific mechanism, not by the P30 or from the CCSG budget with which it is inconsistent. The subcommittee recommended that current awards be continued without interruption until a new initiative with competitive funding opportunities is developed by NCI.

Mrs. Bynum asked why cancer control and outreach in minority populations is not consistent with the CCSG, since this topic was recently added to CCSG activities. Dr. Salmon replied that the answer relates to the timing of renewal of the program. There are a large number of renewal programs and planning grants coming up in fiscal years 1993 to 1995. Several programs will not be funded if these programs and the minority enhancement are funded. The core grant is often very useful for starting an activity to test its feasibility. For example, the core grant initially funded the National Black Leadership Initiative, but it later found its own funding outside the core grant line. Once a program shows evidence of being successful, it is usually best to fund it as a separate initiative using a distinct mechanism.

The subcommittee asked that projections of the funding needs of the Centers Program be provided for FY 1994 and FY 1995 at the next meeting.

Subcommittee on Interactions With Voluntary Organizations

Dr. Lawrence pointed out that the Board had received a description of this subcommittee meeting compiled by Dr. Paul Van Nevel and his staff. He stated that the previous day's discussion of the work of the National Breast Cancer Coalition and Dr. Freeman's report on the President's Cancer Panel had prompted the subcommittee to discuss planning a national conference with a targeted agenda that might offer some long-term methods for more effective NCAB interaction with outside groups.

The subcommittee chose to examine the interaction with a particular voluntary organization and found that the NCI had a great deal of communication with this organization. Nevertheless, this first experiment strengthened the planning for the next group of breast cancer summits.

The group also discussed plans for a future all-day committee meeting that would deal with issues in an open fashion. One issue will be an update on the ASSIST program, which is a partnership between voluntary organizations and the NCI. Another issue discussed was

collaboration between the NCI and the American Cancer Society on epidemiology and statistics.

Dr. Lawrence concluded that it was a useful meeting and the group plans to proceed with the concept of developing stronger collaborations.

Dr. Greenwald offered to provide an update on the ASSIST program and the Board unanimously approved the idea. This subcommittee's minutes were also approved unanimously.

Dr. Calabresi announced the formation of the following three working groups, which will report back to the Board in May 1993: a working group on the budget, chaired by Dr. Bettinghaus; a working group on the R01/P01 initiative, chaired by Dr. Wells; and a working group on clinical investigation, chaired by Dr. Calabresi. Mrs. Bynum will serve as staff contact for the R01/P01 initiative group, which will consist of Drs. Salmon, Day, and Becker and Ms. Mayer. Dr. Bruce Chabner will serve as staff contact for the clinical investigation group, which will consist of Drs. Salmon, Wilson, Bragg, and perhaps one or two more people.

Dr. Calabresi stated that new members will be added to committees after they have informed him of their preferences. He then apologized for the interruption and proceeded with the regular agenda.

XVII. NEW BUSINESS

Dr. Day requested a discussion about funding for clinical trials and clinical research under various proposals for National Health Care Coverage. Dr. Calabresi agreed that this is an important issue, noting that it would be discussed at the next meeting. Dr. Broder confirmed that this would be discussed at the February meeting and asked that the Subcommittee on Clinical Investigations provide insight into their group as well.

XVII. ADJOURNMENT

There being no additional business, Dr. Calabresi thanked the group for their participation and adjourned the 84th National Cancer Advisory Board proceedings at 1:00 p.m, December 15, 1992.

Date

Dr. Paul Calabresi, Chairman