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

Summary of Meeting
November 25-26, 1991

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

Department of Health and Human Services
Public Health Service
National Institutes of Health
National Cancer Institute
National Cancer Advisory Board

Summary of Meeting[1]
November 25-26, 1991

The National Cancer Advisory Board (NCAB) convened for its 80th regular meeting at 8:00 a.m. November 25, 1991, 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. John R. Durant
Dr. Bernard Fisher
Dr. Phillip Frost (Absent)
Mrs. Brenda Johnson
Dr. Walter Lawrence, Jr.
Mrs. Marlene A. Malek
Ms. Deborah Mayer
Mrs. Irene S. Pollin (Absent)
Dr. Sidney Salmon
Dr. Howard M. Temin (Absent)
Dr. Samuel A. Wells, Jr.

President's Cancer Panel

Dr. Harold P. Freeman (Chairman)
Mrs. Nancy G. Brinker
Dr. Geza J. Jako

Alternate Ex-Officio NCAB Members

Dr. Miriam Davis, NIEHS
Dr. David Galas, DOE
Captain Bimal Ghosh, DOD
Mr. Edward Henderson, FDA
Mr. Richard A Lemen, NIOSH
Dr. Hugh McKinnon, EPA
Dr. Lakshmi C. Mishra, CPSC
Dr. Raymond Sphar, DVA
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
Executive Secretary, Mrs. Iris Schneider, 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 Ida Barak, Associate Program Director for Cell Biology, Division of Cellular Biosciences, National Science Foundation, Washington, D.C., representing the National Science Foundation

Dr. J. David Beatty, Executive Vice President, National Cancer Institute of Canada

Mr. Alan Davis, Vice President for Public Affairs, American Cancer Society, Washington, D.C., representing the American Cancer Society

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

Dr. Edward P. Gelmann, Professor of Medicine, Anatomy and Cell Biology, Vincent Lombardi Cancer Research Center, Division of Medical Oncology, Washington, D.C., representing the American Society of Clinical Oncology, Inc.

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

Dr. Marston W. Linehan, Head, Urologic Section, Surgery Branch, DCT, Society of Urological Oncology, representing the Society of Urological Oncology for Dr. Jerome Richie

Ms. Linda O'Connor, President, Oncology Nursing Society, representing the Oncology Nursing Society

Dr. Robert C. Park, Past President, American College of Obstetricians and Gynecologists, Washington, D.C., representing the Society of Gynecologic Oncologists

Mrs. Yvonne Soghomonian, Associate Director of the Candlelighters Childhood Cancer Foundation, Washington, D.C., representing the Candlelighters Childhood Cancer Foundation

In addition to NCI staff members, meeting participants, and guests, a total of 40 registered members of the public attended the meeting.

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

Dr. Calabresi called the meeting to order and welcomed members of the National Cancer Advisory Board (NCAB), members of the President's Cancer Panel, and representatives of the divisional boards of scientific counsel. He announced that this meeting of the NCAB was the annual review of National Cancer Institute (NCI) programs. The first day of the meeting, he continued, would be spent reviewing program activities of the Division of Cancer Biology, Diagnosis and Centers, followed by several presentations by staff of the Division of Cancer Treatment. The second day, a symposium would commemorate the 20th anniversary of the passage of the National Cancer Act.

Dr. Calabresi introduced several guests representing medical, research, and professional organizations. He then stated that members of the public wishing to express views regarding items discussed during the meeting could do so by writing to the NCAB Executive Secretary, Mrs. Barbara Bynum, within 10 days after the meeting.

Dr. Calabresi pointed out that copies of the September minutes had been distributed in the Board members' notebooks. He asked members to review the minutes before the end of the first day so that a vote of acceptance could be taken.

Dr. Calabresi announced meeting times and locations for the Subcommittee on Planning and Budget and the Subcommittee on Women's Health and Cancer and urged the attendance of all Board members.

II. FUTURE MEETING DATES—DR. PAUL CALABRESI

Dr. Calabresi called attention to the scheduled dates for NCAB meetings in 1992 and 1993. He noted that, as in 1992, the May 1993 meeting is proposed to begin on Tuesday rather than Monday to allow members of the Board to attend the American Society for Clinical Investigation meeting. Without discussion, the Board confirmed these dates for the 1993 NCAB meetings.

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

Dr. Freeman reported that two panels have been held. Secretary of Health and Human Services Dr. Louis Sullivan and National Institutes of Health (NIH) Director Dr. Bernadine Healy attended the first panel on Poverty and Cancer, which was held in July. The second panel concerned training in science, particularly the training of minority scientists, and was held in September in Atlanta. Dr. Freeman stated that breast cancer will be the focus of the next panel to be held in November at M.D. Anderson Hospital in Houston, Texas. He announced that two more panels have been planned; one will concentrate on technology transfer from research to the public, and the other will concern lifestyle factors and will be held in New York City.

Dr. Freeman described follow-up work being done in response to Vice President Quayle's request for creation of a subpanel to study the research, detection, and treatment of breast cancer. Approximately 130 candidates for the subpanel have been submitted to the Panel for consideration. Dr. Freeman indicated that he, Mrs. Nancy Brinker, and Dr. Geza Jako, along with NCI staff, would review the list of names and reduce it to less than 20. Dr. Freeman also noted that he planned to meet with Mrs. Quayle to discuss cancer control matters.

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

Dr. Broder began his report with a discussion about the commemoration of the 20th anniversary of the National Cancer Act. He reminded the audience that it is not the 20th anniversary of the National Cancer Institute, which was established in 1937, but that "with the National Cancer Act the National Cancer Institute was born again." The National Cancer Act was signed by President Nixon on December 23, 1971. The National Cancer Program was created in that document to expand and intensify the nation's efforts against cancer. Also, the National Cancer Advisory Board, which consists of 18 Presidentially appointed scientific and lay advisors, was established. Dr. Broder urged the Board's attendance at this event, which he described as a good opportunity to reaffirm our commitment to the future.

New Developments Within the NCI

Dr. Broder announced that the NIH Recombinant DNA Advisory Committee (RAC) approved the first experimental cancer vaccine (engineered by gene therapy) to immunize patients against their own tumors on October 8th. Two patients were treated less than 24 hours after the approval by the RAC and NIH Director Dr. Bernadine Healy. This project, Dr. Broder explained, involves taking a small piece of tumor and inserting the gene for tumor necrosis factor (TNF) into the tumor cells using a retroviral vector. The modified tumor cells are then tracked as they enhance regulatory and cytotoxic lymphocytes that become sensitized to and directed against other tumor cells deposited throughout the body. By priming the tumor cells to produce large quantities of tumor necrosis factor, Dr. Steven Rosenberg and his coworkers hope to hasten an immune-mediated destruction of cancer cells. Dr. Broder added that the use of a recombinant vaccine is highly experimental, but represents an innovative strategy for gene therapy and builds on other foundations in this area.

As Dr. Freeman explained in his report, Vice President Quayle has asked him to create a subpanel of the President's Cancer Panel on breast cancer. Vice President Quayle, acting in his capacity as Chair of the Council on Competitiveness, asked that there be greater emphasis on research into the cause and cure of this disease. He wishes to speed up government approval for new drugs and therapies for cancer and other life-threatening diseases. Dr. Broder explained that the subpanel was charged to undertake a detailed study of the state of breast cancer research, detection, and treatment, with emphasis on prevention. This subpanel is analogous to the Committee on Drug Approval Issues, requested by then Vice President George Bush and headed by Dr. Lasagna. Dr. Broder reminded the Board that many of the major recommendations of the Lasagna committee either have been implemented or are under serious consideration at the Food and Drug Administration (FDA). Vice President Quayle asked Mrs. Brinker, member of the President's Cancer Panel and Director of the Susan G. Komen Foundation for Breast Cancer Research, to chair the subpanel. The subpanel will include both medical experts and lay people. Dr. Frederick Becker will host the next President's Cancer Panel meeting on December 9th at the University of Texas M.D. Anderson Cancer Center. The subject of the meeting will be "Breast Cancer Research: Progress and New Perspectives."

On October 4, 1991, the NCI awarded grants to 17 States to conduct the American Stop Smoking Intervention Study (ASSIST) for cancer prevention. ASSIST is a joint, 7-year project of the NCI and the American Cancer Society that will be implemented through State health departments. This program is expected to reach approximately 90 million Americans and 20 million smokers. It is anticipated that ASSIST will help approximately 5 million adults and 2 million adolescents to stop smoking, thereby saving an estimated 1 million lives.

Honors, Awards, and Staff Changes within the NCI

Dr. Broder reported that Dr. Jane Henney, former Deputy Director of NCI, will be appointed the FDA's Deputy Commissioner for Operations. She is currently the Vice Chancellor for Health Programs and Policy at the University of Kansas Medical Center in Kansas City. He then congratulated Dr. Walter Lawrence, Professor of Surgery and Director-Emeritus of the Massey Cancer Center at the Medical College of Virginia, on his succession as the President of the American Cancer Society. Mrs. Irene Pollin received Maryland Governor William Schaefer's Salute to Excellence in recognition of her extensive volunteer work and efforts to increase public awareness about breast cancer screening. Mrs. Pollin helped develop the Bullets Wives Save Lives initiative, which will enlist the wives of the Washington Bullets basketball team to educate the public about breast cancer. Mrs. Nancy Brinker received the Fox Chase Cancer Center's Reimann Honor Award on November 8th. She was honored for her advocacy for breast cancer patients and breast cancer research.

Dr. Broder then announced staff honors and charges. Dr. Bruce Chabner was promoted to a Public Health Service (PHS) Commissioned Corps flag rank. Dr. Eli Glatstein, who is leaving the NIH, received the Senior Executive Meritorious Service Rank Award. Dr. Broder commended Dr. Glatstein as an exemplary academic leader who has trained seven of the chairs of academic radiotherapy departments throughout the country.

Numerous NCI, NIH, PHS,and DHHS awards to NCI employees were announced. In addition, the Surgeon General's Medallion for Exemplary Service was awarded to Ms. Clarissa Wittenberg. Dr. Stuart Yuspa received the Robert L. Anderson Award from the Toxicology Forum and Ms. Kate Duffy received the Marian Morra Award for her work with the Cancer Information Service. Dr. Werner Kirsten received the National Leadership Award from the Luekemia Society of America and Dr. Steven Rosenberg was selected for the Jeffery A. Gottlieb Memorial Award. The Gold Cytoscope Award was given to Dr. W. Marsten Linehan, Head of Urologic Oncology in the Surgery Branch. The American Health Foundation presented NCI and its Director a certificate of appreciation on the occasion of the 20th anniversary of the National Cancer Act.

Dr. Broder announced that Ms. Judith Whelan, Chief of the Planning, Analysis and Evaluation Branch and Executive Secretary of the NCAB Subcommittee on Planning and Budget is leaving to become Chief of the Office of Science Policy and Analysis at the National Institute of Child Health and Human Development. He reminded the Board to attend the Budget and Planning Subcommittee meeting after the NCAB meeting, at which time Ms. Whelan would give an update on the NIH-wide strategic plan.

Dr. Broder reported the following senior level staff changes: Dr. Kirt Vener, from the National Institute of Arthritis and Musculoskeletal and Skin Diseases, is the new Section Chief of the Prevention, Epidemiology, and Control Review Section, Grants Review Branch; Dr. Doug Weider is the new Chief of the Prevention Oncology Branch, Early Detection and Community Oncology Program; Dr. Carmen Allegra has been appointed to replace Dr. John Minna as Chief of the NCI Navy Medical Oncology Branch in the Division of Cancer Treatment.

Dr. Broder outlined other important appointments. In the Clinical Oncology Program, Dr. Etienne Shalone joined the Surgery Branch in August as a visiting scientist. Dr. Shalone is an internationally known surgical oncologist and immunologist who will participate in the ongoing development of new and effective immunotherapy for patients. In the Developmental Therapeutics Program, Dr. Edward Sausville was appointed Chief, Laboratory of Biological Chemistry. Dr. Sausville was formerly a senior research investigator in the Clinical Pharmacology Branch of the Clinical Oncology Program.

Community Service and Outreach Activities

Dr. Broder described the current activities of Mrs. Pollin's effort to educate women about breast cancer through the Bullets Wives Save Lives initiative. The project was pilot tested in the communities of Baltimore and Washington, DC with NCI participation coordinated by Dr. Claudia Baquet, Associate Director for the Cancer Control Science Program. The project will now be expanded to other NBA cities and area cancer centers and Cancer Information Service offices have been invited to collaborate. Mr. Paul Van Nevel, Associate Director of Cancer Communications, will serve as coordinator while Dr. Baquet is on detail to Senator Kennedy's committee. Mr. David Stern, Commissioner of the National Basketball Association (NBA), has been enlisted to help with the January briefing of the wives of players and coaches for all 27 NBA teams to take place in Washington. Dr. Broder stated that he hopes that the NCI clinical and comprehensive cancer centers will view this project as a logical outgrowth of their own activities and will participate in this effort on a voluntary basis when activity is consistent with their own programs. Although the NCI will not be involved in the fundraising aspect of the initiative, it views this project as an important extension of its community service and outreach activities.

The NCI cosponsored a workshop entitled "Perspectives on Ovarian Cancer in Older Women" with the Aging Institute and the American Cancer Society. Approximately 20,000 new cases of ovarian cancer and 12,500 related deaths are expected this year. Over the last 15 years, the death rate for ovarian cancer has fallen by over 40% in women under 50 years and 25% in women under 65, but has risen by 16% in women over age 65. Data from the NCI Surveillance Epidemiology and End Results (SEER) program indicate that there is a 5-year survival rate of 87% for Stage I disease, 39% for regional disease, and 19% for distant disease among women diagnosed with ovarian cancer. Dr. Broder stated that he looks forward to the recommendations of this workshop.

Update on Taxol

Dr. Broder presented an update on taxol, a scarce new drug with promising activity in ovarian and other cancers. The NCI has set up a taxol referral center as a means of providing access to investigational drugs for patients with refractory ovarian cancer. In this program administered by the Cancer Therapy Evaluation Program, patients participate in a research protocol and data are gathered. If a patient is not eligible for a specific taxol-based protocol, she may be referred for entry into other clinical trials. The taxol referral center attempts to distribute the limited supply of taxol in a fair and compassionate way throughout the country and provide for optimal clinical research and treatment programs for women with ovarian cancer. Dr. Broder highlighted an advance in solving the taxol supply problem—taxol has been produced by plant tissue culture on a pilot basis.

Congressional Update

Dr. Broder testified, along with Dr. Bernadine Healy, Dr. Jim Watson, and Mr. Reid Adler, about several issues related to patents and technology transfer at a hearing on biotechnology and patent law before the House Judiciary Subcommittee on November 20th. The Congress is very interested in this issue and feels that the government essentially pays for new drugs three times by: 1) supporting research that leads to therapeutics; 2) maintaining and administering the Patent and Trademark Office to provide protection of new discoveries; and 3) underwriting the purchase of drugs once they are available. Dr. Broder commented that it is important to ensure that new agents are available, stimulate competition in the open marketplace, and have an interest in the cost of products that are developed with government funded research.

Science Enrichment Program

For two years, NCI has conducted a successful science enrichment program for high school students on the NCI campus near Frederick, Maryland. Last summer, a group of 157 students from all over the country attended. The group comprised students from minority or underserved populations. A Request for Applications (RFA) was recently issued to set up regional science enrichment programs nationwide. Other Institutes are supporting this effort as well—the National Institute of Child Health and Human Development has allotted up to $150,000; the National Institute of Environmental and Health Sciences, up to $100,000; the National Institute of Arthritis and Musculoskeletal and Skin Diseases, up to $25,000; and the Division of Research Grants, up to $10,000.

Specialized Programs of Research Excellence (SPORE)

A new funding initiative designed to stimulate multi-disciplinary research efforts directed at breast, prostate, and lung cancers was announced. These Specialized Programs of Research Excellence (SPOREs) will be supported through the P50 grant mechanism which will fund research and core resources. Together with R01s, P01s and other mechanisms, they add a degree of flexibility to supporting efforts directed at these major solid tumors. More than 100 scientists from nearly 50 institutions attended a briefing meeting in St. Louis on October 8, 1991 and an RFA has been published. These grants will be available to all cancer research institutions, including those that currently hold P30 cancer center support grants. NCI plans to award three or more SPORE grants for each tumor and an institution may compete for and receive one P50 award in each area.

NIH Strategic Plan

The NCI is participating in the NIH-wide effort to create a strategic plan. Dr. Broder expressed his support for this activity and urged the input of the NCAB on this issue. Dr. Broder discussed the goals of molecular medicine in relation to the NIH strategic plan. The following will be trans-NIH initiatives: 1) gene therapy; 2) molecular genetics of disease and disease susceptibility; and 3) growth factors and signaling. Dr. Broder listed other initiatives that require discussion: animal models; family registries and tissue repositories, better biomarkers; and better computer databases. He also mentioned other issues of importance, such as investigating whether study sections are adequately constituted to address some of the interdisciplinary programs; making more innovative use of centers mechanisms, including P30s, P40s, and P50s; and developing better laboratory-to-clinical approaches, including an improved regulatory process and improved information exchanges.

Discussion of the NCI Budget

Dr. Broder reported that both houses of Congress have passed a budget, which awaits the President's approval.

Regarding fiscal year 1991 actual obligations, the NIH total budget was approximately $8.2 billion and the NCI total budget was approximately $1.7 billion. The original President's budget for fiscal year 1992 was approximately $8.8 billion (7.6% increase) for the NIH and approximately $1.8 billion (5.7% increase) for the NCI. In the House, the initial total NIH budget for fiscal year 1992 was approximately $8.8 billion (8.2% increase) and the total NCI budget was approximately $1.83 billion (6.9% increase). In the Senate, the total NIH budget for 1992 was slightly less than $9 billion (10.1% increase) and the total NCI budget was slightly more than $2 billion (17.4% increase). The conference amount for NIH was $9 billion (10.5% increase) and the NCI budget was slightly less than $2 billion (16.2% increase). Dr. Broder commented that these proposed increases signify that the message of the National Cancer

Program and the cancer community was heard. The fact that these allocations were proposed during this time of extraordinary budget problems is significant, he added.

Dr. Broder detailed some technical issues. The conference level will be reduced for travel, salaries, and expenses because many members of Congress feel that certain aspects of the travel budget are not scientifically useful. Focusing primarily on the conference level, Dr. Broder discussed issues related to delayed availability. The NIH was given approximately $400 million to be available only on September 30, 1992—the NCI's share is $63 million. The method by which this will be done is still under discussion, but will probably primarily affect grants. The purpose of this delayed availability is to postpone actual outlays. As part of the negotiations on the overall conference amount, the NIH budget specifically contains a portion for the NCI—an additional increase of $160 million—which also becomes available only on September 30, 1992. Dr. Broder stated that the $160 million is technically part of the NCI budget, but the language is explicit in providing the Director of the NIH with the authority to transfer any or all of this money to any categorical institute at the NIH for cancer research.

The fiscal year 1991 budget level for research project grants was slightly more than $790 million, and the figure for new and competing proposals was slightly less than $200 million. The fiscal year 1992 budget for research project grants theoretically will total slightly more than $900 million. This is an increase in excess of $113 million—over 14% of which, $87 million, will be for competing awards.

In fiscal year 1991, cancer centers received approximately $110 million. The fiscal year 1992 conference amount includes an increase of approximately $15 million (approximately 13.5%) for existing cancer center activities. The SPOREs—P50s—will receive new money of $17.5 million. Therefore, the total centers line is increasing from $110 million in fiscal year 1991 to more than $142 million in fiscal year 1992. This is an increase of approximately $32 million, or 29%. The following budgets will increase: research career program, nearly 26%; the cancer education program, approximately 114%; and the clinical cooperative groups, approximately 28%. The budget for certain smaller grant programs will decrease, but the total grant mechanism will increase nearly 17%.

The National Research Service Awards (NRSAs) are essentially flat. The following lines will receive an increase in budget: research and development contracts which had declined the most in 1980 constant dollars, will increase approximately 16%; intramural program by approximately $15 million, or 12.3%; research management and support by approximately 17%; prevention and control by approximately 28% to $10 million; and construction would receive a total of $12 million. Dr. Broder explained that the research project grant line increased the most in absolute amount, but all of the fundamental mechanisms also increased.

The total number of noncompeting grants actually funded in fiscal year 1991 was about 2,200. There were 840 new and competing awards. Therefore, approximately 3,050 total grants were funded. The fiscal year 1992 conference projection for the number of non-competing grants is approximately 2,254. The number of competing awards will be in excess of 1,000 and, therefore, the total funded will be in excess of 3,200 grants. Approximately 29% of competing grants were funded in fiscal year 1991, and there will be in excess of 32% of competing grants funded in fiscal year 1992.

Dr. Broder concluded that this budget is a "phenomenal anniversary present from the Congress to the National Cancer Institute" and that the NCI, he hoped, can repay the Congress and the public by developing new preventions, diagnostic methods, and cures for cancer.

In answer to Dr. John Durant's question about the effects of the delayed availability of funds to September 30 and whether it would result in funding gaps between the end of one grant period to the beginning of another, Dr. Broder explained that there is a difference between what is appropriated and what is spent. Sometimes, payment is due over a period of several years, so

the cash flow issue varies. To give the NIH this budget for fiscal year 1992, the actual cash flow had to be restricted (i.e., the availability of $400 million will be delayed).

Dr. Samuel Wells asked why the NRSAs did not increase. Dr. Broder replied that because this program has not been reauthorized, the appropriations committee will not consider a budget increase. The NCI will attempt to develop innovative ways of using other mechanisms to help fund training at multiple levels. Other types of education grant mechanisms will be used, and the P50 SPORE program will have the flexibility to identify and support people at various stages of training.

Dr. Erwin Bettinghaus stated his concern about support for the P01 mechanism in the new budget. A view was expressed, Dr. Broder replied, that the P01 funding instrument would be terminated, yet the P01s have always been supported. Dr. Broder replied that the same number of new and competing P01s were issued in fiscal year 1991 as in the previous year, and the funding rate remains the same as it has in the past—about 42% of new and competing proposals. The average cost of P01s has not increased as rapidly as the cost of R01s, and the system cannot be recallibrated to account for P01s as multiple single awards, even though they include multiple projects. Dr. Broder described P01s as an important mechanism, especially for applied or translational research.

V. SPECIAL REPORT ON NBA/NCI MAMMOGRAPHY INITIATIVE—DR. CLAUDIA BAQUET

Dr. Baquet presented an overview and reported on the status of an initiative developed by Mrs. Pollin, member of the NCAB and co-owner of the local NBA franchise, the Washington Bullets.

The NBA/NCI Mammography Initiative is an outreach initiative designed to increase awareness of mammography, capitalizing on the credibility and visibility of the 27 NBA wives' organizations throughout the nation. The NBA wives represent credible and positive role models in their communities who are influential sources of health information, including information on the importance of mammography.

The overall goal of the initiative is to reduce avoidable mortality from breast cancer in American women. A secondary goal is to enhance the outreach activities of the NCI Cancer Information Services, as well as the cancer centers. This initiative will not pay for medical care. Fundraising by NBA wives for the cost of mammography is separate and independent of the NCI.

A key component of enhancing the success of this initiative is the establishment of strong and positive links between the NBA teams and their local Cancer Information Service (CIS) and cancer centers. As Dr. Broder mentioned, the national initiative was preceded by a 1-year pilot project with the Washington Bullets. Through the local initiative, entitled Bullets Wives Save Lives, the NBA wives conducted outreach and education activities in various settings, including halftime at NBA games, and presented information on mammography in churches and at PTA meetings. Questions that the NBA wives could not field were referred to the local CIS. A plan is being finalized in which all wives from 27 NBA teams will be trained and oriented on the importance of mammography, so that they will have the ability to conduct outreach programs.

The National Basketball Association office in New York, in collaboration with the NCI, will design and implement a national Mother's Day promotion in May of 1992. This project will utilize various celebrity players and their mothers to promote mammography as a life-saving message.

The NCI is in the process of facilitating strong linkages with the Cancer Information Service, as well as cancer centers, in NBA team areas. Mr. Paul Van Nevel will be the central contact for these relationships.

VI. NCI DIRECTOR'S PLAN FOR BREAST AND WOMEN'S CANCERS—DR. DANIEL IHDE

Dr. Ihde began by describing the Senate NIH Reauthorization Bill introduced by Senator Kennedy, which includes the requirement that the Director of the National Cancer Institute prepare and submit a plan in regard to research on breast cancer, ovarian cancer, and other cancers of the female reproductive system. This initiative is to be coordinated with those of other institutes, and the Director shall ensure that research programs described within it are implemented in accordance with the plan. Dr. Ihde explained that the plan will include comments and recommendations considered appropriate by the Director, with due consideration provided to the professional judgement needs of the institutes as expressed in the annual bypass budget. The Director, in consultation with the National Cancer Advisory Board, will periodically review and revise such a plan.

According to Dr. Ihde, NCI has prepared a report describing the institute's commitments, approaches, and plans, although the Kennedy Bill has not yet been passed. He then stated NCI's unswerving commitment to women's health and, specifically, to the eradication of death and suffering from cancers that affect the length and quality of survival of women. This commitment is expressed in many research strategies; for example, in the basic research on the biology of cancer and prevention research, in epidemiology, clinical trails—where women are always proportionately represented—in education, and in information dissemination.

Dr. Ihde noted that there is an active, ongoing campaign to increase public understanding of cancer issues and to encourage early detection. Special attention has been given to reaching women who are underserved or who belong to minority groups, where cancer rates have been disproportionately high. Examples of this creative approach are the NBA Bullet's Wives Save Lives program, the Women's Leadership Summits on Breast Cancer, and Second Generation Regional Summits.

Three promising areas of basic research detailed in the report were singled out by Dr. Ihde, including: 1) studies of metastasis, which hopefully will lead to effective interventions in many cancers; 2) prevention clinical trials, including the dietary intervention trial of reduced dietary fat in the women's health initiative; and 3) the new tamoxifen chemotherapy prevention trial in women at high risk for breast cancer. Several innovations, such as the new multidisciplinary, specialized programs of research excellence which will focus on breast, prostate, and lung cancer, are also included. Dr. Ihde noted that while lung cancer is not limited to women, it has surpassed breast cancer as the major cancer-related killer of women.

NCI's collaboration with other institutes is also described in the report. Institute participation in the trans-NIH study of women's health, which evaluates not only outcome in terms of breast cancer but looks at the potential impact of estrogens on heart disease and bone density, is also contained in the report.

Dr. Ihde closed by noting that many NCAB members have already provided input into the report and added that further review and comment is welcome. The report makes clear that NCI has structure and specificity to back up the strong language in its commitment to women's health. Dr. Ihde said he expects this report to be submitted to the Senate in the near future.

Dr. Bettinghaus noted that smoking is mentioned in the plan only twice, both times in terms of smoking cessation, yet smoking is related to more than lung cancer. He suggested that this topic be reviewed.

Dr. Ihde agreed to look further into Dr. Bettinghaus' point about cervical cancer being smoking related and to revise the draft accordingly.

Dr. Jako suggested that input from the American College of Surgeons and the Society of Surgical Oncology be considered for incorporation into the report.

Dr. Ihde agreed with Dr. Jako and expressed his intention to seek additional input in regard to both breast cancer and gynecological cancers.

Dr. Yodaiken asked how the NCI was dealing with the problems women in the workplace face in obtaining mammographies.

Dr. Ihde informed Dr. Yodaiken that one of the recent mammography summits focused on ways in which mammography availability could be brought into the workplace—where many women spend the majority of their days. He noted that it is one effort underway but, clearly, it could be emphasized more and perhaps should be mentioned to a greater extent than it is in the report.

Dr. Becker described how M.D. Anderson has instigated a series of mobile van mammography operations that are involved in the work place.

Mrs. Brinker mentioned that, as a result of the summit mentioned, a program currently enjoying greater popularity among company's that cannot afford mammography equipment is one in which time off during the day is offered during which women can go to the nearest, best, and most economical mammogram facility.

VII. REPORT OF THE PRESIDENT, AMERICAN ASSOCIATION FOR CANCER RESEARCH (AACR)—DR. HAROLD MOSES

In a brief preface to his remarks, Dr. Moses noted that his presence at the NCAB meeting related to recent correspondence with Dr. Broder expressing the AACR's desire to provide more input into the Institute's bypass budget. Dr. Moses mentioned that the request grew from discussions of the AACR's Board of Directors, who are frustrated with the direction recent funding for the National Cancer Program has taken.

AACR

Dr. Moses then presented an overview of the AACR. He noted that it is the oldest cancer research association in the United States, founded in 1907 with the mission of fostering cancer research through communication. A unique aspect of the Association, Dr. Moses said, is its combination of basic and clinical investigators who encompass all subfields within cancer research. There are 7,500 investigators throughout the United States and in 50 other countries as well. Journals entitled *Cancer Research, Cell Growth and Differentiation,* and *Cancer Epidemiology, Biomarkers, and Prevention* are published by the Association. The annual meeting of the AACR averages around 5,500 registrants and small special conferences are also held periodically. The Association also has a public education effort as well, on which Dr. Moses said he would focus.

The AACR has formed a Public Education Committee comprising basic and clinical investigators, which meets regularly with Congress and other government bodies. The AACR,

Dr. Moses said, is trying to increase the quality and quantity of mass media reporting of cancer research.

The Cancer Problem

Dr. Moses then described the scope of the cancer problem. There are 1 million new cases diagnosed every year, he said, and 500,000 American deaths from cancer each year. It is the leading cause of death in children aged 3 to 15. Fifty percent of all cancers are in persons over age 65 and two-thirds of the deaths from cancer occur in this age group. There is one cancer death every 62 seconds. Dr. Moses stressed that there have been successes—seven million Americans currently living have had cancer. However, in spite of these successes, the National Cancer Program is in a crisis. Federal funding for cancer is seriously inadequate and there is a rapid decline in education, which the inadequate funding only serves to worsen. More foreign-trained scientists are staffing laboratories, and this, unless the trend is reversed, Dr. Moses said, will hamper the ability to take advantage of the research advances made in the last two decades in molecular biology and cancer research.

Funding

Reviewing the recent history of cancer funding, Dr. Moses said that the decade of the '80s was a period of spending for big programs, such as the supercollider/superconductor, and not for basic research. In the early 1980s there was a decrease in science spending. In the middle 1980s, funding for NIH improved, while funding for NCI did not. Funding for NCI decreased from 1981 to 1991 by 6.2%, Dr. Moses remarked, and if AIDS research is accounted for, then the decrease was 18.5%.

Dr. Moses recounted that Congress mandated NIH to maintain a specific number of research grants. While NCI did direct the required resources to research, he said, it did so at the expense of the National Cancer Program as a whole, including cancer centers and cooperative groups. Later in the decade, there was an increase in funding for basic research, however, Dr. Moses pointed out, the level was inadequate to meet the demand.

The next area Dr. Moses discussed was the competing research project grants. In 1971, the NCI was funding 55% of the approved applications. This year, if pending legislation is enacted into law, funding will only cover 35% of the approved applications. Another problem, Dr. Moses said, is downward negotiations. After showing nondefense research and development expenditures as a percentage of the Gross National Product, Dr. Moses concluded that not enough money is being put into research and development. In comparison to France's percent of GNP, which has increased, and Germany's and Japan's levels, which are twice that of the United States, the flat level of increase for the United States could spell a problem in which past accomplishments by the United States are capitalized on by other countries. This, in turn, could push the United States from its preeminent position in the biological sciences.

Some cancer institutes, Dr. Moses said, are seeking funding from private companies and, in many cases, these companies are foreign-owned. This is not an adequate substitute for Federal funding of basic research, and collaborative arrangements with foreign companies, Dr. Moses added, reserve the financial incentives and rewards for the other countries.

Another area of concern, Dr. Moses mentioned, is the growing shortage of biomedical scientists. In the 1970s, enough biomedical scientists were being trained to fill the openings; currently, the shortage is approximately 2,000 scientists. In 1971, training was more than 18% of the research and development budget, in the mid 1970s the funding fell to 11%, and today it is less than 11%.

Bypass Budget

To address the problems in the National Cancer Program, Dr. Moses said, a stable funding base is needed, and the bypass budget can be a tool to achieve that goal. However, Dr. Moses pointed out, there are a number of obstacles to the use of the bypass budget. The Congress is relatively unaware of the bypass budget, its message, and its mission. Furthermore, the bypass budget is difficult to comprehend by people without a scientific background, has too strong an emphasis on intramural programs, and overlooks some of the extramural programs. Also, Dr. Moses said, the budget lacks any correlation to the money appropriated by members of Congress to their districts and States, something in which they are very interested.

Dr. Moses urged the Board to consider reframing the bypass budget into a user-friendly document. This is needed, he said, because there is a significant erosion of public confidence in the war on cancer. While the public has maintained that finding a cure for cancer should be the Federal Government's top research priority, the National Cancer Program and its constituent organizations have not demonstrated that need to the public in a compelling manner. The National Cancer Program has lost champions in Congress, Dr. Moses said, and this is a factor in why the growth of NCI has not matched that of NIH as a whole. During recent House markups of the Labor/HHS appropriations bill, no one could be found on the House side to support the recommendation for a $200 million increase. On the Senate side, it took Senators Hollings and Harkins to sponsor an amendment to increase the NCI budget by the $200 million figure. Once in conference, the increase was debated for 5 days. That such fighting is necessary to get approval for NCI budget increases is a sign that there are problems between the cancer research community and Congress.

Research and Development

Turning to the Administration, Dr. Moses reviewed some of the research and development figures for the Department of Defense (DOD) from 1981 to 1989, which increased 86% over that period, while research and development for all domestic programs increased 9%. In the past 30 months, Dr. Moses said, the DOD has spent more on research and development than NIH has in its entire 105-year history. This shows how policymakers regard biomedical research in relation to other areas. Therefore, it is necessary to reinforce to Congress and the Administration that biomedical research in general, and cancer research in particular, is a good investment that has resulted in economic benefits amounting to billions of dollars in the form of increased productivity, decreased hospitalization costs, and the birth of the biotechnology industry.

Dr. Moses stated that the 16.1% increase in the cancer budget this year is a good development and praised the resolution sent by the NCAB to Congress in support of the increased funding for NCI, but he concluded that more efforts are needed in this area.

Conclusion

Dr. Moses concluded his presentation by outlining ways in which he thought the AACR could assist and work with NCI in formulating a strategic plan for NCI. The AACR would like to be viewed as a partner in defining, crafting, and implementing short- and long-range objectives of the National Cancer Program, and Dr. Moses stated that it is in the best interests of both the AACR and NCI for AACR to play a role in determining funding allocations. He stressed the need for a long-term plan that is comprehensive and cohesive, as well as a user friendly bypass budget that communicates to the American public, Congress, and the President what can be expected from NCI in the future and the support it needs from policymakers. To be effective, stressed Dr. Moses, it is critical that an understandable message to the public and policymakers be formulated that quantifies progress to date and defines challenges to be faced.

Dr. Moses concluded by stating that this needs to be accomplished in partnership with the NCI and NCAB.

Questions and Answers

In response to Dr. Moses' presentation, Dr. Broder noted that the President's Cancer Panel should not be overlooked as an important entity that should be involved in the process. Dr. Broder also stressed the uniqueness and importance of the bypass budget, reminding the audience that the NCI is the only institute with such a tool. He also cautioned those in attendance to maintain a collective memory of the support of the Congress and Executive Branch and not single out specific members who are or are not supportive at any given time.

Dr. Broder then commented that the principle of peer review and the concept that scientific excellence is the measuring stick by which monies are allocated are the guidelines within which the professional needs budget is prepared. He cautioned that taking other considerations into account when preparing the bypass budget could be detrimental.

Dr. Moses remarked that he was in favor of the peer review process and hoped that none of his comments were taken to mean the contrary.

The subtext of presenting the bypass budget by way of Congressional districts, Dr. Broder said, could create problems in the peer review process. There could be strong pressure, especially in a weak economy, to fund scientific projects for reasons other than on pure scientific merit.

Dr. Moses responded by saying that he did not mean to suggest that funds be allocated on any basis other than scientific merit. Showing the budget by district or State was only mentioned as a means of helping to sell the budget to the Congress. He added that he had mentioned the Hollings-Harkins Amendment as an illustration of the problems NCI is having with Congress in obtaining funding for cancer research.

Dr. Lawrence said that the message he got from Dr. Moses was that stronger public education is needed, which will, in turn, affect Congress. Outside organizations, such as the American Cancer Society and the Komen Foundation, can form collaborations and be much more effective in the public education effort, perhaps, than governmental organizations such as NCI, he added.

Dr. Becker said the message he got from Dr. Moses was that the AACR, with a membership of 7,000 to 8,000, felt disenfranchised. He said that the message was a positive one for developing a strategic plan in cancer research not limited to NCI, but open to all who are involved in or have an interest in cancer research.

Dr. Broder mentioned that the bypass budget did go to the coalition, of which AACR is a member, for comment. The AACR is an extremely important group and the NCI needs to have outreach to all of its relevant constituents. The NCI will work on obtaining input from these sources, he stated. Dr. Broder then invited Dr. Moses to attend the Planning and Budget Subcommittee where the NIH-wide strategic plan will be discussed. In closing, Dr. Broder said he wanted to strike a balance between recognizing that the cancer budget is still not as large as they would like and remembering that the increase is larger than what might be expected in these times. Furthermore, the NCI will be funding the largest number of new and competing grants in its history.

Dr. Salmon said that the Congress and the Administration have shown by their votes that they do support the National Cancer Institute, giving proof that the bypass budget did work in its present form. He felt, however, that if a user-friendly version was necessary, the National

Coalition for Cancer Research could publish such a version of the bypass budget and not change the format of the budget version that goes to the Administration.

VIII. DCBDC PROGRAM REVIEW—DR. ALAN RABSON

Dr. Alan Rabson presented a review of the programs of the Division of Cancer Biology, Diagnosis, and Centers (DCBDC). In response to the Board's desire to hear more about the scientific aspects of the Division and less about the budget, Dr. Rabson tailored his presentation accordingly.

DCBDC History and Budget

Dr. Rabson began his presentation with a brief history of DCBDC. The National Cancer Institute was founded in 1937, partly in Boston and partly in Washington, DC. In 1938, the two groups were combined in Bethesda. In a 1966 reorganization, the Division of Cancer Treatment was created—then the Treatment Program and Etiology Program—and DCBDC was given the title of General Laboratories and Clinics, headed by Nat Berlin for the next 9 years. In a 1972 reorganization, General Laboratories and Clinics became the Division of Cancer Biology and Diagnosis.

In 1975, under Dr. Berlin, the annual budget for the Division was $30 million, divided between a $15 million contract program and a $15 million intramural program. Since 1975, the Division's budget has grown from $30 million to $460.8 million and personnel now number 768. The Division is now divided into three programs.

The biggest program is the Extramural Research Program (ERP) which includes the R01/P01 grant program. The 1991 annual budget for ERP was $239.2 million. Dr. Faye Austin is the Associate Director. Dr. John Sogn is Chief of the Immunology Branch, Dr. Colette Freeman is Chief of the Biology Branch, and Dr. Sheila Taube is Chief of the Diagnosis Branch.

Centers, Training, and Resources Program (CTRP), the newly acquired group which Dr. Kimes heads, includes the Centers Branch under Dr. Margaret Holmes; the Organ Systems Coordinating Branch under Dr. Andrew Chiarodo; the Training Branch under Dr. Vincent Cairoli; and the Research Facilities Branch under Mr. Kenneth Brow. The 1991 annual budget for CTRP was $165.8 million.

The Intramural Program consists of 12 laboratories and branches headed by outstanding, distinguished scientists, three of whom are members of the National Academy of Sciences and all of whom are leaders in their field.

Dr. Rabson continued by responding to Dr. Broder's request in the last meeting that Dr. Rabson identify people in an old NCI picture. The picture, Dr. Rabson explained, was taken in 1940 for a *Life* magazine story on the progress in cancer research. The picture comprised many of those in leadership positions at NCI at the time gathered around a table for the photograph.

Dr. Rabson identified Dr. Michael Shimkin, who was a pillar in the Biology Group for many years. Dr. Shimkin was a pioneer in epidemiology and field studies. The next person identified was Dr. Bert Kahler, a biophysicist and key person in the program who became an expert in the use of the electron microscope and developed a number of the modern high speed ultracentrifuges.

Dr. Rabson then briefly described Dr. Murray Shear, a biochemist who went to work for NCI when it was originally located in Boston. He worked with the famous chemists at Harvard on methylcholanthrene. When he moved to Bethesda, he began his work with a bacterial extract

called Coley's toxin, the predecessor of tumor necrosis factor (TNF). TNF has now been cloned and inserted into tumors—work done by NCI Surgical Chief Dr. Steven Rosenberg.

The next person in the picture, "Melroy" according to the magazine caption, has not yet been identified by Dr. Rabson. Chalkley, the next person at the table, was a British physiologist who developed a system of quantitative morphology and was the first to do nuclear counts.

At the head of the table was Dr. Spencer, the Associate Director of NCI. Dr. Spencer, nicknamed "Spenny", was a commissioned officer who was involved in the development of the Rocky Mountain Spotted Fever vaccine. Many at the Rocky Mountain lab, including Spenny, inoculated themselves with the vaccine and then allowed themselves to be bitten by ticks. In 1943, 3 years after the picture was taken, Spenny became Director. He was replaced 3 years later.

Dr. Rabson identified Dr. Mary Maver, a renowned biochemist and one of the few distinguished women scientists at the time in the Institute. Dr. Paul Henshaw, a pioneer in radiobiology, sat next to her. The next person, Dr. Rabson's former boss Dr. Harold Stewart, was the first pathologist hired when the director of the Boston group realized the need for a pathologist in cancer research. Dr. Stewart, now 93, runs a registry for experimental cancer in DCE and is still one of the best diagnostic pathologists for animal tumors in the world, Dr. Rabson added.

Dr. Rabson moved on to Dr. Egan Lorenz, a talented biophysicist who began his work before hydrocarbons were a known cause of cancer; radiation was the only known carcinogenic stimulus at the time. Dr. Lorenz developed a method for making a concentrated suspension of methylcholanthrene, which made it possible to do a whole series of experiments in animals. Dr. Rabson identified Dr. Turner, a commissioned officer who had served in the many facets of the Public Health Service Commissioned Corps.

The last person identified by Dr. Rabson was Dr. Wilton Earl, a man who had a most profound impact on cancer research. The combined efforts of Dr. Earl in Bethesda and Dr. Gey at Johns Hopkins were the forefront of modern tissue culture, Dr. Rabson explained.

Women's Issues

Dr. Rabson continued with a discussion of career opportunities for young women physicians and scientists at NCI. He prefaced this discussion by relating his experience at an American Association of Medical Colleges meeting where the women expressed a great deal of unrest and concern about their chances of succeeding in biomedical research.

In the extramural program of NCI, Dr. Rabson explained, women have done extremely well. Under Dr. Kimes, all three branch chiefs were women. Dr. Rabson then referred to a book called *The Outer Circle*, a collection of essays about women in the scientific community. The title refers to the "inner circle" in science, occupied mostly by men, while women remain largely in the "outer circle."

Dr. Rabson profiled Dr. Maxine Singer, the first woman to become a laboratory chief at NCI. She retired 2 or 3 years ago to become President of the Carnegie Institution of Washington, but she continues to actively run a small laboratory at NCI. In addition to her membership in the National Academy of Sciences and wide acclaim for her work in nucleic acid biochemistry, she is also the youngest scientist emeritus in NIH, a title reserved for those who have retired but continue work in scientific programs.

Dr. Singer has continued her work with repetitive DNAs, which play a significant role in a number of disease processes. They are equivalent to jumping genes of bacterial and yeast

genetics. Repetitive DNAs can move around within the human/mammalian genomes and can inactivate a specific gene. A number of hemophilia cases have been shown to be the result of a repetitive DNA inactivating the gene of the protein necessary for blood coagulation.

Dr. Claude Klee, who was working in the laboratory when Dr. Singer retired, succeeded Dr. Singer as laboratory chief. Dr. Klee is a renowned biochemist who worked as a postdoctorate fellow with Dr. Singer in nucleic acid biochemistry and entomology. She is now primarily a protein chemist interested in protein structure. The laboratory, Dr. Rabson noted, is widely recognized for its basic biochemistry work.

In 1978, after doing extensive work with a protein called calmodulin, Dr. Klee isolated a protein called calcineurin from extracts of brain. In her diligent work with calmodulin and calcineurin over the past 13 or 14 years, she discovered that calcineurin is a phosphatase, removing phosphorus from proteins after kinases have phosphorylated them. Dr. Klee has cloned the gene for calmodulin and for calcineurin.

Dr. Klee has recently generated great research activity in the area of immunity. For some time, Dr. Rabson continued, the immunology community has been trying to understand the signal involved when a T-cell is activated by its antigen; in other words, how the information goes from the outside of the T-cell which is binding into the nucleus to initiate a series of proteins. Studies in this area have demonstrated that immunosuppressant drugs such as cyclosporin, that have proven so effective in organ transplantation, act by binding to their own receptor in the cytoplasm. For example, cyclosporin binds to a receptor called cyclophilin, which in turn acts on calcineurin and stops the whole signal transduction pathway. Calcineurin apparently plays a critical role in turning on the T-cell after it is activated by its antigen, hence Dr. Klee's involvement in this research. There is enormous potential, both for new methods of immunosuppression and at the basic level of understanding T-cells and all of their possible roles in disease, including cancer.

Dr. Rabson discussed some other women scientists who have made their mark at NCI. Dr. Elaine Jaffe of the Pathology Department is one of the world leaders in diagnostic pathology of malignant lymphomas. Dr. Dinah Singer of the Immunology Group is a molecular geneticist who is one of the world leaders in the study of Class 1 MHC molecules. Dr. Susan Gottesman of Dr. Ira Pastan's laboratory is a geneticist who specializes in bacterial genetics and has made important discoveries regarding proteases and bacteria. Dr. Gottesman's discoveries have had great relevance in eukaryotic or mammalian cells, including human cells.

Dr. Rabson concluded his review of the Division by mentioning Dr. Maria Marino, Chief of Surgical Pathology, and Dr. Diane Solomon, Chief of the Cytopathology Diagnostic Group in the Pathology Laboratory, who have both achieved national recognition in their respective fields.

IX. UV LIGHT, IMMUNOSUPPRESSION, AND CANCER— DR. MARGARET KRIPKE

In her opening remarks, Dr. Kripke explained that the topic of her presentation—UV light, immunosuppression, and cancer—may make people wonder how the three are related. Her answer was that the three are all related to the skin. Historically, she said, skin cancer has not received as much attention as some of the other types of cancer because the cure rate for most skin cancers is very high and, even for the most aggressive skin cancer such as melanoma, the mortality rate is only 25% compared to much higher rates for other forms of cancer. Recently, there has been an increased interest in skin cancer due, in part, to President Reagan's skin cancer. Other factors, such as an unexplained increase in skin cancers, have also contributed to the increased interest. Although there are no data to support the theory, it is thought that the increase in skin cancers is due to an increased exposure to sunlight. Another factor that has captured the imagination of the American people, is the systematic decrease in the ozone layer, which surrounds the earth and acts to filter out much of the sun's harmful ultraviolet light.

The type of light that is of concern, Dr. Kripke said, is in the ultraviolet B region of the spectrum. Deterioration of the ozone layer will let in ultraviolet light in exactly the spectral region that causes skin cancers, sun burning, and negative immunological effects.

Dr. Kripke discussed recent findings about the immunology of the skin. She showed mouse epidermal cells, originally thought to be related to melanocytes, which are known to be derived from bone marrow and are part of the immune system. The cells, called epidermal Langerhans cells, are related to macrophages and are the first line of defense in immunologic reactions. The reaction most studied in these cells is the contact hypersensitivity response, such as is found in poison ivy. The antigen, Dr. Kripke explained is taken up by the Langerhans cells, which then migrate into draining lymph nodes. The antigen, which is sitting on the surface of the Langerhans cell, stimulates T-lymphocytes, initiating the immune response.

The recent studies that determined this mechanism followed the fate of the epidermal Langerhans cells using a fluorescent dye painted on the skin as an antigen. From earlier work, it was already known that draining lymph node cells removed from one mouse could induce a contact allergy reaction when injected into another mouse. Using the dye technique, studies have been conducted to determine the types of cells that induce the response. These studies have shown that the cells in the lymph node with antigen attached to them are Langerhans cells, which are in close contact with T-lymphocytes. Another recent discovery, Dr. Kripke said, is that keratinocytes in the epidermis have been shown to produce soluble mediators that are involved in both inflammation and immunity. It is now known that exposure of skin to ultraviolet light can alter the immunologic components of the skin. One of the first discoveries in this area was the dramatic effect ultraviolet light has on epidermal Langerhans cells—their dendritic appearance is lost, and ATPase appears to be clumped in the cell body. These morphological alterations in the skin are also accompanied by functional alterations. Skin exposed to ultraviolet radiation and then sensitized with a contact sensitizer will fail to produce a contact allergy response and, instead, will trigger production of antigen-specific suppressor T-lymphocytes. In this manner, local ultraviolet radiation has the ability to activate a systemic immunosuppression.

It has been shown, Dr. Kripke said, that if epidermal Langerhans cells that have been exposed to ultraviolet light are collected from the draining lymph nodes and transferred to another animal, the cells do not induce the contact hypersensitivity reaction seen when normal epidermal Langerhans cells are transferred. This shows, Dr. Kripke explained, that ultraviolet radiation alters antigen-presenting activity of the skin and that epidermal Langerhans cells are most likely the major target.

A second, indirect way in which ultraviolet light can interfere with the immune response, Dr. Kripke explained, is at distant sites. An animal can be sensitized at a nonexposed site and then tested for a contact or a delayed type hypersensitivity response. In this case, the response is deficient and the animal has instead made antigen-specific suppressor lymphocytes.

The mechanism by which ultraviolet light causes these changes is thought to be through the release of soluble mediators from keratinocytes. This was shown in an experiment where keratinocytes were exposed to ultraviolet light. The culture fluid in which the keratinocytes were grown was then injected into animals, where it mimicked the effects of ultraviolet radiation. Specifically, if culture fluid from ultraviolet-irradiated skin cells is injected into mice, which are then immunized for production of a delayed hypersensitivity reaction, the reaction is reduced and there is formation of antigen-specific T suppressor cells.

The cause of these changes, Dr. Kripke said, is DNA damage, most likely to keratinocytes. This conclusion comes from experiments using lipid vesicles (liposomes) containing DNA repair enzymes, which increase the amount of DNA repair in the skin. If these liposomes are put on the skin of animals exposed to ultraviolet radiation, the increased DNA repair will eliminate the immunosuppressive effect of ultraviolet light.

Dr. Kripke noted two important questions raised by this research: 1) What are the factors that cause immune suppression and lead to suppressor cell induction? and 2) How do these factors work to change the immune response? If the cytokine that has the ability to induce antigen-specific suppressor cells is identified, it may be applied to prevent graft-versus-host disease, organ rejection, and a variety of autoimmune diseases.

Dr. Kripke then moved on to discuss the role of ultraviolet light in the formation of melanomas. Melanoma, Dr. Kripke said, has been proven antigenic in humans as well as mice. Recently, a mouse model for producing primary melanomas was discovered in which a chemical carcinogen, dimethylbenzanthracene (DMBA), was applied to 4-day-old mice. When the treated mice matured, a tumor promoter was painted on their skin and 100% of the animals developed skin cancer, a portion of which were melanomas. In looking at melanomas, Dr. Kripke said, they wanted to find out if they could substitute ultraviolet light for other parts of the carcinogenic process; the answer was yes. During the development of melanomas, they added ultraviolet light exposure to the DMBA and the tumor promotor. This chronic exposure to ultraviolet light dramatically shortened the time of development of melanomas. This was shown to be a direct effect of the ultraviolet light exposure, because ultraviolet light that was not put on the same site as the DMBA had no influence on the rate of tumor development.

To find out if the effect of ultraviolet radiation is on the tumor cells themselves or on the host environment, Dr. Kripke said, another model was prepared—one that separated the two questions. In this model, mouse ears were exposed to ultraviolet radiation and then injected with melanoma cells. In this case, there was a dramatic effect on the development of tumors. Tumors formed in approximately 50% of the mice, whereas in the mice that did not receive ultraviolet radiation prior to the injection of melanoma cells, none developed tumors. Dr. Kripke noted that this shows that ultraviolet light enhances the outgrowth of melanomas. Recent work, Dr. Kripke stated, has involved trying to elucidate the mechanism of this effect. One possibility is that ultraviolet light causes the release of specific melanocyte growth factors that stimulate melanoma growth. Another possibility is the production of inflammatory mediators produced by keratinocytes. The third possibility is that ultraviolet light may influence the immunologic competence of the skin.

To determine the specificity of the effect of ultraviolet light on tumors, Dr. Kripke said, they looked at a number of tumors and found that there was a perfect correlation between tumors that elicit an immune response and tumors that are affected by ultraviolet light. To test the immunology hypothesis, two clonal cell lines were developed from the same melanoma. One of the lines was highly immunogenic and the other was not. In this experiment, only the immunogenic tumor was affected by ultraviolet radiation. In another confirmatory experiment, animals were immunized with melanoma cells and then exposed to ultraviolet radiation on the ear. Half the animals received a challenge tumor at the site of ultraviolet radiation exposure and the other half at a nonexposed site. Those animals challenged in the irradiated site could not reject the tumor, while the other animals could. This was true even though the irradiated animals had plenty of sensitized T-lymphocytes. This shows, Dr. Kripke explained, that ultraviolet radiation prevents an immunologic response at the irradiated site.

Recently, Dr. Kripke said, an experiment was performed to test the hypothesis that the local release of growth factors is the causative mechanism. Culture fluids from irradiated keratinocytes were mixed with melanoma cells and were shown to have a stimulatory effect on the cells when compared to cells mixed with culture fluid from keratinocytes that were not irradiated. It is thought, she said, that local release of immunosuppresive mediators is responsible.

Dr. Kripke then related an interesting observation regarding melanoma—the proportion of melanomas diagnosed rises sharply in the summer months. Dr. Kripke said that this has always been explained as occurring because people bare more skin in the summer and therefore notice flaws in their skin more readily. She speculated that this sharp increase may be due to a

stimulatory effect of ultraviolet light and might be a more serious biological phenomenon than previously believed.

In conclusion, the two messages that Dr. Kripke emphasized were: 1) reduce sun exposure and counsel patients with melanoma to reduce sun exposure; and 2) skin is an immunologic organ, and therefore, the immune system is vulnerable to environmental influences that affect the skin.

Dr. Kripke was asked if populations that live at high altitudes had been studied. She replied that melanoma is predominant in light-skinned people and she was not aware that such a population existed. As a follow-up, she said that there were no animal populations to study with a naturally occurring melanoma.

A question was raised as to whether melanoma cells had been injected intraperitoneally to see if ultraviolet light had an effect and the answer was no, that experiment had not yet been performed. Dr. Kripke added that she thought there would be no effect, because the ultraviolet radiation effect on melanoma was generally very localized.

In response to another question, Dr. Kripke said that ultraviolet light can induce immunosuppression in humans independent of skin color, unlike the ability to induce sunburn and skin cancer. A point was made that 50% of all melanomas are in 5 to 8% of the population that have dysplastic nevi and there is a genetic component to melanoma susceptibility. One last point was discussed relating to the immunosuppression associated with HIV and how ultraviolet light might affect HIV. Dr. Kripke's response was that exposing the skin to ultraviolet light might trigger HIV production, since the skin is one of the places where HIV is harbored in infected individuals; however, there is no experimental evidence to support that possibility at the present time.

X. ROLE OF THE *abl* ONCOGENE IN HUMAN LEUKEMIA— DR. OWEN N. WITTE

Dr. Witte thanked the NCAB for his invitation to speak at its meeting. He explained to the Board that the 20th anniversary of the National Cancer Act coincides with the length of time he has been involved with cancer research. Dr. Witte stated that this Act has greatly influenced his career. He has received NCI funding since the beginning of his career.

Dr. Witte stated that one of the objectives of his presentation is to relate how aspects of basic research can have an eventual impact in the clinic. Although it may be easy to document how such basic research can influence clinical work at a certain point in time, it is impossible to predict which basic research will have such an impact. Agreeing with a message from Dr. Broder, Dr. Witte emphasized that it is important to support basic research for its sake alone because one cannot predict what the outcome of that research will be. If people work on issues in which they are interested, then the outcome of their work will be positive.

Work on the role of the *abl* oncogene in human leukemia has a broad context. It is the result of the convergence of several different fields, such as cytogenetics and the influence of chromosomal changes on cancer; molecular biology in its broadest context, including recombinant DNA technology; and the study of oncogenes as the etiological agents of cancer. Together, these studies have provided a better focus for new types of diagnostics and therapeutics.

Dr. Witte indicated that he would also talk about the concept of chimeric oncogenes, the idea that two different genes may need to come together to form an oncogene. This process requires a specific synergistic interaction of two different genetic elements to create the functional oncogene. Dr. Witte stated that he will discuss the *bcr-abl* oncogene.

Discussing the information he had presented in a broader perspective, Dr. Witte asked the audience to consider the impact of the germ theory of disease on the field of biomedical science. In the 1800s or early 1900s, anyone in the fields of pathology or medicine was greatly influenced by the idea that specific bacteria or viruses could be the etiological agents of specific types of diseases. At that point, the great quest for biomedical science was to identify specific types of bacteria. There was no therapy available, but there was hope that understanding of the etiological agent would eventually define the "silver bullets" that would be produced. Dr. Witte suggested that this is the case in cancer today. Instead of looking for specific bacteria or viruses, investigators look for specific molecular events for the creation of oncogenes that influence cancers.

Dr. Witte presented a diagram of families of genes referred to as oncogenes. When these genes are mutated, overexpressed, or somehow altered, they can be associated with specific cancers. Dr. Witte described protein tyrosine kinases, which are proteins that are involved in growth regulation and were discovered about a decade ago. Dr. Witte then discussed the work leading up to this discovery.

Dr. Witte explained several ways to make an oncogene, limiting his examples to those found in human cells. One could make subtle mutations, with little damage to the DNA and significant consequences to the oncogene and its regulation. One could take an oncogene out, which might affect cells. The creation of duplicate, triplicate, or multiple copies of the gene is a type of mechanism seen for the new HER-2 oncogene—important in metastatic breast carcinoma. One could also perform a process called translocation, in which two pieces of different chromosomes recombine, exchanging partners and creating new chromosomes. Various results occur at the site of these chromosome translocations. One result is transcriptional deregulation or "too much of a bad thing." Other results include the activation of the *myc* oncogene in Burkitt's lymphoma, the *bcl-2* oncogene in follicular lymphomas, and some growth factor genes in a few rare instances of lympho leukemias.

Dr. Witte used the analogy that there are many ways to cause pneumonia, but not all of them are associated with pneumococcus. One must have an understanding of what the etiological agent is to correctly treat the pneumonia. Treatment with the wrong antibiotic leads to poor prognosis as does treating for the wrong oncogene. It is important to understand how to diagnose so that the therapies will relate to the molecular events.

Structural alteration is another consequence of the translocation. For example, in several cases of childhood pre-B cell acute lymphocytic leukemia, two different genes from two different chromosomes are rearranged in close proximity to one another and create a chimeric oncogene.

Dr. Witte discussed the chimeric oncogene found in human chronic myelogenous leukemia (CML), which involves a gene called *bcr* that joins to a gene called *abl*. The molecular mechanism that causes the *bcr* gene to abnormally activate the *abl* gene is essential for the transformation of the cells and the causation of leukemia. Dr. Witte presented an interesting case of a specific hormone receptor. A gene called *myl* joined to a gene called *rar* was recently described in acute promyelocytic leukemia. Genes that normally regulate the pattern of development of cells can be structurally altered to cause an abnormal overgrowth of cells.

Most of the work in the area of chromosome translocation has come from studies of leukemias and lymphomas, largely because of access to materials from the peripheral blood or bone marrow. However, dramatic improvements have occurred in cancer cytogenetics on solid tumors showing oncogenic changes.

Dr. Witte then discussed the history of CML and the role of the *bcr-abl* gene in CML. The initial description of CML is over 100 years old. This disease is called chronic

myelogenous leukemia because there is an initial phase of the disease in which the cells retain their ability to undergo normal differentiation, although they expand. Many mature granulocytes and other elements of the myeloid blood-forming cell pathways are found in the peripheral blood of these patients. However, there are too many immature cells, and they eventually accumulate additional genetic damage and convert to the blast crisis or acute phase. At this point, the disease resembles an acute leukemia that is quite refractory to treatment. Dr. Witte cautioned that it is important to make a correct diagnosis in the earlier chronic phase of CML because it is a treatable and curable leukemia. There is some hope that certain biological response modifiers, such as alpha interferon, can provide long remissions from the chronic phase. The most curative therapy for the disease at this time is bone marrow transplantation.

Dr. Witte explained that the landmark discovery that began to unite the fields of cytogenetics in this type of leukemia was made 30 years ago. Researchers discovered, that one of the chromosomes in a normal cytogenetic spread is abnormal. Based on this consistent chromosomal abnormality, Dr. Peter Nowell correctly proposed that there would likely be specific cytogenetic abnormalities found for many types of cancers and leukemias. Almost 100% of patients with this disease either have this specific chromosome change or the molecular remnants of that change, perhaps retranslocated to another chromosome. Knoll's initial observation remained in the literature for about 10 to 15 years.

In the 1970s, a technique called chromosome banding emerged. Janet Rowley and her colleagues began to document specific banding patterns of specific chromosomes and changes to those patterns in different cytogenetic events. They found that the Philadelphia chromosome, as Dr. Nowell had named that small consistent cytogenetic abnormality, was a translocation between a small piece of chromosome nine and another piece from chromosome 22. This information added specificity to the diagnosis.

The next breakthrough came after a long hiatus and involved the identification of oncogenes through the use of retroviral-induced animal models of cancer in leukemia, funded through the National Cancer Act and the Special Virus Cancer Program. The *abl* oncogene is one such oncogene, named after Herb Abelson who discovered it. It was known that the *abl* oncogene, existed and could be found on the same segment of chromosome nine that was translocated to the Philadelphia chromosome CML. From that realization, the work of five or six laboratories was combined to create a detailed map of the molecular event created by the Philadelphia chromosome translocation.

Dr. Witte presented details about this event. He explained that the Philadelphia chromosome joins two different genes together—a gene called *bcr* which initially stood for breakpoint cluster region and a gene on chromosome nine called *abl*. Only a subset of the genes' exons or coding sequences are used. In the case of CML, the exon, or *bcr* is drawn together with a subset of the exons of *abl* by a process of RNA splicing. RNA splicing creates a large mRNA that is eventually converted to a large protein called p210. The p210 protein and the chimeric mRNA are found only in the cells of this specific type of leukemia. Dr. Witte noted that this is valuable in terms of diagnosis and for following patients on the presence or absence of this cancer marker. He said that a different pattern exists in acute lymphocytic leukemia in which the chromosome breakage occurs upstream in the gene and only a small portion of the *bcr* gene is retained in the chimera.

Dr. Witte emphasized that he explained this background to illustrate that there is an understanding of cytogenetic events in specific types of cancer. He then diverted the discussion to the idea of diagnosis. The structures of the *bcr-abl* oncogene lend themselves to a new type of diagnostic procedure called reverse transcriptase prime polymerase chain reaction developed by Dr. Witte's laboratory in collaboration with the Cetus Corporation. Dr. Witte stated that this approach is being used for multiple oncogenic events in cancer and will probably become one of the standard technologies used in the fight against cancer. Since this junction between the *bcr* gene and the *abl* gene is only found in cancerous cells, this information is used as a specific tool

for identification of the genes. The procedure starts with the mRNA and uses the enzyme reverse transcriptase to convert into DNA, and then uses the process of polymerase chain reaction developed to amplify that junction further.

Dr. Witte presented the example of a patient in whom a specific type of junction was identified in the stage before bone marrow transplant . The signal only could have come from the mRNA of that oncogene. After the bone marrow transplant, the signal disappeared, but there was a reaccumulation of that signal in the patient 2 years later. At 36 months there was a dramatic increase in the level of the cancer marker, and the Philadelphia chromosome became positive at 38 months. The patient went into clinical relapse about 6 months later.

Dr. Witte expressed frustration with the coordination of the application of scientific information and techniques through cancer study groups or cooperative oncology trials. He added that this information must be coordinated between both the therapy and clinical trials branch and the diagnostics branch to be put into clinical practice.

Dr. Witte discussed the derivation of the *abl* oncogene. When Herb Abelson was a medical fellow at the NIH, several people were studying a group of viruses that caused leukemias in mice, exemplified by a virus called the Maloney murine leukemia virus. When inoculated into susceptible strains of mice, this virus gave rise to T-cell leukemias (leukemias of the thymus or peripheral T-cells that have a long latency). Abelson was interested in taking away the target cells for that virus. He treated mice with the Maloney virus, but first he treated them with steroids. The idea was to knock out the cells of the thymus that would normally turn into the tumor. After approximately a year, only three mice in the initial group of about 400 came down with the disease. He did not know it at the time, but a mixture of viruses developed—the Abelson murine leukemia virus and the parental virus. The Abelson virus preparation had a different biology—instead of tumors developing in susceptible animals in 4 to 6 months, very different tumors developed in 3 to 5 weeks. The tumors developed in lymphoid tissues throughout the body, instead of occurring in the thymus.

Dr. Abelson moved from the NIH to do a short-term training period at Massachusetts Institute of Technology. By recombinant DNA techniques and cloning and expression studies, they determined that the Abelson virus was a derivative of the Maloney virus. The Abelson virus has the ends of the Maloney genome, but has a unique piece of DNA in its center that it stole from the host chromosome. This is a process of viral transduction and has been extremely useful in identifying these cellular oncogenes.

Dr. Witte explained that his work in the laboratory involved demonstrating the nature of the biochemical activity of that gene product. He and his group identified, isolated, and purified the gene, and could show that it had a unique type of protein kinase activity demonstrated by the ability to autophosphorylate itself and other molecules. Dr. Witte discovered that the end product of this specific type of phosphorylation reaction was phosphotyrosine, which was a significant finding in the field of cell biology and cell signaling. Many of the growth factor receptors that control and regulate all normal processes in cells are carrying out a similar type of reaction. The insulin receptor, EGF receptor, platelet-derived growth factor receptor, and the *her-2* oncogene are all members of the same family and can be amplified in breast carcinoma.

Dr. Witte further explained that the viral transduction and the chromosome translocation systems are structurally very similar. In both cases, the Abelson oncogene is activated by creating a chimera between a virus and a cell gene or between two different cell genes. Both of them activate these tyrosine-specific kinases, but they are not identical. They have different properties and different degrees of potency. In fact, he noted, it was difficult to demonstrate that the *bcr-abl* oncogene is an oncogene. It was found that those same cell culture systems could be infected using techniques of retroviral gene transfer with the *bcr-abl* oncogene and give a prolific growth that could be transplanted in syngeneic mice and demonstrated to be malignant. From this work, an assay was developed to prove that *bcr-abl* is an oncogene. Subsequent work

produced a mouse model for leukemogenesis with the *bcr-abl* oncogene that is a good analog of human chronic myelogenous leukemia.

Dr. Witte said that, initially, he and his group did not think that the structure and function of the *bcr* gene was important. However, they found that the *bcr* segment is critically important for the activation of this chimera and activation of Abelson and that the *bcr* gene has a very unique structure. It has a piece of its own protein that will bind to the control region that regulates the Abelson tyrosine kinase. This information defined a new class of protein-to-protein interaction that had not been seen before. Different from other proteins with binding capacities, this type of chemical glue is not dependent on phosphotyrosine, but is dependent on phosphoserines and threonines. Later work revealed that the *bcr* gene itself is a key signaling molecule within the cytoplasm of all mammalian cells. It harbors a genetic activity called the GTPase activating function at one end of the molecule; these are the genes that regulate the *ras* oncogenes. In the center, there is an analogy to an oncogene called *dbl* , which is known to contain activity at the nucleotide exchange factor—a key intracellular regulatory molecule. There is an SH2 binding capacity and a completely different serine kinase activity within the end of the molecule. It has a sequence structure that makes it a new class and a new family member. Dr. Witte suggested that specific drug inhibitors for this class of enzymes will eventually have an impact on intracellular signaling transduction, at least in the case of CML.

Dr. Salmon commented that fluorescent *in situ* hybridization could be useful in diagnosis because it gives a rapid ability for cellular genetics, including interphase, to recognize translocations and additional copies. Dr. Witte agreed with Dr. Salmon and stated that there are so many varieties of diagnostics that the critical issue is to decide on the correct study protocols. Dr. Salmon asked if anyone knew the causative factor for these translocations. Dr. Witte answered that it is an open question, except, possibly, for those translocations that involve the immunoglobulin loci as one of the partners, in which case there is probably an involvement of the normal genetic factors that regulate immunoglobulin or T-cell receptor gene rearrangement. Dr. Witte stated that he has a program project grant section from the NCI to study this issue.

Dr. Jako asked whether a selective event that occurs is initiated once or repeatedly. Dr. Witte stated that, based on the molecular genetics of the disease, once an event like the Philadelphia chromosome occurs in a cell, it confers an advantage upon that cell. It is not an absolute advantage and its pathway to the frank malignancy is not always the same in terms of timing or the secondary events that may complement it. But, those events do get fixed in the population and there are multiple integrations of those retroviruses and, eventually, one dominates. One can only see the chromosome changes when the patient comes to the clinic and the tumor load is tremendous. Dr. Witte explained that this is why he feels the model systems under development to study the process of leukemia from the initial interaction of oncogene and stem cell will be useful.

Dr. Henderson asked if the double Ph1 chromosome becomes initiated at the same point in time. Dr. Witte stated that the most common secondary cytogenetic abnormality in this type of leukemia is the duplication of the Philadelphia chromosome. Duplication of the Philadelphia chromosome has been documented in a few cases at the molecular level in kinetic fashion during the disease in which there was a single copy and then duplication.

Dr. Werner Kirsten asked if the *bcr* was initially described to characterize increased rates in that particular region. Dr. Witte answered that there are regions of the chromosome, called fragile site regions, that can be tested for unusual structural features, but the question is still unanswered as to what makes chromosome rearrangement occur.

XI. TREATMENT OF LEUKEMIA/LYMPHOMA WITH GENETICALLY ENGINEERED MONOCLONAL ANTIBODIES ARMED WITH RADIONUCLIDES—DR. THOMAS WALDMANN

Dr. Waldmann began his presentation by explaining that he would discuss the application of basic scientific findings in immune intervention and the use of monoclonal antibodies in cancer treatment. More specifically, he would discuss the use of humanized, genetically engineered monoclonal antibodies armed with toxins or radionuclides for cancer therapy.

Reviewing the science, Dr. Waldmann noted that it had been 15 years since monoclonal antibodies had been produced using hybridoma technology. Although the monoclonals have had an impact in cancer biology, he said, they have not reached their potential, because, while murine proteins elicit an immune response, they are poor cytocidal or cytostatic agents on their own.. In other words, he said, they know where to go, but they don't know what to do once they get there. In the past few years, however, some of these problems have been addressed. The approach to this type of therapy is being revolutionized by using human monoclonal antibodies that are genetically engineered to generate agents with better pharmacokinetics, lowered immunogenicity, and greater efficacy.

The lessons learned from the study of the interleukin-2 receptor, Dr. Waldmann said, can be applied to others. The rationale for using the IL-2 receptor, he said, was that it is a receptor that is not expressed by resting cells but, rather, by abnormal cells in patients with leukemia, lymphoma and other tumors, and autoimmune disorders. What is wished, he concluded, is to eliminate the T-cells causing disease while retaining the immune response cells that do not have the IL-2 receptor in their resting state.

Discussing the IL-2 receptor, Dr. Waldmann stated that nothing was known of the receptor before their work began. Using hybridoma technology, a mouse monoclonal called anti-Tac was produced and used to molecularly clone the gene coding for the IL-2 receptor. Subsequently, cross-linking studies showed two molecules responsible for binding IL-2. There is a form of the receptor that cleaves from the cell surface that can be measured using an ELISA technique on biological fluids. Normal individuals have low levels of the cleaved form of the IL-2 receptor, but patients with cancer have dramatically elevated levels. Therefore, he said, there are a series of neoplastic diseases as well as autoimmune disorders that might be targets for IL-2 receptor-directed therapy. Furthermore, the greatest area of interest for pharmaceutical companies for this therapy is in allograft rejection and graft-versus-host disease.

Dr. Waldmann said he would limit his discussion to studies in adult T-cell leukemia, which is an extremely aggressive cancer, killing patients with or without chemotherapy at a mean rate of 20 weeks. This disease is a malignancy of CD3 and CD4 cells, which infiltrate the skin, lungs, and liver, and produce profound immunodeficiency. The patients in the study had malignant cells displaying 10,000 to 35,000 IL-2 receptors per cell, whereas the normal T-cells do not display the IL-2 receptor. They wished, Dr. Waldmann said, to block the interaction of the growth factor with its receptor and thereby act on the malignant cells without acting on the resting cells of the immune system.

Initially, Dr. Waldmann reported, they used the mouse monoclonal antibody to treat patients because the patients were so immunosuppressed they could not make antibodies to the mouse immunoglobulin. There was no toxicity in the 20 patients treated and seven patients underwent remissions, three of which were complete. There were no responses in 13 of the patients. The failures were not due to antibodies to the monoclonal, but to a selection of tumor cells that neither make nor need IL-2.

Mouse monoclonals have also been used in organ transplantation but have not always been successful due to the development of antibodies to the mouse monoclonal. Dr. Waldmann

noted that for this reason, mouse monoclonals are not adequate for this type of work. They turned instead to using genetic engineering to change the mouse monoclonal and yet maintain the high affinity of the antibody. What they produced was an antibody with improved pharmacokinetics and a longer survival rate. The ability to inhibit IL-2-mediated proliferation is identical between the mouse form and the humanized version. Looking at immunogenicity, Dr. Waldmann said they are beginning to achieve their goal—all five test monkeys used in the study made antibody to the mouse version, while none made antibody to the humanized version. Unfortunately, Dr. Waldmann said, on its own the monoclonal antibody is not enough to prevent allograft rejection.

Dr. Waldmann then reminded the audience that there are two binding proteins for IL-2. If only one is blocked, it has an effect on but does not fully abrogate, IL-2-mediated events. However, when antibody to both IL-2-alpha and IL-2-beta are used, IL-2-mediated events are completely abrogated. Since IL-2-beta has also been humanized, Dr. Waldmann speculated, a combination of the two will be used in allograft protocols and in the treatment of graft-versus-host disease. However, in cancer, Dr. Waldmann thought toxin or radionuclide conjugates would be necessary. In this manner, a toxin is identified, the element that binds it in an unwanted manner is removed and is replaced with a targeting agent that targets IL-2 or a fragment of the antibody.

The concern with toxins, Dr. Waldmann said, is their immunogenicity. A system is needed where the humanized antibody is combined with a nonimmunogenic cytocidal agent. To do this, the monoclonal must first be linked with a chelator that tightly binds a radiometal, the key is use of a chelator that does not release the radiometal. Twelve patients with adult T-cell leukemia have been treated with such a therapy using yttrium-90 in a dose escalation study. With 5 and 10 millicuries there was no or low toxicity, but, when the dose was increased, granulocytopenia and thrombocytopenia emerged as dose-limiting toxicities. Of the first eight patients, one died and seven had partial or complete remissions. These studies have used a beta emitter, and Dr. Waldmann suggested that alpha emitters may make even better candidates—namely, astatine-211, lead-212, and bismuth-212. The future in cancer therapy, Dr. Waldmann concluded, will involve the use of humanized or human antibodies chelated to have beta- or alpha-emitters on their surface.

Dr. Waldmann was asked about the host's immunologic response to the toxin. Dr. Waldmann responded by saying that they are going to have to work around the immunogenicity if they are to treat patients with 6 or 10 cycles of therapy, and, he added, there are ways around it.

Dr. Waldmann was then asked about rotating the different toxins. He answered that there would still be problems; however, it could be done.

In response to a question about the fate of bismuth, Dr. Waldmann said that it is excreted in the urine. A problem with bismuth is that it has a half-time of only 1 hour and 1 minute.

Dr. Waldmann was asked how a therapy against such an aggressive disease could show such a high survival rate with mostly only partial responses. He answered that, he too, was perplexed by the situation. The cells in circulation had been studied and shown to be malignant. He did state that a patient had been showing signs of escalating IL-2 receptor presence and that he thought that the patient would relapse.

In response to a query as to the benefit of making an antibody toxin construct as opposed to other constructs, Dr. Waldmann answered simply that it depends on what works.

Dr. Waldmann was then asked about using the conjugates for areas other than treatment. He responded that they have used them for studying pharmacokinetics and in scanning.

Dr. Waldmann was asked about the price of the therapy. He said that shipments of 100 millicuries of yttrium, for five patients, cost $2,000 and the production of 10 grams of humanized gmp antibody, at 10 milligrams a dose, costs $62,000; however, he had no idea how much it would be sold for.

XII. DCT PROGRAM REVIEW—DR. BRUCE CHABNER

Dr. Chabner presented a broad overview of the Division of Cancer Treatment (DCT) and he began by discussing the budget. He showed the budget, by program, for 1991 and noted that it was a tough year and that the overall budget change was only +2%, most of which was accounted for by AIDS research increases. Breaking the budget down by mechanism, Dr. Chabner explained that the only increase was in the RFA line, much of which is related to the proton facility design project. Overall, he concluded, a number of aspects of the DCT program had decreases. Research and development contracts decreased by 13% and intramural research related to cancer decreased by 4%.

The DCT's use of its Board of Scientific Counselors was Dr. Chabner's next topic of discussion. Dr. Chabner said that the Board was active in helping the DCT make decisions in many areas including the drug development program, intramural research laboratories, and clinical trials. The Board also provides concept review and budgetary advice, and makes site visits. This past year they reviewed approximately $40 million in concepts and, of this amount, they approved $33 million. Dr. Chabner emphasized that the DCT listens to the Board's advice carefully.

Dr. Chabner said that the Board conducted two important site visits in 1991—one at the Laboratory of Drug Discovery and the other at the Clinical Research Branch of the Biological Response Modifiers Program (BRMP). At the first visit, the site visit team made a number of important recommendations including that the laboratory was to emphasize their medicinal and natural products chemistry and deemphasize some of the biology with which they were involved. The Board also advised that the laboratory was too large, initiating the separation of the pharmacokinetics group. In the BRMP site visit, the team was very impressed with several of the clinical trials being conducted and with the cooperation between the laboratory and the clinic. The site visit team noted the difficulty the program was having accruing patients, and a suggestion was made to try to establish better cooperation with outside institutions. Another major suggestion by the team was to recruit a full time branch chief. Dr. Chabner added that, during the upcoming year, site visits are planned for: the Surgery Branch, the Clinical Pharmacology Branch, the Medicine Branch, and the Laboratory of Molecular Immunoregulation.

Two major new appointments have been made over the past year—Dr. Carmen Allegra was named to take Dr. John Minna's place as the Navy Medical Oncology Branch Chief and Dr. Edward Sausville was named the Chief of the Laboratory of Biological Chemistry.

Dr. Chabner described some of the more important events occurring in the drug development program and in clinical trials. First, he discussed taxol, noting its activity in ovarian and breast cancer. He stated that they have gone a long way in solving the drug supply problem for the time being. There is now a sufficient supply to make the drug available to patients with ovarian cancer on an open protocol, and there are plans for applying for drug approval next year. Dr. Chabner continued by noting that the tamoxifen trial through the National Surgical Adjuvant Breast and Bowel Project (NSABP) started this year, which is an extremely important initiative, and makes use of the cooperative groups for cancer prevention studies.

Turning to natural products screening and drug discovery, Dr. Chabner stated that a number of compounds have been found to be positive in the AIDS screening area and are being

pushed toward clinical development as quickly as possible. He also said that there are supply problems associated with some of the natural products and that several important conferences were held to address the issue. One conference was held on biodiversity and the need to preserve biodiversity, the outcome of which was an initiative between NCI, the Agency for International Development, and the National Science Foundation to support projects to collect and test natural product extracts from abroad. A second conference in this area was on molecular screening. The consensus is, he said, that screening systems must be diversified beyond examining cell lines to looking at molecular targets.

Cytokines and monoclonal antibodies are coming into their own at the DCT, Dr. Chabner said. Studies in breast cancer using monoclonal antibodies and IL-2 R24 studies in melanoma are both showing anticancer activity. Looking to the future, Dr. Chabner mentioned several new high-priority trials that will begin this year, including adjuvant trials in breast cancer, the autologous bone marrow trial, and a second intergroup trial on carcinoma *in situ* and the effect of tamoxifen in preventing recurrence. There are also additional trials in lung cancer, gastric cancer, and melanoma.

Under the rubric of management initiative, Dr. Chabner mentioned that there is an attempt being made to fund more clinical trials through the Research Program Grant pool as opposed to doing it strictly as a cooperative group activity. He also noted that a treatment referral center for patients who will be eligible for taxol and other experimental drugs was established, and a taxol Cooperative Research and Development Agreement (CRADA) was signed with Bristol Meyers. Dr. Chabner said the intramural program received accreditation for the intramural training program in medical oncology, the first program at NIH to be accredited in internal medicine. Another significant intramural event, he said, was the transfer of the clinical trainees to the United States Public Health Service, which provides the trainees with a career track and higher pay.

Dr. Chabner reported that a number of new drugs were approved by the FDA, including: BCG for bladder cancer; Levamisole for adjuvant therapy in Duke's C colon carcinoma; Fludarabine for refractory chronic lymphocytic leukemia; hexamethylmelamine, a second-line drug in ovarian cancer; Idarubicin, the best anthracycline, for AML; G and GM-CSF for neutropenia related to cancer chemotherapy and marrow transplant; and DCF, deoxycoformycin, for hairy cell leukemia. Dr. Chabner also mentioned active new drugs which are in the early phases of clinical trial, including: R-verapamil; trans-retinoic acid, for refractory acute promyelocytic leukemia; anthrapyrazoles, for breast cancer; suramin, for prostate cancer; and topotecan, which has shown anticancer activity in breast cancer. Temozolomide studies have been performed in England, and the DCT, said Dr. Chabner, is trying to begin trials in the United States with this drug in brain tumors.

In conclusion, Dr. Chabner said that he hoped his presentation brought out the growing relationship between the laboratory and the clinic in the Division of Cancer Treatment and made it clear that ideas coming from the laboratory are quickly applied in the clinic and vice versa.

XIII. CLINICAL ONCOLOGY GROUP—DR. GREGORY CURT

Dr. Curt began his presentation by describing the Clinical Oncology Group (COP), which he said consists of six branches: the Medicine Branch; the Pediatric Branch; the NCI Navy Medical Oncology Branch; the Radiation Oncology Branch; the Surgery Branch; and the Clinical Pharmacology Branch. All the work being done by these branches, with the exception of the Navy Medical Oncology Branch, is done at the Clinical Center in Building 10 at NIH. Dr. Curt reported that the NIH Clinical Center contains half the beds dedicated to clinical research in the United States. The COP currently has 100 inpatient beds, and during the past year has had approximately 30,000 inpatient days. Outpatients have increased from 30,000 to 40,000 a year.

In the arena of AIDS, Dr. Curt said, the Medicine Branch has played an important role by characterizing the folate pathways in toxoplasmosis and pneumocystis and looking at novel therapeutic agents. The role of cytokines, particularly G-CSF and GM-CSF, is being studied in HIV replication in monocyte pools and drug resistance to ddI and AZT is also being examined.

Quantitation of patients' viral loads using polymerase chain reaction (PCR) is being undertaken, with the advantage that it can be completed in 2 days as opposed to 2 to 3 weeks using other techniques. As an example of what PCR technology can do, Dr. Curt described an assay that showed activity in HIV products from 1 milliliter of plasma in a patient with AIDS and two asymptomatic HIV-positive patients. This assay, however, did not show activity in normal controls or even in patients with HTLV-1-related disease. In a larger study, Dr. Curt explained, 24 out of 25 patients with either AIDS or AIDS-Related Complex (ARC) were positive for the assay, while HTLV-1 patients and normal volunteers did not have a positive reaction . Dr. Curt then compared this assay with the P24 assay used to determine the viral burden for HIV. He noted that asymptomatic HIV patients will be P24 antigen positive only half the time, and even patients with AIDS or ARC will only be positive three-fourths of the time—not nearly as good a response as seen with the PCR technique. In summarizing this research, Dr. Curt noted that this could be an alternative endpoint to determining which patients might respond to antiviral therapy.

Dr. Curt reported on clinic activities, including a current study of AZT and ddI in combination with other drugs. During the past year, he said, Phase I and Phase II studies of ddI were conducted that led to its prescription status. He noted that a pilot study using human growth hormone and insulin-like growth factor, which have complementary toxicities, is also being planned.

Turning to research on cancer, Dr. Curt stated that the Medicine Branch is studying transcriptional regulation of *c-myc* at binding sites and binding proteins. The role of ERCC-1, a platinum DNA repair enzyme, is being studied in patients with ovarian cancer. A series of polyclonal and monoclonal antibodies have also been developed, which are directed against the human thymidylate synthase (TS) enzyme in mice. When colon cancer cells exposed to 5FU are observed using Western blot, the folate enzyme complex can be seen. This assay is two to three logs more sensitive than others in determining bound versus free drug levels. Looking at these same antibodies with immunoflourescence, Dr. Curt said, reveals even more findings, including that the thymidylate transferase is localized within the cell adjacent to the basement membrane in normal cells, but in colon cancer cells, the TS is uniformly distributed throughout the cytoplasm. Dr. Curt suggested that this finding might make this assay useful as a type of colon pap smear. This hypothesis is being tested in patients who are at high risk for developing colon cancer. Researchers are investigating whether staining of primary tumor or lymph nodes will be useful as an indicator of response or as a surrogate survival indicator.

In the Medicine Branch, the effectiveness of 5FU in gastrointestinal cancer is being modulated with interferon, with a response rate of 40% and a small but consistent group of complete responses in patients with metastatic colon cancer. A series of dose intensity studies using growth factors in breast and ovarian cancer and lymphoma is being conducted as well as an investigation on the role of the p170 glycoprotein, the product of a multiple drug resistance gene in refractory lymphoma. It has been discovered that when cells become resistant to cholchescein, they also become cross-resistant to structurally unrelated molecules with dissimilar mechanisms of action. Work is being done to determine if the protein is extruding natural products out of the cell. In related work, noncancer drugs can bind to the binding site and allow the natural-product drugs like adriamycin to remain within the cell, effectively reversing the drug resistance. When patients who had relapsed using the standard protocol were studied, they were found to have detectable levels of MDR gene product. Reversing this drug resistance was attempted using R-verapamil. These patients were treated at the time of relapse with an infusional drug regimen. Of the patients treated at the time of relapse with the standard therapy and verapamil one had a complete response and one had a partial response, while two had progressive disease. The hypothesis is, Dr. Curt said, that if the p170 glycoprotein contributes

to the drug resistance, then verapamil may help those in which the amplification of the gene product is low.

Dr. Curt then turned to a discussion of research into the pathophysiology of HIV infection in children, noting that it is primarily a neuropsychological disease with immunological correlations. With respect to pharmacology, Dr. Curt said that ddI has discrepant absorption curves and varies from patient to patient. The absorption seems to correlate well with mean change in IQ score, suggesting that it may be important to achieve certain target drug levels to achieve the biologically relevant endpoint.

Dr. Curt reported that in the Pediatric Branch laboratory, they are studying antisense constructs and how they might be used to take advantage of the molecular biology of Burkitt's lymphoma. A correlation was discovered between *n-myc* amplification and lamin expression in neuroblastoma, which may be a surrogate marker for invasion and metastasis. The role of Epstein-Barr Virus (EBV) in Burkitt's lymphoma is also being studied, Dr Curt said. What has been discovered is that EBNA-1, the only latent gene expressed in EBV-containing Burkitt's lymphoma, can bind directly to an enhancer/promoter region in the immunoglobulin locus and lead to a 100- to 10,000-fold increase in transcriptional upregulation of *myc* expression. The antisense constructs to EBNA-1 are being examined to see if they can break the loop and inhibit synthesis of the oncogene and, possibly, inhibit cell growth.

In the clinic, the Pediatric Branch has developed a diagnostic test for candida infection using an enolase radioimmunoassay. They have also shown that antibodies to enolase predict for a good therapeutic response. Currently, they are working on an assay to detect aspergillus infection.

At the Navy Medical Oncology Branch, Dr. Curt reported, they have begun to focus on the retinoblastoma gene product. Researchers noticed that the area where the retinoblastoma gene is found in normal cells is also a site of frequent cytogenetic abnormalities. By dissecting the gene, they were able to determine that a single mutation, G to T, led to the substitution of phenylalanine for cysteine. They are now looking into the question of whether the synthesis of the normal retinoblastoma gene will inhibit tumorigenesis. Their preliminary findings showed that when transfected into mice, the retinoblastoma gene did show inhibition of tumor growth, suggesting that gene therapy may play a role in treating lung cancer.

In the clinic, the Branch has been treating patients with mycosis fungoides using the seragin fusion protein. Following infusional therapy, Dr. Curt said, there is a very good clinical response. This study is also correlating treatment response with the presence or absence of IL-2 receptors, both in primary tumors and in circulating malignant cells.

Turning to the Radiology Oncology Branch, Dr. Curt discussed some of the work being conducted in the laboratory focusing on nitroxides and radiation protectors. These are stable free radicals, he explained, that can protect cells from radiation damage and may also be useful in treating stroke and heart attack. In the clinic, the Branch is doing photodynamic studies using hematoporpherine dyes with laser light in ovarian carcinoma and bladder cancer, with some of the patients maintaining an untreated response for more than 2 years.

In collaboration with the Navy Medical Oncology Branch, the Radiology Oncology Branch is looking at relevant endpoints in radiosensitization using IUdR. By infusing patients for 3 weeks with IUdR, Dr. Curt said, biopsies of relevant tissue show incorporation of IUdR into the DNA in sarcoma and head and neck cancer. In one large study, 45 patients with high-grade glioma showed no improvement with IUdR therapy, but in patients who had massive localized sarcoma, local control rates in excess of 60% were seen. In addition, all nine of the head and neck patients treated who had T4 lesions had complete responses.

In the Surgery Branch laboratory studies have focused on the insertion of new genes into target cells. Researchers have also begun to take DNA from sensitive and resistant tumors and construct DNA subtraction libraries to see what antigens are present on the sensitive cells that are absent on the resistant cells. This work may lead to the identification of epitopes that are responsible for immune cell recognition in humans and, possibly, the first step toward a cancer vaccine. The Branch, Dr. Curt said, is also continuing to work on immunotherapy of metastatic melanoma and renal cell carcinoma using TIL cells that have been transfected with tumor necrosis factor. This trial is showing approximately a 50% response rate for patients with metastatic tumor.

In the Clinical Pharmacology Branch, the focus for the past 2 years has been on molecular and cellular biology of prostate cancer. The Branch has shown that prostate cancer exhibits certain neuroendocrine markers at differentiation, including bombacin, neurotensin, and vasopressin. They have also found that hormone-resistant prostate cancer expresses high levels of *c-src* and its protein product, *c-src* kinase, and are looking at natural-product inhibitors of these enzymes. This group was the first to show that prostate cancer cells have purinergic receptors, Dr. Curt added. The Branch has also been studying phenyl acetate as a potential antitumor agent and suramin is being studied in prostate cancer. Suramin is showing a 50% response rate in patients who are refractory to hormone treatment. This study has been controversial, Dr. Curt noted, because of high toxicity in approximately 70% of the patients. Subsequently, the toxicity has been shown to be proportional to the levels of free drug. Toxicity increased in patients when drug levels reached a concentration of 225 micrograms per ml. Keeping blood levels of the drug to below 215 micrograms per ml. has reduced the high toxicity to roughly 10%.

In conclusion, Dr. Curt stated that medical oncology had been given full accreditation in the clinical center. Medical oncology has now joined intensive care, endocrinology, hematology, and infectious disease as accredited programs.

Dr. Curt was asked if methotrexate or 5FU has been used to enhanced IUdR/BUdR sensitization. Dr. Curt replied that the IUdR trials have been done with IUdR as a single agent.

XIV. OLD BUSINESS

Approval of the September Minutes

The September 1991 NCAB summary minutes were unanimously approved with no changes.

XV. COOPERATIVE GROUP PROGRAM—DR. MICHAEL FRIEDMAN

To acquaint members of the Board not familiar with the Cooperative Group Program's activities, Dr. Friedman summarized some recent results that indicate current problems and forecast opportunities for the future.

Dr. Friedman explained that the primary mission of the group is to test hypotheses in a definitive, complete manner. The group system, unique in terms of its scale and scope, is an essential feature of clinical therapeutic research at NCI. The group program is multi-institutional, multicenter, and cooperative, not only from one institution to another, but among staff at NCI and extramural investigators.

Dr. Friedman displayed a list of the current groups and group chairmen. The groups vary between large, adult-focused groups with many disciplines to those with a subspecialty interest, such as the gynecological group, the brain group, the breast and bowel group, the pediatric groups, and the radiation groups. There are even smaller groups with a narrower

focus, including a collaboration with the EORTC statistical office to link investigators in Europe and the United States.

Dr. Friedman reported that there are more than 4,600 investigators at about 1,300 hospitals or practices distributed throughout the United States and Canada who are part of the group. Currently, they are accruing about 24,000 new patients each year into about 500 therapeutic trials. The vast majority of patients—almost 20,000—are involved in Phase III comparative trials; however, there are more Phase II trials than Phase III trials.

Three areas that have been the focus of the group program over the past several years have been to: 1) increase efficiency and expand and focus accrual and improved methodology; 2) enhance science; and 3) broaden the scope, access, and support for the groups.

Dr. Friedman first addressed increasing efficiency. A comparison between 1988 and 1990 figures indicates that the number of patients has increased and the number of studies has decreased; hence, Dr. Friedman concluded, one could expect the sample size per study to increase for Phase III studies in the median from 270 to 400. In 1988, it took approximately 4 years to complete a study, compared with approximately 3 years now—a great improvement in efficiency. Also, there has been an increase in the number of intergroup studies with approximately 5,000 more patients now involved. Dr. Friedman explained that with the increased accrual per year, fewer studies, more intergroup collaboration, and larger sample size comes greater precision and time limits, enhanced focus, and better prioritization.

Dr. Friedman highlighted four special accrual initiatives. The cooperative group outreach program, started in 1976, is a highly successful effort to enfranchise local physicians and smaller institutions into the cooperative group network. The high-priority trials are also effective in increasing accrual, Dr. Friedman explained. Approximately $1.4 million has been distributed to supplement select programs of high interest or protocols of high importance either scientifically or because they have potential to result in increased cure rates. Although these trials account for only 12% of all Phase III studies, more than one-third of all Phase III accruals are to this 12%, indicating that they are drawing clinical attention.

Another important priority has been the attraction of minority patients into the cooperative group therapeutic trials, Dr. Friedman continued. Started in 1990, the program for minority accrual increase has received almost $1 million. Seven cooperative groups are currently participating, and early data indicate that 15% of all female patients and 18% of all male patients are minorities, roughly national norms for minority representation.

Lastly, Dr. Friedman highlighted the treatment of malignancies that affect women. Data indicate that of the roughly 24,000 patients treated each year, more than half are women. Approximately 8,000 patients of the 24,000 treated each year are treated for breast cancer and gynecologic malignancy, uniquely feminine diseases. For diseases such as lung and colorectal cancer, there is substantial representation of women.

Dr. Friedman presented some measures, in addition to increased accrual, of the group program's success. He first mentioned the three consensus development conferences within the last 3 years. The conferences have focused on important issues for which data generated from the Cooperative Group Program have resulted in national attention to treatment of early breast cancer, early and adjuvant stage II and III rectal cancer, and stage III colon cancer.

In an example of how the group program provides practical assistance, Dr. Friedman stated that more than half of all products that have FDA approval have received approval based upon studies supplied by the Cooperative Group Program. Dr. Friedman added that very contentious, scientifically difficult, or scientifically demanding issues—such as autologous bone marrow transplantation or drug resistance—have been addressed by the groups in a timely fashion.

Dr. Friedman addressed the influence of the clinical trials program on the standard of practice. He presented a list of trials from the groups over the past 3 years that have been published in a general journal not strictly devoted to oncologic literature—specifically, the *New England Journal of Medicine*. He commented that these and many other publications are among the most important studies that the oncologic community sees. These studies are major adjuvant trials for many situations. Through these publications, the group program has a real influence on oncology practice in the United States.

Dr. Friedman continued with a discussion of financial considerations. He noted that funding has been flat and that there have been increasing monetary demands in accrual, science, and the correlative laboratory studies. To address the financial situation, Dr. Friedman stated, parts of the RPG pool must be identified which might support large, multi-institutional clinical trials. He presented several of the ongoing program announcements and requests for applications that have been approved by the Board of Scientific Counselors for the future.

Dr. Friedman reported that over the past several years, eight groups have been phased out, funding has been relatively flat, at least two of the groups have announced accrual caps, and the number of new patients has been fixed at 24,000. Otherwise, he noted, there would be much larger growth, possibly closer to 30,000 new patients. However, he said, the money is not presently available to support this activity, and two groups are presently accruing patients more rapidly than they can pay for those patients. These groups are dealing with anticipated deficits by seeking funds from pharmaceutical companies and charitable organizations.

Dr. Friedman argued that the groups are providing considerably more than their funding allows, both with their own funds and funds from other institutions. He stated that with an unprecedented number of fine scientific opportunities and many more on the horizon—combined with the limited resources in terms of funding, patients, investigators, and time—managing a highly successful program and getting the most out of it is difficult. In an attempt to increase the scope and support for the cooperative groups, efforts have been made to work with other divisions within NCI, such as the Division of Cancer Prevention and Control and the Division of Cancer Biology, Diagnosis, and Centers, as well as other agencies such as the (AHCPR).

XVI. SOUTHWEST ONCOLOGY GROUP—DR. COLTMAN

Dr. Coltman reported that there are 3,363 investigators at 389 institutions in the Southwest Group and he presented the categories of institutional membership, the number of institutions, and the investigators in each category. There are institutions in 44 States and the District of Columbia, he said, and the operations office, which he runs, is located in San Antonio. The statistical center is located at the Fred Hutchinson Cancer Research Center in Seattle.

Dr. Coltman presented a map of the 8,157 patients registered in the Southwest Oncology Group intergroup clinical trials of 1990. He explained that a computer converts the zip code of every patient, color coded by type of institution, to longitude and latitude and places a dot on the map. Among the 33 member institutions, 19 are funded and accrue a median of 133 patients to clinical trials, with a range of 63 to 359. The remaining 14 institutions without funding accrue a median of 74, patients with a range of 20 to 171. The median cost per patient is $705. Institutions that fall below the $1,500 per patient level are required to increase accrual or they will lose some of their type 5 funding. As of July of 1991, Dr. Coltman reported, all institutions were above this level.

Dr. Coltman further commented that the total support for cooperative group trials has diminished by 30% over the past 10 years, while the research project grant pool has increased by over 30%. Recently, the Southwest Oncology Group received approval for funding in a gastric

cancer study and applied for an R01 entitled "Biologic Correlates of Poor Prognosis of Soft Tissue Sarcomas."

The Southwest Oncology Group established data monitoring committees for all Phase III clinical trials. The data monitoring committees, explained Dr. Coltman, were designed to monitor Phase III clinical trials for an extreme result, as well as to prevent premature disclosure of interim therapeutic results. These committees are comprised of the study coordinator, the committee chair, the discipline chairs, the statistician of record, a neutral observer, the group and statistical chair, and an observer from the NCI. This approach has prevented the presentation and publication of interim analyses, as well as the informal disclosure of clinical trials.

Since 1987, Dr. Coltman reported, 251 quality assurance audits have been conducted involving 1,252 patient records. No instances of research fraud were found. Currently, the Southwest Oncology Group is developing a conflict of interest policy.

Dr. Coltman noted that of the 28 approved institutions for bone marrow transplantation, 21 are approved for both autologous and allogeneic marrow transplant and 7 for autologous transplants only.

Dr. Coltman reported that under the leadership of Dr. Sydney Salmon, the Myeloma Committee is in the forefront of the design of clinical trials to study P-glycoprotein-mediated multidrug resistance. A Southwest Oncology Group study compares vincristine, adriamycin, and decadron (VAD) with VAD plus verapamil and quinine in previously untreated patients to test the hypothesis that verapamil and quinine can block or delay the development of multidrug resistance as measured by evolving P-glycoprotein. A total of 117 patients have been studied in 13 months. Another Southwest Oncology Group study compares VAD versus VAD plus verapamil in patients who have previously failed combination chemotherapy to determine whether or not verapamil can circumvent drug resistance problems. A total of 125 refractory patients have been studied to date.

Dr. Coltman then discussed the leukemia biology program of the Southwest Oncology Group. The program was established to develop a laboratory and centralized repository for both myeloid and lymphoid leukemias to establish group-wide cytogenetics with 26 approved submitting laboratories and six reference laboratories, and a computerized database for all biological data from the University of New Mexico, University of Oregon, and St. Jude's Hospital (with all data transferred to the statistical center in Seattle). Between September 1, 1987, and September 30, 1991, there have been 5,725 studies conducted by the leukemia biology program.

The leukemia biology program, with three biologic protocols and 11 therapeutic protocols, has published 12 manuscripts and 11 abstracts—seven manuscripts will be submitted by December of 1991. Ten additional manuscripts will be submitted by February of 1992. Topics of the manuscripts include the biological identification of an MDR positive CD34 positive set of AML cases that may benefit from therapies designed to circumvent MDR resistance; clinical features of this group; clinical features of EVI-1 positive AML cases with abnormalities at 3q; association of CD56 with translocation at 8:21; CD56 CD32 positive true NK cell leukemia; *bcr-abl* fusions in adult ALL; and the biological heterogeneity of hairy cell leukemia. Tumor repository resources of this program are available to scientists across the country who study the specimens and return to the group for the clinical, laboratory, and cytogenetic correlates.

Dr. Coltman said that the Southwest Oncology Group is the first group to report the genomic cloning of the translocation 15:17 DNA breakpoint region using probes from chromosome 17 developed in the human genome project. It was discovered that this locus contains the alpha retinoic acid receptor at about the same time a group from Europe reported a PML retinoic acid receptor fusion mRNA in translocation of 15:17 patients. Continued studies

have indicated that there is considerable molecular heterogeneity in the 15:17 AML M3 patients. Dr. Coltman noted that Dr. Ihle had provided the gene probe for the ecotrophic viral integration site one, which was a sequence disrupted by integrating retroviruses in mouse leukemia. The screening of 100 Southwest Oncology Group AM1 cases revealed that this gene represented at high levels only in the cases with cytogenetic abnormalities of 3q. Dr. Ihle then mapped this gene in humans to chromosome 3q. He cloned the breakpoint in four Southwest Oncology Group patients who were identified as expressing EVI-1 and that had abnormalities of 3q. Dr. Coltman concluded this discussion by noting that Drs. David Callen and Grant Sutherland of Australia are involved in the mapping of chromosome 16 and that, recently, Dr. Callen made stable hybrids by fusing AML cells with rodent cells and selecting for chromosome 16.

Switching to women's health issues, Dr. Coltman mentioned that the number of women registered to member institutions ranges from 52% to 71% in all categories, except the urologic cancer outreach program (6%). The majority of the studies show a higher mortality risk for men than women. The Southwest Oncology Group developed a Women's Health Task Force to identify potential differences in the biologic behavior of cancer in men and women and to establish a series of criteria for the task force to examine. Dr. Coltman reported that the first meeting of this task force was held on November 1, 1991. Iris J. Schneider, Assistant to the Director for Program Operations and Planning at NCI and Co-Chair of the NIH Advisory Committee of Women and Health Issues, consulted at the first meeting, where the task force accomplished a great deal and made plans to continue this effort.

In October of 1990, said Dr. Coltman, the Southwest Oncology Group began collecting detailed race and ethnicity data on all patients registered to group studies. Three percent of the patients are Hispanic, 10% are Black, 83% are White, and 3% represent other ethnicities. Between 1985 and 1990, 17 Black patients and 398 White patients registered to brain cancer studies. Blacks are overrepresented in head and neck cancer studies, sarcoma studies, and myeloma studies, and underrepresented in melanoma and brain cancer studies. Between 1986 and 1990, more than 12,000 White patients and almost 1,400 Black patients were registered to treatment studies. The survival of White patients was significantly better, with 3-year estimates at 41%, compared with 33% for Black patients.

Dr. Coltman presented data on the distribution of household incomes of patients registered to treatment studies between 1986 and 1990. The patients' zip codes were compare with data from the 1970 U.S. Census. Thirty-seven percent of the patients came from areas where the median household income was less than $15,000 per year; 35% came from areas of medium incomes of $15,000 to $20,000; and 28% came from areas where the median household income was greater than $20,000 per year. Black patients were found to come from areas of lower income. Dr. Coltman reported that socioeconomic status varied with the type of disease. Myeloma and head and neck cancer were associated with more Black patients and lower socioeconomic status, while melanoma was associated with fewer Black patients and higher socioeconomic status. Patients with lower income had shorter survival rates. The 3-year estimate ranges from 36.5% for low economic status to 44.6% for high economic status. White patients with high socioeconomic status had the highest survival rate and Black patients with lowest socioeconomic status had the lowest survival rate.

A hometown news release program was developed for the Southwest Oncology Group, continued Dr. Coltman. He cited the intergroup studies of 5FU with levamisole used in the adjuvant treatment of Duke's colon cancer, for which press coverage identifying the 127 investigators and their institutions was generated in 44 newspapers in 37 cities, with a readership of 3,575,000 patients.

Dr. Coltman then reported that of the 38 intergroup Phase III clinical trials, 17 are coordinated by the Southwest Oncology Group, and that both the intergroup and Southwest Oncology Group clinical trials have led to FDA approval of seven new drugs in the past 4 years. These have included Flutemide in prostate cancer, carboplatin in recurrent ovarian cancer, BCG

in bladder cancer, Fludarabine in chronic lymphocytic leukemia, levamisole in Duke's C colon cancer, carboplatin as first-line therapy for ovarian cancer, and deoxycoformycin in hairy cell leukemia. In March of 1991, Dr. Coltman noted, the Group estimated that patients were accruing at a projected rate of 11,698 a year—a level which exceeded its ability to manage data from the clinical trials. In 1987, the Group was approved to accrue patients at a rate of 4,500 to 5,000, so an accrual cap of 6,451 patients was established. The projected increase in Phase II and Phase III accrual decreased to the cap 22 weeks after it was established on March 3, 1991. Donations totaling $305,000 from various sources has helped to control the accrual crisis, and now accrual is being modulated around the cap and the group is in the black.

Dr. Coltman concluded that cooperative groups provide access to sufficient numbers of patients so that the value of new cancer therapies and effective new cancer agents can be established, data can be used to support new drug applications to the FDA, new standards of care can be established, and tumor tissue repositories and uniformly treated patients with long-term follow-up provide investigators with a unique resource. The Southwest Oncology Group provides socioeconomically deprived patients with access to state-of-the-art therapies. It can address the impact of race, ethnicity, gender, and socioeconomic status on cancer and its outcome. Finally, it provides a mechanism through which large-scale cancer clinical trials can be conducted.

Dr. Calabresi thanked Dr. Coltman for his presentation and added that Dr. Coltman is the Medical Director and Chief Executive Officer of the Cancer Therapy and Research Center and a professor of medicine at the University of Texas.

Dr. John Durant asked Dr. Coltman what the comparison is between the contribution of labor hours and monetary contributions. Dr. Coltman answered that monetary contributions are large, but he could not disclose an exact figure. Dr. Salmon asked Dr. Friedman if the dollar amount spent per patient has dropped significantly over the last decade. Dr. Friedman answered that he did not know the dollar amount, but institutional and other resources have been used to support the system. Dr. Salmon then asked if the budgets for the cooperative clinical trials are similar or are the budgets larger for cancer or heart disease. Dr. Friedman answered that this issue has been discussed, and most of the clinical trials in the National Heart, Lung, and Blood Institute (NHLBI) are conducted under contracts that are larger than the $60 million spent on clinical trials in the group program. However, NHLBI is converting to a U01 system, similar to the group program's U10 system. Dr. Chabner added that NHLBI spends a relatively greater amount on clinical trials, but the group program also supports some clinical trials on contract. This budget, including the group programs and BRMP, is about $8 million. Dr. Chabner added that he thinks that the NCI spends less proportionately on clinical trials than NHLBI.

Dr. Salmon expressed concern that Phase II and Phase III clinical trials will be delayed to facilitate the technology transfer of new discoveries in clinical trials. Dr. Broder explained that NHLBI uses R01s for multi-institutional clinical trials. He continued by saying that a good monetary strategy has been carried out until this fiscal year, given that the research project grant line increased 33% in constant dollars, and the cooperative group line fell 33% in constant dollars throughout the 1980s. Dr. Broder stated that "a fresh look" at how to support investigator-initiated clinical trials is needed. He reminded the audience that the cooperative group line will increase from $60.8 million to approximately $78 million (28% increase) in fiscal year 1992, providing that the President signs the 1992 budget.

Dr. Chabner stated that one of the best examples of how the centers program and R01 grants support the pilot studies that lead to cooperative group trials is in the area of multidrug resistance. He introduced Dr. Bill Dalton of the University of Arizona Cancer Center who has conducted significant studies on the clinical importance of multidrug resistance and its reversal.

XVII. CLINICAL DRUG RESISTANCE—DR. WILLIAM DALTON

Dr. Dalton began his presentation by describing the complexity of drug resistance at the cellular level, explaining that drug resistance can be conferred as a result of decreased drug uptake, metabolic alterations, subcellular redistribution of the drug, and enhanced drug efflux. Enhanced drug efflux has been shown to be attributed to P-glycoprotein and this mechanism was the focus of Dr. Dalton's presentation as it occurs in hematologic tumors such as myeloma and leukemia.

P-glycoprotein, Dr. Dalton explained, spans the entire membrane and drugs enter the cell through passive diffusion. Before the drug reaches a level high enough to kill the cell, the drug binds P-glycoprotein and is actively effluxed so that a lower intracellular accumulation of drug occurs. Dr. Dalton first studied multiple myeloma to see if drug resistance occurred in this cancer. They selected for resistance to the 8226 multiple myeloma cell line and used it as a model of drug resistance. P-glycoprotein, Dr. Dalton said, not only occurs in drug resistant cells, but also in some normal tissue, so an assay must be sensitive and specific and needs to detect which cells are actually expressing the protein. Immunocytochemistry, Dr. Dalton stated, is such an assay—it can detect 1 in 100 cells positive for the P-glycoprotein. Dr. Dalton then described two assays used in detecting MDR P-glycoprotein in myeloma, the immunocytochemical assay and the confirming PCR assay.

First, describing the immunocytochemical assay, Dr. Dalton presented the results from 96 patients whose specimens were evaluable for detection of MDR. Only 3 of 47 had P-glycoprotein on their cells. Melphan and prednisone did little to change that incidence. When doxorubicin was added, and it is almost always used with vincristine, a substantial increase (55%) was seen. A clear dose-response relationship was seen. Fifty percent of the patients who accumulated greater than 20 mg of vincristine had P-glycoprotein. In patients who had accumulated less than 340 mg of doxorubicin, only 3 of 13 showed P-glycoprotein. However, in patients who accumulated greater than 340 mg of doxorubicin, 15 out of 18 (83%) had P-glycoprotein on their cells. Dr. Dalton then investigated combining the vincristine and doxorubicin at greater than 20 mg of vincristine and 340 mg of doxorubicin accumulated, and all of the 11 patients tested had P-glycoprotein on their cells.

In myeloma, Dr. Dalton said, P-glycoprotein expression is very low *de novo*, but as patients are treated, they begin to acquire the expression of this protein, and this is also seen in leukemia patients.

Dr. Dalton then described an assay that was being used to confirm the immunohistochemistry results. It is a quantitative PCR, he said, where the synthetic RNA serves as an internal standard so that cellular RNA for MDR1 can be quantitated. The number of molecules in each cell or the amount of RNA added can be calculated. When the results from the PCR are compared to the immunohistochemical assays, there is good corroboration. Both assays are necessary. The immunohistochemistry has the advantage of directly determining the protein, whereas the quantitative PCR allows actual quantification of MDR expression.

Certain agents, Dr. Dalton said, have been shown *in vitro* to allow increased intracellular accumulation of drug by inhibiting the function of P-glycoprotein. Verapamil was found to be very active in reversing drug resistance in selected cell lines, so a protocol was developed where patients relapsing from a vincristine, adriamycin, and decadron therapy were given verapamil. Resistance was reversed in 5 of 22 (23%) patients. The median duration of response was 5.4 months, indicating that P-glycoprotein expression does occur in myeloma and that it can be modulated in a subset of patients. Prospective randomized studies are underway to determine the effectiveness of verapamil.

Dr. Dalton was asked if there was any correlation between the degree of response and the P-glycoprotein positivity and he answered that it had not yet been studied.

In conclusion, Dr. Dalton said that verapamil is capable of reversing drug resistance, but that effective, less toxic drugs are needed to reverse P-glycoprotein. Another agent that may be useful, Dr. Dalton said, is cyclosporin-A, which has proven very effective in some cell lines. In a Phase I trial studying the chemomodulation in patients with high-risk AML, cyclosporin-A did induce hyperbilirubinemia in 59% of patients. Reviewing treatment outcome, Dr. Dalton said, 63% had a complete response and 11% had a partial response, for an overall response rate of 74%. Dr. Dalton then discussed two cases that appeared to show patients responding to cyclosporin and then relapsing with a new mechanism of resistance. Therefore, he cautioned, everything that pumps drugs out of the cell is not necessarily P-glycoprotein. Dr. Dalton then described mitoxantrone, a completely synthetic molecule. He emphasized that many people feel that P-glycoprotein expression may be due to the cell's efforts to try to resist natural products. For this reason, the synthetic mitoxantrone may prove useful.

Dr. Dalton then presented breast cancer cells selected for resistance to mitoxantrone. Their mechanism of resistance—shown to be drug efflux—is energy dependant, similar to P-glycoprotein resistance. In four different cell lines tested, mitoxantrone resistant cells have shown no overexpression of P-glycoprotein. In closing, Dr. Dalton emphasized the need to define exactly the mechanism of resistance.

In response to a question, Dr. Dalton said that melphelan did not appear to select for MDR-type resistance. Dr. Dalton was then asked if there was development of MDR simply from exposure. Dr. Dalton responded that they looked at the natural evolution of the tumor to see if P-glycoprotein begins expression by itself over time. No evidence of this was found.

XVIII. ADJOURNMENT—DR. PAUL CALABRESI

There being no further business, the 80th National Cancer Advisory Board was adjourned at 5:26 p.m., November 25, 1991.

Date

Dr. Paul Calabresi, Chairman