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

Summary of Meeting
February 22 and 23, 1994

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

Department of Health and Human Services
Public Health Service
National Institutes of Health
National Cancer Institute
National Cancer Advisory Board
Summary of Meeting[1]
February 22 and 23, 1994

The National Cancer Advisory Board (NCAB) convened for its 89th regular meeting at 8:00 a.m., February 22, 1994, in Building 31, C Wing, 6th Floor, Conference Room 10, National Institutes of Health (NIH).

NCAB Members

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

President's Cancer Panel

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

Alternate Ex Officio NCAB Members

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

Members, Executive Committee, National Cancer Institute, NIH

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

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

Liaison Representatives

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

In addition to NCI staff members, meeting participants, and guests, a total of 15 registered members of the public attended.

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

Dr. Calabresi called the 89th meeting of the National Cancer Advisory Board (NCAB) to order and asked those in attendance to observe a minute of silence in memory of Board member Dr. Howard Temin, who died in February. He noted that Drs. Frederick Becker and Erwin Bettinghaus, both NCAB members, had been asked to draft a memorial resolution to be framed and presented to Dr. Temin's family. This resolution, he added, would be made available for the Board's consideration and approval during the second day of the meeting.

Dr. Calabresi asked the Board to welcome Dr. Marvin Kalt as Acting Executive Secretary of the NCAB, replacing Mrs. Barbara Bynum, who retired in January. He noted that Board member Ms. Deborah Mayer had been asked to chair a small subcommittee to prepare a resolution in honor of Mrs. Bynum to be presented at the May 1994 NCAB meeting.

Dr. Calabresi introduced several guests representing medical, research, and professional organizations. He welcomed members of the public and informed them that they could express their views on issues discussed during the meeting by writing to the NCAB Executive Secretary within 10 days of the meeting. Dr. Calabresi called for approval of all proposed meeting dates for 1994 and 1995 except the meeting scheduled for September 5-6, 1995. The Board unanimously approved the remaining dates and asked Dr. Kalt to explore dates in September 1995 that would not conflict with the Labor Day holiday. Dr. Calabresi called for approval of the minutes of the previous meeting, which were unanimously approved without change.

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

Dr. Freeman explained that the President's Cancer Panel (PCP) recently concluded a series of meetings associated with the evaluation of the National Cancer Program. The first two meetings, held in September and November 1993, were the subject of Dr. Freeman's report to the NCAB at its December 1993 meeting. Those meetings focused on the achievements of the National Cancer Program and cancer statistics from regions identified as "chronic disaster areas." The third meeting, held in January 1994, assessed the role of Government agencies in the research mission of the National Cancer Program.

Dr. Freeman began his review of highlights from the January meeting by describing the role of the Environmental Protection Agency (EPA) in cancer research. EPA's cancer-related basic and applied research programs—as well as its regulatory authorities concerning the protection of human health—overlap the goals of the National Cancer Program. The Agency's intensive research into the prevention of cancer caused by occupational and environmental exposures to carcinogens, Dr. Freeman noted, has recently focused on tobacco smoke, radon, and dioxin.

The Health Research Extension Act of 1985, Dr. Freeman continued, requires NCI to coordinate its cancer prevention research with other components of the National Institutes of Health (NIH). One institute that plays a major role in this area, he stated, is the National Institute of Environmental Health Sciences (NIEHS), which is the home of the National Toxicology Program and reports annually to the Congress on carcinogens. The NIEHS also collaborates with the Department of Energy (DOE) in research on electromagnetic fields, which is also the subject of NCI-supported research.

Dr. Freeman explained that the Agency for Toxic Substances and Disease Registry (ATSDR) is a component of the Public Health Service that works with the EPA, DOE, and Centers for Disease Control and Prevention (CDC) to prevent adverse health effects of exposure to hazardous substances and examine the biological effects of environmental contamination. Dr. Freeman pointed out that the cancer-related surveillance studies carried out by the ATSDR and CDC parallel NCI's epidemiological activities; examples of their ecological research include brain, bladder, esophageal, and pancreatic cancers as well as leukemias and childhood cancers that occur near hazardous worksites. The emphasis of these studies on the improvement of analytical methods, Dr. Freeman observed, is highly relevant to the research mission of the National Cancer Program. He added that representatives of the California Environmental Protection Agency who were present at the January meeting stressed the need for improved risk assessment technology to help risk managers make informed public health decisions.

Dr. Freeman noted that cancer-related research projects being conducted by the DOE include long-term follow-up studies of atomic bomb survivors in Japan and survivors of the Chernobyl disaster. This agency also conducts a variety of epidemiological studies and has developed tissue registries and other data resources. The DOE, he added, has initiated a worker surveillance program and is involved in applying research products of the Human Genome Project to the detection of disease precursors.

The National Institute of Occupational Safety and Health (NIOSH), which Dr. Freeman explained is a part of CDC, plays a major role in the National Cancer Program by seeking to identify cancers caused by occupational carcinogens and reduce exposures responsible for those cancers. As a result of its research, NIOSH makes recommendations concerning the control of carcinogenic substances. The Institute's quantitative risk assessments contribute to the regulatory efforts of the EPA and the Food and Drug Administration (FDA) and the efforts of the Department of Energy on radiation exposure.

Within the Department of Labor (DOL), Dr. Freeman continued, the Occupational Safety and Health Administration (OSHA) works through State occupational safety and health agencies to apply information provided by NCI, EPA, NIOSH, DOE, and other Federal agencies in protecting workers against recognized hazards. OSHA is involved in setting standards and arbitrating between industry and the worker.

Dr. Freeman observed that an unusual contribution to the National Cancer Program is made by the Department of Commerce's National Institutes of Standards and Technology (NIST). This agency, he stated, plays a major role in monitoring environmental carcinogens and radioactivity, identifying biomarkers for measuring micronutrients that are useful in chemoprevention studies, and developing standards for external radiation, brachytherapy, and palliative radionucleotide therapy.

Dr. Freeman described the activities of the CDC as a partnership with other Federal agencies, State and local agencies, professional and community organizations, corporations, labor unions, and other groups to investigate health problems and develop public health policies. As part of this mandate, the CDC has launched the National Breast and Cervical Cancer Early Detection Program, a surveillance effort using current health technology to focus not only on detection but also on quality assurance and education for health care providers and the public. Dr. Freeman noted that the key feature of such a program, as NCI has also found, is building a coalition of patients and providers.

The CDC Division of Cancer Prevention and Control, he continued, maintains a national program of cancer registries in response to a mandate included in Public Law 102-515, which requires that existing State registries be enhanced and new registries be implemented where needed. This program, Dr. Freeman noted, overlaps and complements

data from the Surveillance, Epidemiology, and End Results (SEER) Program. CDC also cooperates with NCI through activities such as workshops, clinical trials, and cooperative agreements that aid in the early detection of prostate cancer, and through its efforts in the area of tobacco control.

Dr. Freeman reported that Dr. Jane Henney represented the FDA at the January meeting. She issued a challenge, he said, to NCI and its grantees by stating that the FDA currently has no backlog of New Drug Applications in oncology.

One of the most ambitious and successful tobacco control efforts highlighted at the meeting, Dr. Freeman stated, was presented by the Massachusetts Tobacco Control Program. As a partner in the America Stop Smoking Intervention Study (ASSIST), a project jointly supported by NCI and the American Cancer Society (ACS), the Massachusetts group is coordinating its efforts with the State's Department of Education. Massachusetts, Dr. Freeman explained, has established a Health Protection Fund with revenue generated by a hard-won 25 percent increase in the excise tax on cigarettes. One goal of the Tobacco Control Program is to reduce the proportion of adolescents who smoke to less than 12 percent by 1999.

Representatives of the Hospital Mortgage Insurance Staff, part of the Department of Housing and Urban Development (HUD), presented information on the agency's new role in examining community demographics to determine service needs. Dr. Freeman explained that this agency will play a role in outreach efforts to identify local needs for upgraded equipment or facilities.

Dr. Freeman suggested that the Health Resources and Services Administration (HRSA) is a somewhat underrated partner in the National Cancer Program, particularly in its efforts to better meet the needs of underserved populations. HRSA manages the Ryan White Care Act, which educates staff of health care facilities; maintains the National Health Service Corps, which staffs community health centers; and operates the Organ Transplant Registry and Vaccine Injury Compensation Program. Dr. Freeman noted that the Medicare claim files maintained by the Health Care Financing Administration (HCFA) are a formidable resource for tracking patient care that can provide important perspectives on mortality, morbidity, and utilization of preventive services.

The Agency for Health Care Policy and Research, he added, provides guidelines concerning the effectiveness and quality of health care and examines patient outcomes to determine what works best in a given community.

The final presentation, Dr. Freeman stated, was made by the Department of Defense (DOD). Dr. Bimal Ghosh pointed out that the cancer-related goals of the DOD are similar to those of NCI—to diagnose and treat cancer patients and to educate military personnel and their dependents about cancer. The DOD recently initiated a breast cancer research project and also cooperates with NCI through interagency agreements in adult oncology, pediatric and surgical services, and physician education. The Department also maintains a database similar to SEER called Defense Eligibility Enrollment Reporting (DEER) System, which contains a wealth of information, by name and serial number, on DOD beneficiaries' eligibility for medical and dental services. The Automated Central Tumor Registry (ACTUR) contains records of all cancer patients. Records on prenatal care and morbidity are maintained by individual hospitals.

Dr. Freeman observed that presentations at the January meeting illustrated the breadth of the National Cancer Program. He suggested, however, that there is need for greater cooperation and synergism among the various government agencies involved in the war against cancer. While the Department of Education was not discussed at the meeting,

Dr. Freeman added, that agency should also play a role in teaching young people about health care and disease prevention.

Dr. Freeman concluded by announcing that the President's Cancer Panel plans to hold a workshop on April 7-8, 1994, to review current knowledge concerning avoidable causes of cancer.

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

Dr. Broder described the late Dr. Howard Temin as a brilliant scientist and a valued member of the NCI family. Dr. Temin's suggestion, early in his career, of the possibility that genetic information could flow from RNA to DNA was met with derision, Dr. Broder related. He was later proved correct when he and Dr. David Baltimore independently identified reverse transcriptase, making it possible to describe the new class of viruses now known as retroviruses. Dr. Temin shared a Nobel prize with Dr. Baltimore and his former teacher, Dr. Renato Dulbecco, for this discovery in 1975. Dr. Broder noted that Dr. Temin also provided leadership for a new generation of scientists through his teaching at the University of Wisconsin.

Dr. Broder also noted the recent death of Mary Lasker, whom he described as "the science advocate *par excellence*." Ms. Lasker, he explained, played a role in the establishment of the National Cancer Institute in 1937 and was instrumental as a catalyst for the passage of the National Cancer Act of 1971.

Dr. Broder reviewed several recent NCI staff changes. Dr. Daniel Ihde left the Institute to become Chief of Medical Oncology at Washington University in St. Louis. At NCI, Dr. Broder noted, Dr. Ihde served not only as Deputy Director but also as Editor-in-Chief of the *Journal of the National Cancer Institute*. Dr. Broder expressed the opinion that Dr. Ihde had raised the journal to the status of a valuable and widely cited publication. Dr. Ed Sondik, he announced, has been appointed as Acting Deputy Director of NCI in addition to his duties as Deputy Director of the Division of Cancer Prevention and Control (DCPC). Dr. Broder reiterated Dr. Calabresi's announcement of the retirement of Mrs. Barbara Bynum and the appointment of Dr. Marvin Kalt as Acting Executive Secretary of the NCAB and Acting Director of the Division of Extramural Activities (DEA). He added that a more detailed list of staff and organizational changes would be made available to NCAB members and others in attendance.

In reference to Dr. Freeman's presentation on the activities of the President's Cancer Panel, Dr. Broder strongly encouraged NCAB members to attend the Panel workshop on avoidable causes of cancer mortality planned for April 1994.

Reminding the Board that the Congress had asked NCI to study potential environmental risk factors for breast cancer on Long Island, building on previous studies by the Centers for Disease Control and Prevention and other Federal agencies, Dr. Broder announced that the Institute has launched the Long Island Breast Cancer Study Project under the leadership of Dr. Iris Obrams, the Extramural Program's Branch Chief for Epidemiology and Biostatistics in the Division of Cancer Etiology. He reported that an open meeting on this topic was held recently at Adelphi University in Garden City, Long Island, and that further meetings will take place. The study, he added, will rely heavily on the cooperation from established Cancer Centers in the New York metropolitan area.

For some factors to be studied, Dr. Broder continued, such as the role of aircraft emissions in cancer risk, the Institute will be charting new ground in the development of technologies for quantifying individual exposures. A corps of scientific advisors has been assembled to assist in the design of the study, and a number of other organizations will contribute their expertise, including Federal, State, and local agencies as well as regional and local utility companies. Dr. Broder noted that several requests for applications (RFAs) relevant to this study have been or will be issued. The goal, he stated, is to develop knowledge on environmental causation that is applicable not only to Long Island but also to the country at large, with a special emphasis on potential practical interventions for women at risk. Dr. Obrams, he announced, would present an update on this study to a joint meeting of the Subcommittee on Environmental Carcinogenesis and the Subcommittee on Women's Health during the current NCAB meeting.

Dr. Broder reported that the Surveillance, Epidemiology, and End Results Program presented its Twentieth Anniversary Symposium on December 8, 1993. The symposium stressed the significance of SEER and emphasized the need for a continued commitment to this program. The issue of how best to nurture clinical research, Dr. Broder added, was highlighted by a recent visit by First Lady Hillary Rodham Clinton to an NCI pediatric ward, during which she demonstrated a clear understanding of the importance of investigator-initiated clinical research.

Dr. Broder announced that NCI is in the process of developing three new award programs designed to expand the menu of application options for investigators. He emphasized that these awards are meant to complement, not replace, the Institute's ongoing array of funding instruments. The first of these new awards, Dr. Broder continued, is an RFA aimed at clinical investigators who are beginning their research careers and are seeking support for experimental therapeutic research and innovative clinical trials. Dr. Broder described this mechanism as a hybrid award designed to fit between the current NIH R29, which is called a First Independent Research Supported Transition, or FIRST, award, and the regular R01 grant. He explained that the R29 has posed challenges for clinical researchers because the 5-year post-training time limit for submitting an application can exclude some physicians who have taken time out from research to complete residencies and fellowships, and the 5-year timeframe and cap of $350,000 in total direct costs do not always fit the clinical model.

The proposed hybrid funding mechanism, which has been presented to the Division of Cancer Treatment (DCT) Board of Scientific Counselors, allows awards for a maximum of 4 years and a total direct cost of $500,000 over the life of the award. This new R01 mechanism also opens competition to all investigators who have not previously served as principal investigators on R01 grants, regardless of the amount of time since they completed their training. The Division of Cancer Prevention and Control, Dr. Broder added, is launching a similar award for prevention studies that will provide opportunities for environmental and occupational carcinogenesis research.

The second new award, Dr. Broder described, is a continuing announcement for small R03 grants for innovative pilot clinical projects. This will make available up to $50,000 per year in direct costs for projects for up to 2 years. Dr. Broder noted that the application process for this award will be made as streamlined as possible; NCI will try, he said, to limit the research project description to five pages for this type of award.

The third award, Dr. Broder continued, will be a new program for R21 exploratory grants. This, he said, will be an ongoing program with three annual receipt dates that will allow investigators to request up to $100,000 in direct costs per year for 2 years for new ideas in clinical cancer research in the broadest sense. Dr. Broder stated that this award, which is appropriate for investigators at any career stage, will be funded through a special budget category that is separate from the conventional research project grant pool. The Institute, he

said, believes that the R21 mechanism could serve as a bridge to a conventional R01 award when the value of a novel concept in experimental therapeutics or prevention has been demonstrated.

Dr. Broder stressed that a strong corps of clinical investigators capable of generating new knowledge is essential to the success of health care reform. He observed that few organizations other than NCI are capable of creating new opportunities for clinical investigators; the Institute, he said, takes this very seriously and is going to considerable lengths to support clinical investigators. Dr. Broder added that NCI has requested that these new mechanisms receive a review by special committees convened within the Division of Extramural Activities rather than the Division of Research Grants (DRG). While clearance has not yet been given by the DRG (clearance subsequently has been denied), he noted, these procedures are likely to be approved and should fill a void by providing a constructive approach to the current dialog concerning clinical research. The larger issue of a standing clinical research study section within the Division of Research Grants, Dr. Broder added, will continue to be discussed.

Dr. Broder explained that NCI anticipates making the first awards in each of these programs in fiscal year (FY) 1995. He challenged NCAB members and the clinical cancer research community at large to make aggressive use of these opportunities to invigorate their respective fields with innovative ideas and to convince their colleagues that there is a future for them in clinical research.

Dr. Broder called the Board's attention to a set of reports on *Measures of Progress Against Cancer*, which will be used by the Subcommittee to Evaluate the National Cancer Program, and asked members to review these documents and share any comments with Dr. Calabresi. He thanked NCI staff members Cherie Nichols, Anne Middlesworth, Elaine Lee, and Judy Karp for their work in compiling these reports.

Turning to the NCI budget, Dr. Broder reported that a recision for the current fiscal year was signed into law on February 12, 1994. This includes a budget reduction for NIH of about $18 million. The NCI share of this recision, he said, has not been determined. Dr. Broder noted that this recision is limited to administrative costs and explained that the entire Intramural Research Program is included within administrative costs. Thus, he stated, the recision poses special challenges for the Institute.

NCI, Dr. Broder continued, remains under a hiring freeze, which is tied to the administration's goal of reducing overall Federal employment and the specific target of reducing senior-level positions. Although the freeze may be lifted within 2 months if separations continue as estimated, he stated, it could remain in effect for a longer period, since normal attrition rates have slowed recently. Dr. Broder explained that the freeze applies to senior-level employment at the level of GS-14 and above. He stressed the extreme difficulty of recruiting highly trained scientists at lower levels of employment.

Concerning a recent proposal, which was announced at the last NCAB meeting, to increase stipend levels for National Research Service Awards (including both predoctoral and postdoctoral awards), Dr. Broder reported that NIH has requested permission from the Department of Health and Human Services to implement this increase, but a final decision has not been made.

Dr. Broder used a series of slides to present a review of budget information. In 1993, he noted, NCI spent approximately $1.978 billion. The Institute's 1994 expenditures are expected to be approximately $2.082 billion, which represents an increase of about $104 million. The 1995 President's Budget, which was recently made public, includes approximately $2.190 billion for NCI.

Dr. Broder explained that the 1995 budget request for NCI includes approximately $223 million that will be set aside for the centralized Office of AIDS Research, for which other Institutes are also contributing portions of their allocations. The remaining budget amount for NCI is about $1.97 billion. Dr. Broder noted that the $223 million for AIDS research is still technically available, and NCI could receive more or less than that amount by, in effect, competing with other Institutes.

In comparing the increases in the cancer and AIDS portions of the NCI budget, Dr. Broder reported that the overall increase of $108 million represents a 5.2 percent increase; the increase in the cancer-related portion is just under $100 million, representing a 5.2 percent increase, while the increase for AIDS of slightly more than $9 million represents an increase of approximately 4.3 percent.

Noting that more detail on the budget presentation would be made at the meeting of the Budget and Planning Subcommittee, Dr. Broder presented a breakdown by funding mechanisms. The Research Project Grant line is increased by approximately $32 million and the Cancer Centers by more than $11 million. Dr. Broder stated that his slide showing an approximate $6 million increase in funding for the Intramural Program did not reflect the potential impact of the upcoming recision or the set-aside funding for the AIDS program. Prevention and control is increased by about $51 million, an increase of approximately 35 percent. In part, Dr. Broder explained, this results from statutory language requiring NCI to spend 9 percent of its budget in FY 1995 and 10 percent in FY 1996 on cancer prevention and control.

Dr. Broder suggested that for a variety of reasons, there will be a substantial increase in the number of competing grants in FY 1995 compared with 1994, noting that just under 1,100 grants are currently projected. He recommended that Board members submit any planned applications for grants as soon as possible so they can be considered during FY 1995.

Dr. Broder reported that the President's Budget for 1995 contains a statement concerning indirect costs that applies to all Government agencies that use any assistance mechanism to provide what are called "grants in aid." This statement, which implements a 1-year "pause," instructs grantee institutions not to seek additional payments for indirect costs above amounts claimed in FY 1994. Grantees must notify the agencies from which they receive the largest amount of grants concerning any increased indirect costs and must agree to a cancellation of the increase in indirect costs over the amount for 1994.

This pause, Dr. Broder stated, cuts overhead by approximately $150 million Government-wide, affecting institutions that report outlays in excess of about $10 million in FY 1994. It is theoretically possible, Dr. Broder explained, that some institutions may find themselves unable to undertake any additional new grants in FY 1995 due to this ceiling on indirect costs. Suggesting that there are other implications as well, Dr. Broder said that he will keep the Board informed of new developments. He added that many of the facilities that house scientists and laboratories were constructed, in effect, through the availability of an indirect cost mechanism; thus, Dr. Broder concluded, this pause requirement could have an effect on the operational performance of science.

In a brief summary of clinical research funding, Dr. Broder reviewed several funding mechanisms: the R29 FIRST awards, with a maximum award in direct costs of $350,000 and an average yearly budget of $70,000 for 5 years, which can go as high as $100,000 in any 1 year, for a total of 5 years; the new R21 exploratory grants, with a maximum award of $200,000 for 2 years with an average annual award of $100,000; the R03 pilot small research grants, with a maximum award of about $100,000 given over 1 or 2 years; and the new R01/R29 hybrid grant under development, which would allow individuals to apply for their

first grants without limitations concerning the timeframe related to their training and would award about $125,000 in direct costs per year for 4 years, to a total of $500,000.

Questions and Answers

Dr. Becker asked whether these new awards have been announced yet. Dr. Marvin Kalt replied that the R01 mechanism that reflects the modified R29 has just been through the DCT Board of Scientific Counselors. The program announcements for the R21 and the R03, he said, are in the process of publication and will be "on the street" within the next month.

Dr. Diane Bronzert added that the first receipt date for the new investigator award will be in September 1994 and the first receipt dates for the R03 and R21 are expected to be in early June.

Dr. Sigal asked about the total dollars allocated for the new awards. Dr. Kalt responded that the DCT and DCPC RFAs provide up to $1.5 million each. Dr. Broder added that "no good application will be returned." He explained that the intent of peer review is to find a way to give very serious consideration to any application that has high scientific merit. He noted that in the past a perception had developed that applications for clinical research competed at a disadvantage. Dr. Broder declared that these new mechanisms exist to establish a separate "pot" of money so that excellent applications can be funded.

Dr. Salmon asked whether comments had been made by other Institutes, questioning the willingness of NIH to reduce the number of NRSAs to increase the stipend. Dr. Broder stated his understanding that a decision has been made within NIH to increase the stipend and that it appears that this is no longer a topic for negotiation. In reply to Dr. Salmon's question concerning a reduction in the number of awards, Dr. Broder acknowledged that some reduction in the number of awards will probably take place, adding that some reduction in tuition support for institutions is likely to maintain some measure of stability in NRSAs. He expressed concern that this might result in different tuition policies for various institutions, with the possible result that individuals receiving NRSAs from institutions would have different tuition repayment schedules than those receiving grants from NCI. Dr. Broder compared this to the possibility of having differing indirect cost structures. He expressed his belief that most institutions are using their assistance mechanisms very wisely and suggested that reductions in any resource will create problems for institutions in allocating all of their resources. Reducing tuition reimbursements or putting caps on indirect costs, Dr. Broder suggested, is likely to have an effect on the actual performance of science. Certain institutions, he speculated, may be forced to pass certain charges, such as rent, along to their investigators to be paid from the direct cost line.

Dr. Calabresi introduced Dr. Erwin Bettinghaus to make a special presentation. Dr. Bettinghaus thanked Dr. Broder for his 6 years of service as NCI Director. In light of the fact that the Director will be required to present a strong case to maintain progress against cancer in the context of health care reform, he presented Dr. Broder with a copy of his latest book entitled *Persuasive Communication*. Dr. Broder thanked Dr. Bettinghaus and announced that he would be distributing certificates to NCAB members who have served for 6 years.

With respect to health care reform, Dr. Broder emphasized that the cancer research community must work to make the case that clinical and basic research—the generation of knowledge—are parts of health care reform. He observed that many people die of cancer not due to failures in health care but due to inadequate knowledge. He stressed the importance of making a long-term, durable commitment to research and argued that it is the responsibility of NCI and the grantee community to convey the importance of continuing research and generation of knowledge as a part of health care reform. He also stressed the importance of

avoiding pessimism about cancer and ensuring that the needs of cancer patients are considered in the formulation of health care strategies.

Following the presentation of certificates to retiring Board members, Dr. Calabresi introduced Ms. Dorothy Tisevich to present a legislative update.

IV. LEGISLATIVE UPDATE—MS. DOROTHY TISEVICH

Ms. Tisevich reviewed a number of hearings and briefings in which NCI staff participated during the past several months. On October 4, 1993, at the beginning of Breast Cancer Awareness Month, the Institute's Deputy Director, Dr. Daniel Ihde, testified on that topic before the Senate Cancer Coalition, which is chaired by Senators Connie Mack (R-FL) and Diane Feinstein (D-CA). Other speakers included medical experts, cancer survivors, and women's health advocates. The coalition, Ms. Tisevich added, plans a series of hearings.

On October 15, 1993, Ms. Tisevich continued, Dr. Edward Sondik, Deputy Director of DCPC, testified before the House Subcommittee on Human Resources and Intergovernmental Relations, which is chaired by Representative Edolphus Towns (D-NY). During this hearing on "The Standard Health Benefit: The Impact on Women's Health Care," Dr. Sondik discussed NCI's breast cancer screening guidelines, including the scientific basis for considering changes in the guidelines.

On October 21, 1993, Dr. Richard Adamson, DCE Director, testified at a hearing on "The Relationship Between Estrogenic Pesticides, Breast Cancer, and Other Health Effects" conducted by the House Subcommittee on Health and the Environment, which is chaired by Representative Henry Waxman (D-CA). Dr. Adamson described NCI's research on the possible role of pesticides and other environmental agents as etiologic factors for breast cancer.

On October 30, 1993, Drs. Aaron Blair and Susan Sieber, both from DCE, testified at a field hearing, convened in Huntington, Long Island by Representative Towns, regarding NCI's research on environmental agents and cancer. Several questions were raised about the Congressionally mandated Long Island Breast Cancer Study, which at that time was in the early planning stages.

On November 9, 1993, Dr. Michael Grever, Associate Director of the Developmental Therapeutics Program in DCT, testified before the House Subcommittee on Merchant Marine and Fisheries, chaired by Representative Gerry E. Studds (D-MA), on "Medical Uses of Plants: Protection for Plants Under the Endangered Species Act." Dr. Grever provided an overview of the NCI Natural Products Program's development of anticancer and anti-AIDS agents. He also discussed several issues concerning intergovernmental, private sector, and international cooperative agreements, including marketing, compensation for host countries, and conservation of biological diversity.

On November 10, 1993, several NCI staff—including Dr. Broder and Dr. Iris Obrams—briefed several members of Congress who represent Long Island in New York State concerning the Long Island Breast Cancer Study Project. Ms. Tisevich reported that the briefing was well received.

On November 15, 1993, Senator Paul Sarbanes (D-MD) toured the Frederick Cancer Research and Development Center (FCRDC) and was briefed on programmatic activities at that facility. During a media interview following the tour, Ms. Tisevich reported, Senator

Sarbanes expressed his support for the vitally important biomedical research being conducted as part of the fight against cancer, AIDS, and other fatal diseases, and he stressed the significance of the Federal Government's role in providing adequate levels of funding and maintenance of the physical infrastructure for public institutions such as the FCRDC.

On November 20, 1993, Dr. Otis Brawley, Director of the DCPC Community Oncology and Rehabilitation Branch, participated in a public education fair that focused on breast cancer and prostate cancer in Nevada. At this event, which was sponsored by Representative Barbara Vucanovich (R-NV), Dr. Brawley discussed the importance of early cancer detection.

On January 26, 1994, Dr. Broder testified before Representative Waxman concerning the scientific basis for NCI's current statement on screening mammography. The hearing focused on women's health benefits under the administration's health care reform legislation known as the Health Security Act.

On January 31, 1994, Dr. Bruce Chabner, Director of DCT, testified at a forum on health care reform and clinical research convened by Senator Bob Kerrey (D-NE). Other witnesses included representatives of academia, the scientific community, the insurance industry, and patient advocate groups. Dr. Philip Lee, Assistant Secretary for Health, testifying on behalf of the administration, agreed that the portion of the Health Security Act addressing clinical research needs revision to address concerns discussed during the forum.

Ms. Tisevich reported that a hearing originally scheduled for February 10, 1994, by Representative Towns to discuss women's health benefits under health care reform, particularly as it relates to mammography, has been postponed and has not yet been rescheduled.

In 1993, Ms. Tisevich recalled, the Senate Appropriations Report urged NCI to undertake a study of underlying factors associated with high breast cancer rates in the Northeast and Mid-Atlantic States. Subsequently, she stated, a bill known as the Cancer Registries Act mandated an NCI study on the same subject. The sponsors of this bill, Representative Bernard Sanders (I-VT) and Senator Patrick Leahy (D-VT) requested a briefing on NCI research plans in response to this mandate. On February 2, 1994, several NCI staff—led by Dr. Adamson, conducted a well-received briefing in which the National Institute of Environmental Health Sciences (NIEHS) and one of NCI's funded investigators also participated.

In response to the Board's expressed interest in learning more about the health care reform legislation currently pending, Ms. Tisevich reviewed several features of the administration's bill, adding that summaries of major bills would be prepared for the next NCAB meeting. While NCI and NIH are not prominently featured in these bills, she stated, some provisions are of interest to these agencies.

During the first session of the 103rd Congress, Ms. Tisevich related, more than 150 bills concerning health care and health care reform were introduced. The administration's proposal—the Health Security Act—was introduced on October 27, 1993, in the identical companion bills identified as S. 1757 and H.R. 3600. She explained that the primary jurisdiction over health care reform in the Senate belongs to the Committee on Labor and Human Resources, chaired by Senator Edward Kennedy (D-MA), and the Finance Committee, chaired by Senator Patrick Moynihan (D-NY). In the House, she continued, the three committees with primary jurisdiction over this area are the Committee on Energy and Commerce, chaired by Representative John Dingell (D-MI), the Ways and Means Committee, chaired by Representative Daniel Rostenkowski (D-IL), and the Committee on Education and Labor, chaired by Representative William Ford (D-MI).

Ms. Tisevich reported that all of these committees have held hearings on health care reform and subcommittee markup of this legislation is expected to begin by the end of February 1994. Most of the provisions of the Health Security Act that relate to NIH appear, she said, under Title 3, "Public Health Initiatives." Within this section, under Subtitle B, is a section called "Academic Health Centers," which authorizes payments to qualified academic health centers for costs that are not routinely incurred by other entities but are a function of the academic nature of these centers. This could include, for example, costs resulting from reduced productivity of faculty due to teaching responsibilities, uncompensated costs of clinical research, or costs associated with treating health conditions for which that institution has specialized expertise.

Under Subtitle C of Title 3, Ms. Tisevich continued, is a section called "Health Research Initiatives," which requires the Director of NIH to ensure that its Institutes conduct and support biomedical and behavioral research on promoting health and preventing diseases, disorders, and other health problems. Some areas for research are stipulated, such as Alzheimer's disease, breast cancer, heart disease, and stroke. The bill further requires that certain areas, such as child and adolescent health, chronic and recurrent health conditions, reproductive health, mental health, elderly health, substance abuse, infectious diseases, wellness and health promotion, and environmental health, be given priority. The bill authorizes $400 million for fiscal year 1995.

Under Subtitle B, Ms. Tisevich continued, funding is provided for investigational initiatives to develop community-based strategies for health promotion and disease prevention.

Title V of the Act includes establishment of a National Quality Management Council, which is charged with developing national measures of quality performance to assess the provision and accessibility of health care services. Members of this Council would include the Administrator for Health Care Policy Research, the NIH Director, and the Administrator for the Health Care Financing Administration.

Finally, Ms. Tisevich noted, the bill allows (but does not require) coverage of investigational treatments, including peer-reviewed clinical trials such as those supported by NIH, at the discretion of individual health plans. This issue, she added, was a topic of intense interest at the workshop sponsored by Senator Kerrey.

Questions and Answers

Dr. Sigal said that it was her understanding that the health care reform bill encourages coverage for participation in clinical trials but does not specifically mandate such coverage. Ms. Tisevich confirmed that interpretation of the current wording of the bill, noting that Senator Kerrey expressed willingness to consider a possible revision of that language.

Concerning the pending bills on smoking (S. 262 and H.R. 881), Dr. Sigal asked whether there is a provision requiring that buildings leased by the Federal Government be nonsmoking buildings. Ms. Tisevich said that she would look into that issue, suggesting that the bills probably only require that the portions of buildings leased by the Government be nonsmoking areas.

Dr. Salmon stated that the issue of whether coverage for participation in clinical research is optional or required is very important. He pointed out that under many State health care reform plans, particularly in the Western United States, patients covered by HMOs are being told that they must pay their own way if they participate in clinical research.

Dr. Broder speculated that the whole idea of innovative therapy is likely to face problems in the future. It may be difficult or impossible, he said, for individual doctors—as they did more easily in the past—to act on intuitive insights to develop novel applications and build on these foundations to develop larger studies. Dr. Broder suggested that new practical mechanisms to accomplish this may have to be found. He said that this problem is particularly acute in the field of cancer research, where, for example, flexibility is necessary to discover novel combinations of drugs.

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

Dr. Sydney Salmon requested that the new business session be designated an earlier time on the agenda of the second meeting day to attain a quorum. Dr. Calabresi stated that he and Dr. Marvin Kalt agreed to hold the business meeting before the subcommittee reports. A quorum, Dr. Calabresi added, would still be needed for the subcommittee reports. The new business session, he said, would be held at 11:40 a.m., followed by presentation of subcommittee reports. Dr. Salmon suggested that future new business sessions be conducted at the earlier time; Dr. Calabresi replied that this suggestion will be taken.

Dr. Salmon then read the following motion that was suggested and deferred at the previous NCAB meeting and distributed to Board members by mail:

"Inasmuch as cancer research is the primary mission of the National Cancer Institute, the NCAB recommends that the NCI not involve itself directly in the setting of health care policy, including the development of formal guidelines."

Dr. Salmon explained that the rationale of the motion was that there are both governmental and private agencies that are better equipped to develop and implement health care policies than the NCI. The NCI is encouraged to communicate published information that is relevant to its mission and in the areas of cancer causation, prevention, early detection, diagnosis, treatment, and rehabilitation to the medical and scientific communities, the Government, and the general public. New research information, Dr. Salmon continued, often leads to changes in health policy; communication of such information to all interested parties falls within the scope of the National Cancer Program. The motion was seconded and tabled until the second new business session on the second day of the meeting.

Dr. Calabresi then recognized Ms. Marge Foti, Executive Director of the American Association of Cancer Research (AACR), for her contributions to the organization. Starting on February 23, 1994, Ms. Foti will chair the National Cancer Coalition.

Dr. Calabresi explained that, last year, the Board made it a policy to invite the president of the AACR to speak at the NCAB meeting. He introduced Dr. Margaret Kripke, who is the current President of the AACR as well as professor and Chair of the Department of Immunology at the University of Texas, M. D. Anderson Cancer Center.

VI. REMARKS BY THE PRESIDENT, AMERICAN ASSOCIATION OF CANCER RESEARCH—DR. MARGARET L. KRIPKE

Dr. Kripke thanked Dr. Calabresi and other members of the Board for the opportunity to speak and stated that she would provide an overview of current activities and goals of the

American Association of Cancer Research (AACR) and discuss important opportunities in and obstacles to cancer research in the immediate future.

Dr. Kripke described the AACR as America's oldest and largest cancer research association, with nearly 10,000 researchers representing primarily the USA and Canada as well as about 50 other countries. She pointed out that the Association's membership has doubled in the past 5 years and that attendance at the AACR annual meeting has tripled in the past 10 years, along with the number of submitted abstracts.

Dr. Kripke also noted the concurrent growth in the Association's scope of activity, describing several of its major projects, including *Cancer Research,* a journal dating from 1941. She related that Dr. Carlo Croce is the current editor-in-chief of this premier cancer research journal. Other journals produced by the AACR include *Cell Growth and Differentiation,* a new journal on the molecular biology of cancer whose editor-in-chief is Dr. George Vande Woude; *Cancer Epidemiology, Biomarkers and Prevention,* which was added in 1991 and is edited by Dr. Pelayo Correa; and *Clinical Cancer Research,* scheduled for release in 1995 as a forum for translational research. Dr. John Mendelsohn will be the editor-in-chief of *Clinical Cancer Research,* which will be a companion to *Cancer Research.*

Dr. Kripke also mentioned the Association's annual scientific meeting and its series of other smaller conferences that were initiated to address more clearly defined topics in cancer research and are held six to eight times per year. Other AACR activities, she continued, include cosponsorship of several international scientific conferences with cancer research associations in other countries and courses in cancer histopathology and molecular biology. Such scientific meetings, she noted, have helped to strengthen international collaboration. Dr. Kripke also cited the Association's outreach activities, including career mentoring for women, minorities, and young researchers in the cancer field and its extensive program for public education.

Dr. Kripke then summarized the AACR's mission as stated in its current bylaws: "to facilitate communication and dissemination of knowledge among scientists and others dedicated to the cancer problem; to foster research in cancer and related biomedical sciences; to encourage presentation and discussion of new and important observations in the field; to foster public education, science education, and training; and to advance the understanding of cancer etiology, prevention, diagnosis, and treatment throughout the world."

Dr. Kripke explained that as President of AACR and through her involvement in developing AACR programs and her affiliation with a number of policy committees, she has gained knowledge about the major activities in the field of cancer research. Today's overriding priorities, she said, are translational research, which uses findings from molecular biology, molecular genetics, and basic research over the past 20 years for the benefit of the cancer patient, and untargeted basic cancer research. Dr. Kripke stressed that it is a productive time to translate research into clinical usefulness, but cautioned against losing momentum or losing sight of previous efforts in untargeted basic research. She asserted that researchers must pursue current opportunities for advancing basic research, which represents tomorrow's progress.

Dr. Kripke outlined some challenges to progress in cancer research. She referred to the great sense of demoralization in the cancer research community because of diminishing funding, particularly for untargeted basic research, and earmarking of funds for special organ sites and programs by special interest groups. Since there is a limited amount of return derived from targeting money to a particular field, these developments are especially disheartening to basic scientists.

She related some of the scientific community's frustration with the peer review system. Quality is almost indistinguishable among the top 20 to 30 percent of grants submitted, and only one (maximum of two) reviewer reads each proposal. Dr. Kripke summarized that these factors create a climate that is not conducive to creativity or productivity in research. She related that it is difficult to recruit superior researchers into biomedical and cancer-related careers under these circumstances. Thus, these problems affect the current, as well as the future, cancer research community.

Dr. Kripke described the challenges of actually implementing translational research, that is, transferring knowledge "from the bench to the bedside," because of the lack of infrastructure and funding. She explained that collaboration and interaction among scientists, clinicians, nurses, and others who understand clinical issues should be encouraged to facilitate the application of existing knowledge, leading to productive clinical treatment, diagnosis, and prevention of cancer.

Dr. Kripke noted that health care reform is likely to have a significant impact on medical research and urged the scientific community to address the question of funding for medical research under a managed health care system. She emphasized the necessity of not impairing academic health centers and their ability to provide and design innovative approaches to cancer care. She urged cancer researchers to hear and understand the concerns of cancer patients and their families. Conversely, Dr. Kripke suggested that cancer advocates should try to understand the process of research and scientific discovery and what motivates scientists to pursue science and be creative. All who care about cancer research, she emphasized, need to speak in a unified voice to achieve an "integration of goals." Dr. Kripke outlined ways that the AACR can play a role in addressing concerns of the scientific community. First, it can help develop strategies for enhancing funding for basic and translational research. Second, the AACR can become a partner in determining the priorities for cancer research on the national level. Dr. Kripke suggested that research priorities must be based on opportunities for real progress.

Finally, Dr. Kripke reiterated the Association's commitment to serving as a means of communication about the contributions, needs, and strategies for cancer research and urged the Board to communicate its views and ideas to the AACR to help further the goals of the national cancer effort.

Dr. Calabresi thanked Dr. Kripke for her presentation and called for questions or comments. Dr. Sigal suggested that lobbying has jeopardized translational and untargeted basic research and asked what mechanism the AACR has to inform the general public and legislators about the issues they consider most important.

Dr. Kripke responded that the AACR is trying different strategies to disseminate its message. Various Association members have testified at Congressional hearings to describe the current situation in cancer research. She urged the scientific community to speak out and try to educate the public about the benefits, processes, and possibilities of research, so that people do not have unrealistic expectations about "what science can do."

Dr. Calabresi then adjourned the meeting for a short recess.

VII. COLON CANCER GENE—DR. BERT VOGELSTEIN

Dr. Rabson introduced Dr. Bert Vogelstein and, noting that he has been told that outstanding scientists often have undergraduate degrees in the hard sciences, said that

Dr. Vogelstein earned his bachelors of science degree in mathematics from the University of Pennsylvania. In comparing Dr. Vogelstein's varied talents and interests with those of NIH Director Harold Varmus, Dr. Rabson mentioned that Dr. Vogelstein received the Rosenbaum Award for Outstanding Undergraduate in Semitic Languages and Literature. Dr. Rabson stated that Dr. Vogelstein's cancer research has changed the way people think about cancer.

Dr. Vogelstein began his presentation by showing a slide depicting various colorectal neoplasms. He remarked that in the past 10 years it has been shown that the neoplastic process in the colon and other organs is dictated by mutations in oncogenes and tumor suppressor genes. A third type of gene, called a mutator gene, has been shown to play a role as well.

Dr. Vogelstein stated that, through efforts to understand the etiology of hereditary colon cancer, the gene that causes familial adenomas polyposis (FAP) was discovered approximately 3 years ago. Because this type of cancer accounts for approximately 1 percent of all colon cancer, Dr. Vogelstein said his group, in collaboration with that of Albert de la Chapelle at the University of Helsinki, decided to additionally investigate hereditary nonpolyposis colorectal cancer (HNPCC), which may account for 15 percent of all colon cancers.

In reviewing the history of HNPCC, Dr. Vogelstein stated that it was one of the first inherited cancer predisposition syndromes ever described in the medical literature, first appearing nearly 100 years ago. Before Dr. Henry Lynch's research on the disease, little work was done on HNPCC, particularly due to the fact that, unlike FAP patients, HNPCC patients do not have any obvious signs of the cancer. It is, therefore, often difficult to distinguish patients from families with a genetic predisposition to HNPCC from those who contract colorectal cancer by chance. Dr. Vogelstein explained that a disease as common as HNPCC is likely to appear clustered in some families by chance alone. He added that some epidemiologists now believe that between 40 and 80 percent of all colon cancers have some familial component.

Dr. Vogelstein then described the diagnosis and pathology of HNPCC. According to International Collaborative Group criteria, a diagnosis of HNPCC requires that an individual have at least three primary relatives affected with colon cancer, with at least one of them under 50 years of age. Tumors in HNPCC, he said, often appear on the right side of the colon but can also appear in the rectum. Other tumor types, such as endometrial and ovarian, tend to also occur in these families.

Dr. Vogelstein then showed a slide representing a typical family with HNPCC. The family included a young woman with colon cancer whose father had died of colon cancer in his thirties or forties, and whose grandmother had died in her forties or fifties of endometrial cancer. These families, Dr. Vogelstein said, are hard to analyze because affected individuals are not identified until they have cancer and, once the individuals have cancer, they often die, which makes studying them difficult.

In an effort to get around this problem, the Vogelstein-de la Chapelle group attempted to identify large families suitable for linkage analysis. After much searching, two families were identified—one from Newfoundland and the other from another part of Canada. Standard linkage analysis was performed, and, after considerable effort, a linkage on chromosome 2p was demonstrated. The lod score for the first family showed a greater than 10,000 to 1 probability that the marker was very close to the involved gene and proved that HNPCC was caused by a single gene. The lod score for the second family was also very high, increasing the likelihood that the same gene was involved in both families. After obtaining the linkage analysis results for these two families, the investigators looked at smaller families. Some of these, he said, had positive linkages to markers on chromosome 2p and some did not.

This suggested that there was heterogeneity in the causation of the disease, and that at least half of the kindreds were likely to have the defect in the gene on chromosome 2p.

In attempting to further define the gene on 2p, 15 to 16, Dr. Vogelstein's and Dr. de la Chapelle's groups collaborated with the National Center for Human Genome Research (NCHGR). The NCHGR microdissected the 2p'15-16 region. The DNA was then cloned to develop additional markers. About 20 markers were developed and used in linkage analyses with six families. Using these markers, the location of the gene was narrowed to a region of 8 million base pairs—still too large to begin targeted research. Dr. Vogelstein explained that they then obtained pathology samples from dead relatives in these families and were able to look for additional recombinants. Using this technique, the location was narrowed to less than 1 centimorgan, or 1 million base pairs—a short enough sequence to begin looking at candidate genes.

Dr. Vogelstein then described the functional studies being done by postdoctoral fellows in his and Dr. de la Chapelle's laboratories. They began, he said, by looking at the standard model of the formation of colon cancer. In this model, the APC gene mutation initiates the process, and other genes then play a role in progression of the tumor. Initial expectations were that the gene responsible for FAP would be substituted in HNPCC by another suppressor gene. Unexpectedly, when APC gene mutations were studied in HNPCC patients, over 60 percent were found to have APC gene mutations.

Further analysis showed tumor DNA from an HNPCC patient had new bands when compared to the DNA from a normal colon. This was true for markers throughout the genome—that contained a microsatellite sequence. Independent investigators in other laboratories had obtained analogous results in sporadic colorectal cancer patients.

Dr. Vogelstein noted that this phenotype was named RER, for replication errors, based on the assumption that the new bands resulted from a defect in replication. A forward assay was then employed to gauge the stability or rate of change. Dr. Ramon Parsons, using the forward assay he designed, found instability in the microsatellite sequences, although the reason for the instability was not understood.

Dr. Vogelstein said that soon after publication of his group's initial paper on this subject, he received a call from Dr. Paul Modrich from Duke University. Dr. Modrich thought mismatch repair defects might explain the microsatellite sequences. Dr. Vogelstein stated that he sent Dr. Modrich samples of the relevant lines, on which Dr. Modrich performed *in vitro* assays to determine whether there was an enzymatic defect in mismatch repair. His assays strongly suggested there was, indeed, a defect in mismatch repair.

Genes for mismatch repair, Dr. Vogelstein commented, have been studied for decades. He noted that a paper in *Nature* examined the effects of abnormalities in three mismatch repair genes from yeast on microsatellites. He then described the analogous bacterial genes, which he said were found to confer high rates of mutation in microsatellite sequences when altered. Using this phenotype as a basis, it was hypothesized that the tumors being studied were associated with mutation of the human homologs of these mismatch repair genes. They then attempted to clone such homologs. One gene (hMSH2) was cloned and found to be located on chromosome 2p, within the same 1-centimorgan region containing the HNPCC gene. Another group—at Dana Farber Cancer Institute in Boston, Massachusetts, and the University of Vermont) also identified this same homolog. Dr. Vogelstein pointed out that this illustrates successful integration of the mapping aspect of the work with a functional approach to locate a specific gene.

Dr. Vogelstein commented that the next step was to determine whether the mismatch gene was mutant in the germ line of patients with HNPCC, by identifying the sequence of the

hMSH2 gene and comparing it with the sequence in patients with HNPCC. The first large kindred studied showed a mutation, the second showed a deletion of several codons, and a third family had a germ line mutation that produced a stop codon. All three families, therefore, had a mutation that inactivated the hMSH2 gene product. Another important finding, Dr. Vogelstein stated, was the presence of two mutations in a tumor—a germ line mutation and a somatic mutation. In this tumor, both alleles were knocked out, thereby producing no normal gene product.

Dr. Vogelstein noted that when the mismatch repair capacity was measured in normal cells of HNPCC patients, it was found to be normal. It is only when they develop tumors that the other allele is knocked out and no measurable mismatch repair activity is detected using Dr. Modrich's assay.

Dr. Vogelstein then explained his working model. He said that normal cells from patients with HNPCC have one wild type copy of the hMSH2 gene and the second copy is mutant. These cells have no defect in mismatch repair. When one cell in the colon epithelium acquires an APC gene mutation as a result of exposure to an environmental carcinogen or to a mistake in DNA replication, a small adenoma will form. A second mutation in hMSH2 then occurs and the cell has no normal mismatch repair genes and the progression to tumorigenesis begins. Dr. Vogelstein commented that this mechanism of carcinogenesis differs from that of FAP, in which every cell in the colon has an APC gene mutation. FAP patients, therefore, develop thousands of adenomas, but only a small fraction of the adenomas progress to carcinoma.

Dr. Vogelstein mentioned that many unanswered questions remain, such as whether other human homologs of mismatch repair genes described in yeast and bacteria account for the remaining 50 percent of HNPCC cases. A second question is why the defect in mismatch repair affects only the colon and a few other organs, when logic would suggest that this type of gene would have the same function in every cell.

Discussing the practical implications of this research, Dr. Vogelstein remarked that a blood test can now be done on members of families at high risk to determine who is at risk. Those found to be at high risk can then be monitored through frequent colonoscopy and ultrasound. He said that most cancer deaths in these families could be prevented by combining screening and genetic testing. In those individuals who do not inherit the mutation, the need for yearly colonoscopy is eliminated and tremendous anxiety is alleviated.

Questions and Answers

Dr. Calabresi asked Dr. Vogelstein when a practical test will be available. Dr. Vogelstein responded that a test is currently available, the problem involves doing it on a large scale. He added that HNPCC is probably one of the most common inherited diseases of men. One in 200 people are likely to inherit a mutation, which translates to over one million people in the United States.

Dr. Chabner asked if a simpler, faster method than sequencing could be employed. Dr. Vogelstein answered that a faster screening strategy is used for familial adenomas polyposis, but the mutations in HNPCC are scattered and as many as four or five genes could be responsible for mismatch repair, which could hinder the development of cost-efficient methods of screening.

Dr. Newton asked whether environmental exposure histories had been taken from patients. Dr. Vogelstein remarked that for inherited predisposition syndromes, environment

apparently plays relatively little role in determining the age of onset and incidence. It may be more of a factor in the general population, he added.

Dr. Broder congratulated Dr. Vogelstein on his elegant work and remarked that there is no way to direct this type of research—it was accomplished by enabling an investigator to pursue ideas. Dr. Broder then commented on the diagnostic value of Dr. Vogelstein's research and his concern that, as in the Neurology Institute, they will soon be able to diagnose many diseases for which they will be able to do little. Dr. Vogelstein answered that in this disease, unlike in Huntington's disease, for example, frequent and effective surveillance can result in lives being saved.

Dr. Broder also cautioned that when patients are informed that they are not at an increased familial risk for colon cancer over the general population, it should be made clear that the general population still has a risk for colon cancer. Dr. Vogelstein acknowledged the importance of Dr. Broder's remark and noted that at Johns Hopkins, test results are not released to the referring physician but are explained to the patient by a clinical geneticist.

Dr. Salmon noted that while colonoscopy screening would not be cost-effective for the entire population, it might be cost-effective for a subset of the population if one could be identified. He then asked what other tumors types have the same mutation.

Dr. Vogelstein stated that the major tumor types are colon, endometrial, ovarian, stomach, and some transitional cell carcinomas.

Dr. Greenwald suggested that there might be a way to use the current chemoprevention studies to determine whether any interventions have a selective benefit for those with the gene defect.

Dr. Wells asked what the recommended treatment would be for a patient with a colon malignancy—and whether preventive surgery would be employed for those shown to have the gene defect. Dr. Vogelstein stated that screening with annual colonoscopies is recommended at an age 10 years earlier than the earliest age of onset in any family member. He added that prophylactic surgery is controversial in these cases, as it is in breast cancer. He noted that his personal belief is that at least half the cases in which prophylactic surgery might have been considered can now be eliminated through genetic testing.

Dr. Wells then asked whether informing patients of therapeutic alternatives complicates genetic counseling. Dr. Vogelstein responded that they do not emphasize alternatives other than close surveillance. He also made the point that anti-inflammatory drugs have been shown to shrink tumors in FAP patients; in the future, medical interventions (other than surgery) may be available for HNPCC as well.

VIII. INCLUSION OF WOMEN AND MINORITIES—DR. WENDY BALDWIN

Dr. Kalt introduced Dr. Wendy Baldwin and said that Dr. Baldwin's office is responsible for implementing the Congressionally mandated provisions of the NIH Revitalization Act of 1993 concerning the inclusion of women and minorities in clinical trials.

Dr. Baldwin began her presentation by informing the Board that she was recently named the Director for Extramural Research at NIH and is no longer working in an acting capacity. Dr. Baldwin then told the Board that the NIH guidance that is being issued is derived from the NIH Revitalization Act, in which Congress clearly stipulated the need for

change in the NIH policy regarding inclusion of women and minorities in research. The Office of Extramural Research has been coordinating issuance of the guidance, along with the Office of Research on Minority Health and the Office of Research on Women's Health. Dr. Baldwin added that these guidelines also apply to intramural research.

In preparing the guidance, Dr. Baldwin stated, a large committee was established that included experts in clinical trials and statisticians. It is difficult, she said, to write guidance that meets the needs of all those affected and still remain true to the spirit of the legislation, and for that reason, there is a great deal of latitude in the guidance. There is no predetermined formula, she stressed, to calculate the number of subjects necessary to meet the requirements of a particular trial. The purpose of the guidelines, Dr. Baldwin stated, is to address the concern expressed by Congress that it is still possible to reach the Phase III Clinical Trial level and yet not be sure that the results apply equitably across the population. Dr. Baldwin added that the guidance emphasizes the Phase III stage.

Dr. Baldwin noted that two guiding principles were considered in the formation of the guidelines—the first is that they are science driven and the second is that they reflect a partnership throughout the scientific community. In regard to science, she continued, the guidelines do not suggest that every trial must include a particular number of cases but, rather, if there is reason to believe that there will be a different effect in different populations, this fact cannot be ignored. The concept of partnership suggests that the burden for this aspect of research falls equally among investigators, reviewers, councils, and program staff.

Dr. Baldwin explained that the new guidelines differ from previous guidance in four areas. The first involves subpopulations; it will no longer be sufficient to use broad, diverse categorizations. The second difference is that in clinical trials, if an investigator anticipates that outcome will differ between certain populations, then that factor must be built into the trial so that at the end of the trial, it can be determined whether the intervention was equally applicable to both populations. The third difference is that cost cannot be used as a reason for exclusion. For example, Dr. Baldwin noted that a recruitment that costs $200 dollars for White women and $300 for Black women could not be used as a reason to exclude Black women from a study. She emphasized that Congress has not been vague on this issue. The fourth area of difference from current policy is that special attention will be paid to recruitment and retention. Dr. Baldwin said she thought that while Congress understands that this will not be easy, they will question the extent to which an investigator attempted to recruit and retain women and minorities.

Dr. Baldwin then discussed some areas that will not change, first noting that the type 5 application will continue to include the current reporting form, even though investigators will be collecting additional information. She added that the guidelines will not apply when they would be inappropriate with respect to the health of the subjects or the purpose of the research, or any other circumstance designated by the NIH Director. Dr. Baldwin noted that it would be impossible, as well as inappropriate, to attempt to compile a list of such situations but cited, as an example, a disease that is more prevalent in a particular population subgroup, such that recruiting the appropriate number of cases would mean enrolling every member of the subgroup with that disease.

Dr. Baldwin then explained that they are in a transition period. The NIH Revitalization Act was passed in June, yet the guidelines have not been released. The NIH Director is looking at each Phase III trial to ensure that it is compatible with the legislation. To date, she said, no application has been incompatible with the legislation; if one were, however, it would not necessarily disqualify a clinical application based on 5 years of solid work, just because it happened to be submitted after the new inclusion criteria were adopted. In such a situation, Dr. Baldwin emphasized, the applicant would be assisted in determining corroborative work that could be done or adjustment to be made so that the trial could be completed.

Another activity underway, Dr. Baldwin reported, is the outreach notebook, in which case material has been collected on effective outreach, recruitment, and retention strategies for hard-to-reach populations. This material is being made available to the investigator community. At the same time, she added, "inside outreach" is being performed throughout NIH to brief program and review administrators on the new guidelines.

Dr. Baldwin mentioned that there has been a fair amount of anxiety related to this subject. She expressed her belief that when the full guidance is issued, the level of concern will decline. The guidance will result in change, she stated, and will not be cost-free—it has, however, been written with much flexibility, which is its greatest strength.

Questions and Answers

In view of the fact that cost is not an exclusion, Dr. Sigal asked how treatment is paid for in underserved and minority populations. Dr. Chabner answered that routine medical costs are paid by third party carriers such as Medicare and Medicaid or are picked up by the institution in many cases.

Dr. Baldwin added that health care reform may in some instances facilitate compliance with the guidelines, citing new alliances between university hospitals and other providers being established in anticipation of reform, which should broaden potential networks for recruitment of research subjects.

Dr. Bettinghaus asked how the guidelines affect Phase I and Phase II trials. Dr. Baldwin responded that while the guidelines include very specific requirements for Phase III trials, they serve to create an environment in which early studies must also take these issues into account. This should be a natural extension, she continued, since most research is undertaken with the expectation of reaching Phase III. For the early stages, Dr. Baldwin said she would characterize the guidelines as saying, "do not exclude unless it is scientifically justified."

Dr. Freeman stated that the guidelines create a dilemma, since in the real world cost is a significant issue, and many Americans are either uninsured or are facing procedures not covered by their insurance carriers. Congress has mandated these inclusion criteria, yet not determined how the costs will be covered.

Dr. Baldwin noted that very little was done concerning the cost issue in moving from the legislation to the guidelines, because Congress did not leave that aspect open for interpretation. Dr. Baldwin then reminded the Board that during her speech at NIH the previous week, Hillary Clinton's remarks addressed the concerns of the academic centers and that health care reform might broaden inclusion and participation.

Dr. Becker responded that support for the type of inclusion required by Congress does not appear in the health care reform plan. He added that the burden will fall heaviest upon the Centers of Excellence, which will not be able meet these criteria and, thus, will not do these clinical trials. He expressed concern that the result will be diminished excellence of medical research and clinical investigation.

Dr. Salmon, reflecting on recent changes in Arizona's Medicaid system that will make recruitment of minorities with low socioeconomic status even more difficult, said that while the Board would endorse the intent of the guidelines, they may prove to be "impractical realities."

Dr. Baldwin reiterated her feeling that by resolving these issues in the earlier stages of research, difficult decisions will not need to be made at the Phase III clinical trial stage.

Dr. Sigal noted that no mechanisms exist, either under the current system or under the proposed health care reform, to pay for clinical trials. This issue, she said, will have to be dealt with in a bigger arena.

Dr. Broder emphasized that the bottom line is that the National Cancer Institute and its grantees will do whatever it takes to comply with the requirements of the Congressional mandate. Eventually, he said, the policy will be enforced not only through a guideline checklist, but also through initial peer review groups. The reviewers will be asked to evaluate a Phase III application on the scientific basis of its patient composition, and that evaluation will be reflected in the priority score.

Dr. Baldwin concluded by saying that there is latitude in the guidelines for scientifically justified exclusion. She also stated that when the guidance is issued it will take effect—there will be no comment period. The guidelines will be reevaluated in 1 year.

IX. UPDATE ON INTERACTIVE R01s—DR. MARVIN KALT

Dr. Kalt explained that during its last meeting, the NCAB asked for an update on the Interactive Research Project Grant (IRPG) mechanism, which was first implemented in October 1992. He noted that NCI now has experience in implementing this mechanism in both the program announcement and RFA formats. Dr. Kalt stated that there has been a substantial response in terms of numbers of applications. Presenting a slide with data on FY 1994 IRPGs, he pointed out that because some applications submitted in late 1993 or early 1994 had not yet been reviewed, the slide did not represent the total number of awards expected to be made during 1994.

With respect to program announcements, Dr. Kalt stated, 162 applications in 48 clusters had been received; 21 awards had been made, for a success rate of 13 percent. Responses to RFAs included 256 applications in 76 clusters; 48 awards had been made, for a success rate of 19 percent. These success rates compare favorably, Dr. Kalt noted, with those for unsolicited investigator-initiated Type 1 R01 grants.

Presenting a slide summarizing IRPGs for FY 1993, Dr. Kalt reported that 93 applications in 26 clusters were received for a clinical research RFA; of these, 21.5 percent were funded. A basic science RFA resulted in a 31 percent success rate. Dr. Kalt observed that initial experience in interactive research has shown that it is difficult to get full clusters of high-quality applications and, as a result, RFAs need to be "out on the street" longer to enable investigators to coordinate research programs among diverse applicants. There were some clusters, he noted, in which some but not all applicants received awards, and a few single awards were also made.

Looking at program announcements for FY 1993, Dr. Kalt stated that a substantial number of unsolicited investigator-initiated applications were received for the general announcement "Interactive Research Project Grants for Cancer" and smaller numbers for two specialized announcements. Dr. Kalt stated that the RFAs and program announcements for 1993 had a combined success rate of 20.3 percent; this, he suggested, represents a typical whole-year success rate.

In FY 1994, Dr. Kalt stated, the number of RFAs increased slightly and the number of program announcements increased significantly—in effect, he noted, due to the updating of guidelines, which have reduced the minimum number of applications required. Dr. Kalt explained that the low success rates shown on the slide for 1994, as well as the low numbers of applications received for program announcements, resulted from the fact that the last rounds of the application receipt and award processes have not been completed. He predicted that, eventually, 80 to 90 applications in response to program announcements would be received in 1994.

Dr. Kalt concluded by observing that NCI has established a program that is attracting substantial numbers of applications and in which the success rate is higher than that for typical Type 1 R01s. He noted that exception funding is being used sparingly in a few cases where some of the applications within a particular cluster are outstanding. Also, NCI is negotiating to ensure that when partial clusters are funded, the necessary resources for each application to achieve its goals are provided.

Questions and Answers

Dr. Becker called attention to the significantly higher success rates for responses to RFAs compared with investigator-initiated applications. Dr. Kalt pointed out that in an RFA, NCI specifies a dollar level which, because of the large number of good applications received, usually represents a minimum level of funding. The RFAs, he noted, have been approved during BSC review and are considered to be worthwhile targeting of funds. Among the investigator-initiated applications, he said, the success rate for the IRPGs is high compared with those submitting first-time regular R01 applications. Dr. Kalt added that some amended Type 1 applications for IRPGs are also likely to be awarded.

Dr. Becker asked about the success rate for investigator-initiated R01s on their first pass. Dr. Kalt stated that for 1993, the success rate for Type 1 R01s was approximately 12 percent.

Dr. Broder observed that applications responding to an RFA for IRPGs are reviewed by a focused *ad hoc* study group, whereas all of the applications in response to program announcements are reviewed by the Division of Research Grants.

X. CLOSED SESSION

A portion of the first day of the meeting was closed to the public because it was devoted to a meeting of the Special Actions Subcommittee. A total of 1,095 applications were received, requesting support in the amount of $226,657,790. Of those, 1,095 were recommended as being eligible for funding at a total cost of $203,472,146.

XI. GENERAL AGREEMENT ON TARIFFS AND TRADE (GATT) RESEARCH SUBSIDY PROVISIONS—DR. ROBERT W. KNELLER

Dr. Calabresi introduced Dr. Robert Kneller, Program Officer for Pacific and Southern Asia at the Fogarty International Center, National Institutes of Health (NIH).

Dr. Kneller began his presentation by explaining that the Fogarty Center is the smallest of the NIH Institutes and Centers, whose mission is to advise on international aspects of NIH's work. He defined the General Agreement on Tariffs and Trade as a set of rules, which originated shortly after World War II, designed to create a framework to promote free trade among most nations.

Dr. Kneller related that the latest round of GATT negotiations, called the Uruguay Round, began in 1986 and concluded in December 1993. Included in these talks was an attempt to further reduce tariffs on industrial goods as well as eliminate nontariff and other barriers to free trade. Dr. Kneller remarked that the United States has been a strong proponent of a more fair and free trade regime.

Early in the Uruguay Round negotiations, the United States was concerned that European companies were, through substantial monetary support, creating a European civil aircraft industry that would compete with American companies such as Boeing and McDonnell Douglas. Government aid supposedly allowed the final product (airplanes) to be priced lower than they would have been under a free trade or free competitive regime. The United States, Dr. Kneller explained, pushed for discipline of this type of activity. A subsidies code—which represents a key aspect of the Uruguay Round agreements—was created that specifically defines industrial subsidies to include any government assistance or cooperation with industry (including research) that benefits the industrial partner.

As a result of this agreement, Dr. Kneller continued, countries are required to notify the administrative body of the GATT about the form, per unit amount, duration, and trade effects of these subsidies. Other countries also have a right to request information on the nature and extent of any subsidy program. Dr. Kneller further explained that a country can apply tariffs to another nation, if it can prove that one of its industries has experienced unfair price competition as a result of the other's industrial subsidies. He offered a theoretical example involving NIH support of U.S. pharmaceutical companies that would result in lower-than-usual drug prices, causing "injury" to another country's pharmaceutical industry. If the country could prove its injury to the GATT administrative body, subsidies could be imposed on the import of the drugs into that country. This process of alleging and proving injury and applying tariffs is called countervailing duty action.

Dr. Kneller indicated that there is a presumption in the new GATT provisions that if the amount of a subsidy is less than 1 percent of total annual worldwide sales of a product, any injury is minimal and there is no basis for a countervailing duty suit. However, if the total amount of the subsidy is greater than 5 percent of total annual worldwide sales, there is a presumption of serious prejudice. Dr. Kneller remarked that it would be relatively easy to succeed in a countervailing duty action in the latter case.

Special exemptions exist, however, for industrial subsidies for research. The original draft of the GATT text stated that nonapplied (basic) research projects for which the government contributes less than 50 percent and applied research projects for which the government contributes less than 25 percent would be shielded from countervailing duty actions. To obtain this shielding, the U.S. Government would have to notify the GATT in advance so that other countries could determine whether the ceilings were met. This raised the concern that companies would have to divulge their research costs, which, Dr. Kneller noted, has implications for all of NIH's technology transfer program, particularly the Cooperative Research and Development Agreement (CRADA), the Small Business Innovative Research (SBIR), and Drug Development programs. Other U.S. agencies that are heavily involved in technology transfer, particularly the Department of Defense, Department of Energy, Department of Commerce, and NASA, also became concerned.

Dr. Kneller related that the NIH and Dr. Ruth Kirschstein played significant roles in persuading the administration to refocus its negotiating stance. The U.S. changed its position during the last 2 weeks of the Uruguay Round, resulting in significantly broadened definitions of the shielded categories. In the final version of the GATT subsidies code, all basic research is exempt from future countervailing duty actions. Also, any products that result from industrial research for which the government contributes up to 75 percent of total research costs are exempt from countervailing duty actions. Another category of research, Dr. Kneller continued, is called "precompetitive development" and is defined as the translation of industrial research findings into a plan or design for new or improved products or services, including creation of a first noncommercial prototype. The government can contribute up to 50 percent of the costs of this type of research and any products would still be shielded from countervailing duty actions. Dr. Kneller added that prospective notification is not necessary to obtain the shielding—a country does not have to prove its contribution percentage until a countervailing duty suit is filed against it.

Although he described the final Uruguay Round provisions as better than those originally proposed, Dr. Kneller highlighted several concerns that remain. In the area of drug development, there is the question of defining the first prototype of a drug. It is uncertain whether the first prototype occurs after a compound has passed Phase II trials, when a therapeutically effective molecule is generated in the laboratory, or when it is isolated from nature. The NIH, Dr. Kneller noted, spends the majority of its approximately $1 billion clinical trials allocation on Phase III trials. The National Cancer Institute has worked closely with companies in developing almost all of the current anticancer therapeutic agents, and there are many NIH research activities that involve cooperation with industry beyond first prototype development. Dr. Kneller pointed out, for example, that the NIH currently spends about $120 million a year on SBIR grants and contracts—most (about $90 million) of which is spent on Phase II grants to help small businesses produce commercial products in the postprototype stage.

Dr. Kneller addressed other questions, particularly whether CRADAs are to be considered subsidies under the GATT provisions and, if they are ruled subsidies, how NIH input can be valued. He indicated that it would be difficult to account for the laboratory space and personnel time that NIH contributes to CRADAs as well as the option to negotiate an intellectual property rights agreement. Another problem will be determining whether any purported injury to foreign competitors is due to price competition or greater efficacy of an NIH-supported drug. Fortunately for the NIH, Dr. Kneller commented, there is not much price competition among pharmaceutical products yet. Another issue, he stated, concerns whether grants to universities engaged in sponsored research agreements are considered subsidies to industry. Finally, Dr. Kneller reviewed questions concerning general notification procedures, which were not changed in the final stages of GATT negotiations. Issues include the level of detail that NIH must report regarding the nature of subsidies, duration, and trade effects; the level of detail that other countries can request regarding the nature and extent of subsidies; and whether NIH might be vulnerable to foreign requests for detailed information on the nature and extent of its CRADA and SBIR programs made in retaliation for aggressive U.S. countervailing duty actions.

Article two of the current GATT states that nonspecific agreements are not subject to countervailing duty actions. According to the GATT, when a granting authority or a granting authority's legislation explicitly limits access of certain enterprises to a subsidy, such subsidies shall be considered specific. In addition, when the granting authority establishes an objective criteria or conditions governing the eligibility for an amount of subsidy, specificity shall not exist provided that the eligibility is automatic and the grantee strictly adheres to such criteria and conditions. The criteria and conditions must be spelled out in law, regulation, or some official document for verification purposes. Based on these terms, Dr. Kneller stated, many of NIH's technology transfer programs probably should be classified as nonspecific subsidies.

Dr. Kneller concluded that the NIH's greatest concerns related to the new provisions are the resulting administrative burden on NIH and the chilling effect that intrusive notification requirements and the threat of countervailing duties may have on industry's willingness to cooperate with NIH.

Questions and Answers

Dr. Broder mentioned that these conditions do not apply for defense-related research activities. He stressed his point of view that a nation should be able to address issues related to public health by any means necessary and added that public health issues, such as cancer and AIDS, should be considered as important as military issues. He expressed concern about the effect of external regulations on the NIH research effort. Dr. Kneller assured Dr. Broder that this issue will be raised with the U.S. Trade Representative's office.

Dr. Broder noted that most public health problems in the United States have international implications. Dr. Kneller indicated that exceptions for defense-related research are based on the need for secrecy and the fact that limited trading is involved. He suggested that benefits for public health can rely on free market and free trade mechanisms. Dr. Broder emphasized that there are public health issues that cannot depend on the free market and reiterated that a nation should be able to respond to these issues without concern for external ramifications.

Dr. Sigal asked if the Fogarty International Center has access to outside counsel on this issue. Dr. Kneller answered that the Center works closely with the NIH General Counsel's Office.

Dr. Becker explained that most research grants are awarded to universities or individual investigators. He asked about the implications of licensing a product that results from basic research to an outside company, when original support was given to a researcher or university. Dr. Kneller responded that such a case would probably be shielded because the GATT language specifies "*direct* assistance from the government to industry." He added that sponsored research agreements would probably also be exempted; although in such cases, the link between government support and industry can be quite close.

Dr. Salmon asked if there are different implications for grants and contracts, since a contract calls for specific development or delivery of a product. Dr. Kneller replied that this point will be raised with the Department of Commerce and the U.S. Trade Representative.

XII. P53 MUTATIONS—DR. CURTIS HARRIS

Dr. Adamson introduced Dr. Curtis Harris, Chief of the Laboratory of Human Carcinogenesis in the Division of Cancer Etiology. Dr. Harris received both his bachelor's and M.D. degree from the University of Kansas and completed a residency in internal medicine before coming to the National Cancer Institute as a research associate in 1970. Dr. Adamson noted that Dr. Harris rose through the ranks, holding positions as a senior investigator and section chief prior to heading the Laboratory of Human Carcinogenesis.

Dr. Harris began his presentation on mutations of the p53 protein by stating that the *p53* gene and its product, a protein of 53,000 molecular weight kilodaltons, were once thought to be obscure findings in basic research but are now found to have a major impact on clinical practice.

In 1979, Dr. Harris explained, a large T protein from the DNA virus SV40 was found to bind to the p53 cellular protein. The protein was later cloned and was found to be a dominant oncogene. Research on the *p53* gene and its products had a minor role until 1989, when several interesting findings came to light. First, it was determined that researchers were not studying the wild type for the normal *p53* gene but, rather, a mutated form of the gene. Secondly, Dr. Bert Vogelstein's laboratory found that the gene was mutated in cases of human colon cancer in one allele and that the second allele was lost. Together with Dr. Susan Baker, Dr. Vogelstein found that when the gene was transfected into colon cancer cells, the gene inhibited tumorigenicity—it had the properties of a tumor suppressor. Dr. Harris noted that a unique property of *p53* is that when it is mutated, it loses its property as a suppressor gene and gains oncogenic activity as a dominant oncogene. This property, he said, differs from that of other tumor suppressor genes.

A third major finding occurred when Dr. Harris' group, in collaboration with Dr. Vogelstein's team, determined that *p53* was not only mutated in colon cancer but in most other types of human cancer. Remarkably, mutated *p53* is the most common genetic lesion found in human cancer today, and it is found in approximately 50 percent of human cancers throughout the world.

Since 1989, research efforts have focused on describing the function of *p53*. Several functions have been identified, including: activity as a transcription factor; regulation of replication; involvement in programmed cell death, or apoptosis; and, most recently, involvement in DNA repair.

Dr. Harris stated that *p53* is also known as "the guardian of the genome" and has been hypothesized to have involvement in cell cycle arrest after DNA damage. The *p53* gene product, when increased, has been associated with G1 arrest. The arrest phase, he explained, allows DNA repair to occur. If DNA repair is sufficient, the cells may then synthesize DNA in S phase and complete the cell cycle. Extensive DNA damage may lead the cell down a second pathway via apoptosis, which, in effect, is a fail-safe mechanism to eliminate cells with severe genetic damage. Dr. Harris emphasized, however, that if the cell contains a mutant *p53* gene and there is DNA damage, the G1 arrest that normally allows DNA repair is not functional. This situation can result in genomic instability, gene amplification, mutations, and, eventually, malignancy.

Dr. Harris then outlined the pathway of cell cycle arrest induced by DNA damage. He stated that *p53* transactivates a gene found downstream called WAF1 or Cip1. WAF1 or Cip1 encodes a 21 kilodalton protein, which is an inhibitor of cyclin-dependent kinases that has an important function in driving cells through the cell cycle. When the inhibitor is activated, cell cycle arrest occurs, which, in turn, allows DNA repair. An alternative mechanism by which the *p53* products allow DNA repair is through their ability to interact with other transcription factors and transcription repair coupling factors, which results in cell cycle arrest.

Dr. Harris showed a diagram of the p53 protein, which is composed of 393 amino acids. He indicated that certain areas of the protein are highly conserved and that most of the mutations in the gene occur in the central hydrophobic region, which is responsible for sequence-specific binding to DNA and transactivation. The transactivation domain is at the amino terminus, and the protein functions best as a dimer or tetramer. Dr. Harris pointed out that cellular proteins and oncoproteins from certain DNA viruses will bind and inactivate the p53 protein, including the SV40 T antigen, the E1B from adenovirus, and the hepatitis BX protein.

Dr. Harris posed several questions related to the rationale for investigating the mutational spectrum of the *p53* gene and its products in human cancers. First, does the somatic mutational spectrum of the *p53* gene reflect exposure to environmental carcinogens?

Can carcinogens in the environment leave a molecular fingerprint that can be detected in the *p53* gene and its product?

Dr. Harris proceeded by discussing the advantages of investigating the *p53* gene in the laboratory. The gene is mutated in 50 percent of all human cancers, is highly conserved in evolution, and has a reasonable gene target size. The main value of this type of investigation is to generate hypotheses—for example, with regard to a selection of mutants that might have pathobiological significance. Mutations that provide a growth advantage to cells are the mutations most likely to be seen in a tumor. Dr. Harris added that cellular context—the type of cell in which tumors occur—may influence selection of mutants.

Dr. Harris then showed another diagram of *p53* that illustrated mutations that have been described by his group and others. Over 2,500 mutations have been described, including those described in the literature. An important finding is that the mutations are nonrandom, and most are associated with the central portion of the gene that is required for its sequence-specific transactivation. Secondly, the distribution of about two-thirds of the mutations within the central portion occur in areas of the gene product that are evolutionally highly conserved. One-third occurs in intervening regions in codons that are themselves highly conserved.

Dr. Harris indicated that there are several mutational hotspots within *p53*, including codons 175, 245, 248, 249, 273, and 282. Five of these six are CpG dinucleotides. Within the *p53* mutational spectrum in human cancer, 17 percent are G-to-T transversions, and 25 percent are C-to-T transitions at the CpG dinucleotide site.

Dr. Harris stated that upon examining cancers at different sites, the mutational spectrum varies from one cancer type to another, and even varies within a particular cancer type. An example is liver cancer and exposure to aflatoxin, a dietary mycotoxin that is highly carcinogenic in experimental animals and humans. In areas of high aflatoxin exposure, the mutational spectrum of liver cancer differs from that found in areas with low exposure.

Dr. Harris then presented a comparison of the *p53* mutational spectrum for human lung and colon cancers to illustrate how different the mutational spectrum can be. In colon cancer, he explained, the predominant type of mutation is a C-to-T transition at the CpG sites. Lung cancer differs, as its predominant type of mutation is a G-to-T transversion. G-to-T transversion is commonly caused by exposure to polycyclic aromatic hydrocarbons such as benzo[a]pyrene (BaP). This mutation may also be caused by some of the tobacco-specific N-nitrosamines that Dr. Steven Hecht discussed in his presentation on lung carcinogens.

In examining the frequency of C-to-T transitions in selected human cancers, Dr. Harris stated that occurrence of this mutation is common in colon cancer, intermediate in brain and breast cancer, and low in lung cancer. Dr. Harris also showed that codon 248, a hot spot codon with a CpG dinucleotide, has more frequent occurrences of C-to-T transition than the other codons with a CpG dinucleotide.

Dr. Harris then discussed how the C-to-T transition occurs. He stated that cytosine, one of the bases in DNA, is methylated by methyl transferase to form 5-methyl C, and that 3 percent of the genome is 5-methyl C. This methylated deoxynucleotide spontaneously deaminates, losing its amino group to form T, thymidine. Oxy radicals, hydroxyl radicals, nitric oxide, and other compounds may enhance the rate of deamination.

An alternative, endogenous pathway of C-to-T transition, also influenced by exogenous factors and oxy radicals, involves C deamination to form a U. Dr. Harris stated that this can occur spontaneously; however, Dr. Peter Jones at the University of Southern California has shown that it is also possible for an enzyme that is responsible for the methylation under

certain conditions in which s-adenosylmethionine is below the KM level to deaminate. The deaminase forms U, and if the level of the repair product enzyme uracil glycosylase is insufficient, resulting in U being encoded as T.

Next, Dr. Harris presented examples of environmental causes of cancer that he said leave molecular footprints in the *p53* gene. Specific examples include: codon 249 serine mutations in aflatoxin-associated hepatocellular carcinomas; sunlight and dipyrimidine mutations in the nontranscribed DNA strand in skin carcinomas; and cigarette smoke and G-to-T transversions in the nontranscribed strand in lung cancers. The G-to-T transversions in the nontranscribed strand in lung cancers have also been associated with a dose relationship between the amount of smoking and the frequency of this mutation.

Other examples include high levels of radon, such as those found in uranium mines, which cause a mutation in the *p53* gene at codon 249. This was recently reported by Dr. Harris and colleagues in *Lancet*, and is characterized by a mutation in codon 249 among lung cancer cases in which there is a methionine amino acid substitution. Dr. Harris cited as a final example individuals who are occupationally exposed to vinyl chloride and have angiosarcomas that are associated with vinyl chloride exposure. The mutations in the angiosarcomas occur at A:T base pairs. This mutation is predictable, he noted, given the active metabolite of vinyl chloride.

Dr. Harris then focused his presentation on liver cancer. Well-known risk factors for liver cancer include hepatitis B virus and hepatitis C virus, chemical carcinogens such as aflatoxin, nutritional and hormonal factors, and, particularly in Western countries, alcohol consumption.

Dr. Harris presented data from a study by Ross, Henderson, Groupman, and Wogan from a prospective study of liver cancer in Shanghai, China. The research question for this study was whether there are interactive effects between aflatoxin exposure and hepatitis B viral status that determine the incidence of liver cancer. The relative risk factor for liver cancer is set at one for individuals with no exposure to aflatoxin and no evidence of hepatitis infection. If there is evidence of hepatitis infection and no exposure to aflatoxin, the relative risk factor increases to seven. If there is exposure to aflatoxin but no evidence of hepatitis infection, the relative risk is about three. In individuals with both hepatitis infection and exposure to aflatoxin, the relative risk factor is much higher than expected (approximately 59); it appears that the two exposures, hepatitis B infection and aflatoxin, have a synergistic relationship relative to liver cancer incidence.

Dr. Harris then indicated on a map of Asia that most mutations in liver cancer are G-to-T transversions in areas of high liver cancer incidence such as Qidong, China. However in areas of China with low liver cancer incidence and low aflatoxin exposure, the mutational spectrum of *p53* is quite different. Different *p53* mutational spectrum by geographic area is also apparent in Japan and Taiwan. With regard to the mutational hot spot at codon 249, where a G-to-T transversion occurs leading to amino acid substitution (arginine to serine), Dr. Harris said that this serine may be a new site for phosphorylation on the p53 protein. However, in areas with low liver cancer incidence, the mutations are spread throughout the *p53* gene.

Dr. Harris then shared data from geographic correlation studies, adapted from Montesano and Kirby, of *p53* mutations at codon 249^{ser} and dietary aflatoxin B1 intake to examine the incidence of human hepatocellular carcinoma. The highest frequency of codon 249^{ser} mutations is found in areas with the highest aflatoxin intake. In areas where the level of hepatocellular incidence and exposure to aflatoxin are intermediate, the level of codon 249^{ser} mutations is around 10 percent. In areas of lower hepatocellular carcinoma incidence

and lower aflatoxin exposure, the prevalence of *p53* mutations is less. The results of these studies, therefore, indicate a strong dose-response relationship between level of aflatoxin B1 exposure and *p53* mutation of hepatocellular carcinoma.

Dr. Harris then offered a working hypothesis to explain how aflatoxin initiates the *p53* mutation. He stated that aflatoxin is metabolically activated to aflatoxin B1-8,9 oxide by cytochrome p450 enzymes. A promutagenic lesion is created when the activated aflatoxin binds to the N7 position of guanine. If DNA synthesis occurs at this point, there is a high probability that a G-to-T transversion *p53* mutation will occur. This, in turn, will lead to a cascade of other events, to genomic instability, and eventually to hepatocellular carcinoma. A possible role of the hepatitis B virus in chronic active hepatitis may be to cause cell proliferation to allow fixation of the promutagenic lesion.

Dr. Harris suggested that another role of the hepatitis B virus in hepatocellular carcinoma may be to produce oncoviral proteins, such as the X protein. Dr. Harris stated that he will have results of this work forthcoming in the *Proceedings of the National Academy of Sciences*, and proceeded to summarize the information. First, the codon 249 serine *p53* mutation is associated with dietary exposure to aflatoxin. The results of a genotypic mutation assay used by Dr. Peter Cerutti and colleagues has shown that in areas of high incidence, this mutation is one of the earliest events, if not the first event, in hepatocellular carcinogenesis. Second, the X protein of the hepatitis virus can form a complex with *p53* to inhibit its sequence-specific DNA binding and its ability to transactivate genes downstream from *p53*. Therefore, hepatitis B virus joins a list of other DNA viruses that inactivate tumor suppressor gene products.

Dr. Harris posed a series of questions, including whether *p53* mutation represents an early or a late event in carcinogenesis. In liver carcinogenesis, he noted, *p53* mutation is an early event. In determining whether this mutation is an early or late event in other types of carcinogenesis, Dr. Harris reviewed work that was done with Dr. Bill Bennett in studying multistage bronchogenic carcinogenesis.

Dr. Harris stated that one can analyze preneoplastic lesions in multistage bronchogenic neoplasia both at the level of the protein of p53, and also the *p53* gene itself, by taking 5-micron sections of the tissue and staining them with hematoxylin and eosin to identify a preneoplastic lesion. Immunocytochemistry for the *p53* gene product is then performed. Dr. Harris pointed to p53 immunopositive nuclei in a histologic section found within a preneoplastic lesion. It is possible, he said, to micro dissect out this area in the paraffin-embedded section for examination, amplify the DNA by the polymerase chain reaction, do direct sequencing, and identify mutations in the *p53* gene .

In an examination of *p53* alterations associated with different degrees of bronchogenic squamous metaplasia, dysplasia, and carcinoma *in situ*, the frequency of altered *p53* increases to approximately 30 percent in mild to moderate dysplasia, and then reaches a plateau of 60 to 70 percent in severe dysplasia carcinoma *in situ* and microinvasive carcinoma. Dr. Harris summarized by stating that the *p53* gene mutation is an early or preinvasive event in esophageal, lung, breast, skin, and liver carcinogenesis. Mutation of the *p53* gene occurs later in most other cancers, but not in all cases of colon cancer, bladder cancer, and cancers of the nervous tissues.

Dr. Harris then posed another research question, asking whether *p53* mutations or elevated levels of protein correlate with survival or treatment response, and whether *p53* mutation is a prognostic indicator. Dr. Harris then showed an example of *p53* mutation in lymph-node-negative breast cancer. A majority of women, approximately 75 percent, with breast cancer with no nodes that are pathologically involved will have a long disease-free survival after initial surgery or radiation therapy. However, the other 25 percent of these

women will have breast cancer recurrence from metastases, despite the fact that there is no evidence of lymph node involvement at the time of clinical treatment. Therefore, there is a great need to identify tumor markers that will identify these women at highest risk. The *p53* gene may be one of these potential markers.

Next, Dr. Harris reviewed data from a survival study of lymph-node-negative breast cancer by Allred and colleagues. In a graph indicating survival in months on the horizontal axis and disease-free survival probability on the vertical axis, individuals with either an immunopositive tumor, indicating an alteration in the *p53* gene, or evidence of a mutation by single strand conformation polymorphism assay, have a poorer survival. If only one of these alterations is present, either a positive immunochemistry or a single strand conformation polymorphism, disease-free survival is intermediate. If the *p53* gene is apparently normal, probability of survival is much better. Similar results may be obtained with erbB-2 or neu amplification, which generally correlate with *p53* mutations. Dr. Harris stated that, in fact, mutations in *p53* that have been shown experimentally to cause gene amplification may be playing a role in the amplification of the erbB-2 gene.

Dr. Harris then reviewed other types of cancer in which *p53* alterations are an indication of poor prognosis, including lung, stomach, prostate, bladder, colon, and esophageal cancers. Dr. Harris stated that there are ongoing prospective studies designed to complement and extend the findings of the lymph-node-negative breast cancer study. Dr. Harris suggested that *p53* status will eventually be used to make decisions in clinical practice, noting that protocols are already in place at Sloan Kettering to evaluate bladder cancer prognosis using information on *p53*.

In summary, Dr. Harris reviewed the clinical implications of the *p53* mutations in human cancer. The first implication is genetic predisposition. Drs. Fred Li and Joe Fraumeni, both distinguished epidemiologists from the National Cancer Institute, recently found that in about 1 in 50,000 births in the United States there is a mutation in the *p53* gene, which is a germline mutation. Individuals with this mutation are predisposed to develop cancer at an early age. Secondly, in the process of using the mutational spectrum to generate hypotheses with regard to etiological agents in cancer and mutagenic mechanisms, the *p53* gene has been used to assay clonality of tumors and to determine whether the tumors are multifocal in nature or multifocal in origin.

The *p53* gene may have value in early detection of cancer by helping detect mutations in preneoplastic cells. It is possible to develop humoral antibodies to the p53 protein prior to the development of clinical cancer.

Dr. Harris stated that *p53* also has implications for therapy. Protocols have been developed and approved for gene therapy using a wild type *p53* to correct the tumor defect. In addition, a number of pharmaceutical companies are now using the *p53* gene and its product as a target to develop rational therapies against cancer. With regard to immunotherapy, polypeptides with specific mutants of the *p53* gene product have been used by Drs. Berovsky and Minna at NCI to increase cytotoxic T-cell response. Other future plans include the use of a plasmid and a "gene gun" to increase the cytotoxic T-cell response in afflicted individuals. The value of *p53* in the immediate future, Dr. Harris concluded, will be in prognosis and early detection of cancer, prediction of genetic predisposition to cancer, and better identification of the causes of cancer and the molecular mechanisms of carcinogenesis.

Questions and Answers

Dr. Frederick Becker asked Dr. Harris to reiterate the parallelism between the *p53* mutation in breast cancer and prognosis versus erb-2.

Dr. Harris responded by saying that other investigators have found that erb-2 or neu is amplified in a high frequency (10 to 20 percent) of human breast cancers, and is over expressed in others. ErbB-2 or neu amplification is an indicator of poor prognosis. Other recent studies have found that these same tumors frequently have *p53* mutations. Work by Drs. Wahl and Tisty indicates that cells which have a *p53* mutation are very susceptible for gene amplification. Therefore, there may be a mechanistic association between the *p53* mutation that allows gene amplification and amplification of erb-2 or erbB-2 in these tumors. The mutant *p53* and overexpressed erb-2 cooperate in the development of a more aggressive type of breast cancer. There has been a similar observation in esophageal cancer, where an association has been found between *p53* mutations and EGF receptor amplification.

Dr. Sydney Salmon then asked whether there are instances of p53 levels increasing on immunohistochemistry assays where there is no evidence of mutation. Dr. Salmon expressed the desire to develop a simple clinical test, and asked about increased levels of p53 in sun-damaged skin, and whether this p53 would be mutated or not.

Dr. Harris responded by saying that the correlation between immunopositivity and mutation varies between cancer types. Breast cancer, lung cancer, and esophageal cancer have a very tight correlation between immunopositivity and mutation. For certain types of skin cancer, the correlation is not good. Melanoma tumors, for example, tend to be immunopositive, but there is rarely a missense mutation in the *p53* gene. A possibility is that there is a mutation in the gene downstream from *p53* (e.g., the cyclin-dependent kinase inhibitor, p21). If *p53* is thought of as a member of a pathway, both genes prior to *p53* and downstream from *p53* may be altered. If there is DNA damage, the level of *p53* increases because of G1 arrest that allows DNA repair. Most of the skin cells that would be immunopositive will have the wild type *p53*. However, Dr. Yamasaki and associates at IARC have detected rare mutant cells in normal-appearing skin by using a very sensitive mutation assay. Therefore, a certain rate of mutations in the *p53* gene are occurring.

Dr. Salmon asked whether antibodies in the serum would be a better guide for genetic alterations because unaltered proteins are nonimmunogenic. Dr. Harris responded by stating that several studies, including those pioneered by Dr. Lionel Crawford and extended by Dr. Davidson at Duke University, Dr. Soussi in France, Dr. Harris' own group, and Dr. John Minna's group at Southwestern University, indicate that 10 to 20 percent of individuals who have tumors with *p53* mutations mount a humoral response.

In addition, Dr. Harris noted that it is possible to detect antibodies in human sera before clinical evidence of disease. Prospective studies have used banked serum repository collections from many years ago to study chronic obstructive pulmonary disease for those exposed to occupational carcinogens. An example includes a historical study of serum from vinyl chloride workers exposed 40 years ago, who, with the present assay technology, show clinical evidence of disease in the form of evidence of antibodies to *p53* in their sera. Dr. Harris said that p53 antibody titer has been shown to decrease after surgical removal of tumors such as breast or lung, and his team is checking to see whether these titers will increase with tumor recurrence. He summarized by saying that humoral antibodies to *p53* have a limited value, as only 10 to 20 percent of individuals with tumors display them; however, antibodies to *p53* may be useful for early diagnosis and for following certain patients.

Dr. Calabresi asked whether asbestos exposure affects the *p53* gene based on knowledge that asbestos exposure has resulted in an increased incidence of lung cancer. Dr. Harris responded that the specific form of lung cancer that Dr. Calabresi mentioned is bronchogenic lung carcinoma. Dr. Harris stated he would address this, but commented on mesotheliomas, saying that mesotheliomas associated with asbestos exposure have a relatively low frequency of *p53* point mutations. With regard to bronchogenic carcinomas, these have been studied in conjunction with cigarette smoking and there is a dose-response relationship

between the frequency of *p53* mutations and tumor incidence. Dr. Harris pointed out that additional studies are being done to see if the frequency of tumors is even higher or if the mutational frequency is altered among asbestos workers who are also smokers; these results are not yet available.

Dr. Broder alluded to a chart that Dr. Harris used to present the use of the single strand confirmation polymorphism assay and asked what percentage of patients who have Stage I breast cancer would be *p53* positive by that assay.

Dr. Harris stated that by using single strand confirmation polymorphism, the frequency for mutations does not appear to be dependent on the stage of breast cancer. Between 35 and 40 percent, he said, will have a mutation even with very small lesions.

Dr. Broder said most people in the field are convinced that adjuvant chemotherapy has a role for certain women with early-stage breast cancer, perhaps premenopausal breast cancer, yet most women are not benefiting from adjuvant chemotherapy. Dr. Broder stated that there is a survival benefit when results are examined from population-based, meta-analysis, or even individual clinical trials. However, the majority of women who have micrometastatic disease eventually relapse, which is essentially fatal. Dr. Broder recalled the results of a CALGB study in which specific subsets of women with a slightly different category of disease benefited from dose-intensive regimens in which Her-2-neu was a marker.

Dr. Broder also asked whether it would be possible to identify a subset of women with very early breast cancer upon whom all of the apparent population benefits would accrue by using a reasonably rapid assay; for example, the single strand confirmation polymorphism assay. He stated that the assay could be fine-tuned to identify women who need or would likely benefit from adjuvant therapy that exists currently, as well as women who would at least benefit from the dose-intensive regimens. Dr. Broder stated that, currently, if one is Her-2-neu-erbB2-positive, it is likely that a dose-intensive regimen is necessary. If one is Her-2-neu-erbB2-negative, a dose-intensive regimen may not be necessary, and other conclusions may be drawn. Dr. Broder then asked whether it would be possible to identify a subset of women presently in clinics around the country who could receive relatively high-dose therapy.

Dr. Harris responded by saying that there are ongoing prospective studies to address this question. He posed the question of whether analyzing the combination of neu amplification or Her-2 amplification plus *p53* would be a better indicator of the higher-risk women than one or the other. Dr. Harris suggested that the future of cancer therapy lies in a series of markers that will identify the more aggressive types of tumors and allow therapies to be modified depending on the molecular lesions in the type of cancer.

Dr. Broder stated that perhaps these kinds of studies may be done retrospectively. Dr. Harris agreed, stating that the retrospective information available has enabled the identification of people with poor prognosis who have the p53 alteration. Dr. Broder wondered whether a randomized trial could be done retrospectively. Dr. Harris said that could be done.

Dr. Broder stated that the dose-intensity question could be asked retrospectively and expressed his belief that answering the dose-intensity question should be a high priority for those who report to the NCI.

Dr. Broder made an additional point that, historically, it is possible to invert natural history by intervention. For example, it is possible to alter the outcome of individuals with a bad prognosis such as Her-2-neu-positive women. With dose-intensive chemotherapy, these women may become the good prognosis group. It could happen that the net overall natural

history of these women will suddenly become better than individuals in a previous era who had a different set of markers. A comparable example is lymphomas, where in an earlier era the so-called extremely bad prognostic lymphomas, or cysticytic lymphomas, became curable in a subset of people, and the lymphomas which previously had a good prognosis became more difficult to handle. Dr. Broder concluded that these are very important questions and urged Dr. Harris to work with the NCI Division of Cancer Treatment and added that Dr. Mike Friedman is moving in this direction as well.

Dr. Calabresi thanked Dr. Harris for a very informative and important presentation and moved on to the next speaker, Dr. Steve Hecht.

XIII. METABOLITES OF A TOBACCO-SPECIFIC LUNG CARCINOGEN IN THE URINE OF ACTIVE AND PASSIVE SMOKERS—DR. STEPHEN S. HECHT

Dr. Hecht explained that his report would describe collaborative research conducted with his colleagues at the American Health Foundation (AHF) with support from NCI's Division of Cancer Etiology. He opened his remarks by noting that lung cancer is the leading cause of cancer deaths in the United States and that smoking caused at least 80 percent of the 150,000 lung cancer deaths reported by the American Cancer Society in 1994. Smoking, Dr. Hecht continued, affects nonsmokers exposed to cigarette smoke passively as well as the estimated 47 million active smokers. Part of the effort to prevent lung cancer, he stated, is research to identify and understand the carcinogens involved.

Dr. Hecht stated that his presentation would focus on NNK, a carcinogen found in tobacco and tobacco smoke. NNK (nicotine-derived nitrosamine ketone), a relative of nicotine that is formed readily in the chemical nitrosation of nicotine, has been found to be a powerful pulmonary carcinogen in rodents, inducing adenocarcinoma of the lung independent of the route of administration—whether administered by subcutaneous injection, in drinking water, or by swabbing the oral cavity, its main tumor site is the lung. It induces tumors in rats at doses similar to human exposure levels and is metabolically activated to DNA and protein adduct in rats and humans through similar pathways.

After evaluating the various carcinogens present in tobacco smoke, Dr. Hecht stated, his team concluded that the strongest evidence for a causative link with lung cancer was found to be associated with NNK and with polycyclic aromatic hydrocarbons, such as benzo[a]pyrene and related compounds. Weaker evidence was found for some metals, aldehydes, and free radicals. There are a number of other factors, Dr. Hecht noted, that can affect the eventual development of lung cancer.

To compare the carcinogenic activities of NNK and BaP, a side-by-side bioassay in mice was performed. NNK proved in this study to be the more powerful carcinogen, resulting in about 47 lung tumors per mouse, compared with about 4.8 tumors with similar doses of BaP.

Dr. Hecht provided some basic information about carcinogen metabolism. Virtually all environmental carcinogens, he stated, are procarcinogens; they undergo enzymatic processes in the host that are important in determining whether the carcinogens will be activated, leading to cancer, or detoxified. P450s and other enzymes add oxygen to carcinogens to form an oxygenated metabolite. Most of these metabolites follow the detoxification pathway, through which they undergo further conjugation and are excreted; others undergo further metabolism and react with cellular constituents to form adducts that are covalent binding products to DNA, RNA, and proteins for these carcinogens. The adducts to DNA are considered to be

particularly important in carcinogenesis. The balance between detoxification and activation, Dr. Hecht explained, will determine whether an individual is susceptible to the carcinogen.

Dr. Hecht showed a slide illustrating the role of multiple genetic changes in lung cancer—changes resulting from DNA interactions not only at the so-called initiation stage but also in the activation of oncogenes and inactivation of tumor suppressor genes. He stated that these changes can result from multiple interactions with environmental carcinogens such as those found in tobacco smoke.

Another slide summarized information, gathered through studies in rodents, primates, and human tissues, on the metabolic activation and detoxification of NNK. Dr. Hecht explained that there are two activation pathways—DNA methylation, which leads to methylated DNA and eventually to G-to-A transition mutations, and the DNA pyridyloxobutylation pathway, which leads to pyridyloxobutylated DNA and to both G-to-T transversion and G-to-A transition mutations. These methylation and pyridyloxobutylation adducts have been identified in rodents and also in both smokers and nonsmokers, although higher levels are found in smokers. Dr. Hecht presented data showing levels of 7-methylguanine, as well as pyridyloxobutylation DNA adducts, in the lungs of smokers that were much higher than those in nonsmokers.

Another important aspect of NNK metabolism, Dr. Hecht continued, is its conversion to NNAL, an alcohol. In human tissues, about 80 percent of NNK is rapidly converted to NNAL, and NNAL is also a major transport form of NNK in rodents and primates. NNAL, Dr. Hecht added, also undergoes activation through the methylation and pyridyloxobutylation pathways and is also carcinogenic. Comparative studies have shown that NNK and NNAL have essentially equal activity in inducing adenocarcinoma.

NNL is also conjugated into glucuronide, Dr. Hecht stated. Although this substance has not been tested for carcinogenicity, he added, one would expect it to be a detoxification product, since most glucuronides are. This material, as well as NNAL, is excreted in the urine of rodents and primates treated with NNK.

Dr. Hecht explained that the goal of his team's research is to employ specific biochemical markers to the understanding of carcinogen metabolic activation and detoxification in humans by relating the metabolites found in humans to specific carcinogens to which they have been exposed, such as NNK and polycyclic aromatic hydrocarbons. The hypothesis, Dr. Hecht stated, is that cancer risk will depend partially on an individual's capacity to metabolically activate or detoxify a carcinogen, resulting in higher or lower risk, respectively.

This research, Dr. Hecht said, involves biochemical markers that serve as quantitative measures of either metabolites or adducts. Hemoglobin adducts and DNA adducts, for example, are markers of internal dose of a metabolically activated carcinogen. Urinary or serum metabolites also provide a profile of carcinogen activation and detoxification.

Dr. Hecht reported that his team has developed a method for analysis of NNAL and NNAL glucuronide in human urine. This involves separating the fractions into a free NNAL fraction that is nonconjugated and a beta glucuronide conjugated fraction; the analysis method is a technique called GC-TEA, which is essentially a selective technique for identifying and quantifying nitroso compounds.

Dr. Hecht displayed graphs that showed peaks corresponding to the presence of NNAL that can be observed in smokers but not in nonsmokers. Data from a study of 11 smokers showed that levels of NNAL and NNAL glucuronide in the urine of the smokers averaged

about 2.5 micrograms per day. This human exposure is similar to the lowest dose shown to induce tumors in rats.

Another interesting aspect of these urinary metabolites, Dr. Hecht stated, is the ratio of NNAL glucuronide (a detoxification product) to NNAL (a carcinogen). This ratio varies a hundredfold among the 11 smokers studied; it is presumed, Dr. Hecht said, that those smokers with higher ratios would be protected. A more recent study with about 48 subjects has also focused on this ratio. Although data are not complete, Dr. Hecht said, findings indicate a polymorphism in which there is a second group with a high ratio of glucuronide to free NNL. Again, this group would presumably be protected.

Dr. Hecht reported that a study is being carried out to compare this ratio in Black and White smokers, noting that Blacks have a higher incidence of lung cancer than Whites who smoke the same number of cigarettes. In this study, he stated, Blacks are disproportionately represented in the group with a lower ratio of glucuronide to free NNL and, thus, are presumably at a higher risk. While data are still being collected, findings suggest a highly significant difference in this ratio, which indicates that this metabolic difference could be a contributing factor in the higher incidence of lung cancer among Blacks.

Recently, Dr. Hecht noted, the EPA published an assessment of the role of environmental tobacco smoke (ETS) in human carcinogenesis based on a review of numerous epidemiological studies. This assessment concluded that ETS is causally associated with lung cancer in adults and belongs in the category of compounds classified by the EPA as human carcinogens. Dr. Hecht explained that this led his team to initiate a study of levels of NNL and its glucuronide in the urine of nonsmokers exposed to ETS.

In this study, Dr. Hecht continued, five nonsmokers were exposed to sidestream tobacco smoke—that is, the smoke that comes into a room in the presence of smokers. On two occasions, subjects were exposed to smoke for 1-1/2 hours in the morning and 1-1/2 hours in the afternoon. The subjects' urine was then analyzed for NNL and its glucuronide. Dr. Hecht displayed graphs demonstrating a statistically significant increase in these materials after exposure to ETS. Dr. Hecht added that this study also found a correlation between cotinine, the most common measure of sidestream smoke exposure, with NNL and its glucuronide in the urine. He stated that this study supports the conclusion that sidestream tobacco smoke can cause lung cancer by demonstrating the presence of a lung carcinogen. The next step, Dr. Hecht stated, is to examine this in larger epidemiological studies, for which the method needs to be further sensitized.

In summary, Dr. Hecht stated, NNK is a tobacco-specific lung carcinogen, its metabolite NNL is also an important pulmonary carcinogen in rodents, and these compounds have induced adenocarcinoma of the lung at exposures similar to those found in smokers. Studies of biomarkers have demonstrated the uptake and metabolism of NNK in humans by pathways similar to those established in rodents. Some interesting differences among individuals may be suggestive of differing risks for cancer. Finally, nonsmokers exposed to sidestream smoke have detectable levels of NNK metabolites in their urine, supporting the EPA's conclusion that environmental tobacco smoke is a lung carcinogen.

Questions and Answers

Dr. Kenneth Chan asked a question concerning the comparison of exposure in the rodents with that detected in the human subjects. Dr. Hecht explained that the rat data were collected during a chronic carcinogen bioassay, compared with the total dose that a cigarette smoker obtains in a lifetime of smoking. He added that individual doses were higher in the rats than in the smokers. Asked by Dr. Chan whether the carcinogen is metabolized in the

liver, Dr. Hecht stated that it is metabolized in the liver as well as in every tissue that had been examined.

Dr. Richard Adamson asked whether the American Health Foundation has any data on the number of lung cancer cases caused by factors other than cigarette smoking and whether they are aware of any changes in the ratio of lung cancer cases by type. Dr. Hecht replied that his organization's studies, as well as studies of SEER data, indicate that adenocarcinoma has increased dramatically and is approaching the point of overtaking squamous cell carcinoma as the main type of lung cancer in smokers. One hypothesis, Dr. Hecht stated, has been developed by his colleague Dr. Detrich Hoffmann, who observed that over the years, benzo[a]pyrene—classically associated with squamous cell carcinoma—has decreased in cigarette smoke, while NNK has increased. Dr. Hecht suggested that there may be other changes in cigarettes that affect the ratio of lung cancer types.

Dr. Hecht reported that AHF studies of tobacco-related cancers, involving 60,000 cases and controls, have shown that smoking causes about 80 percent of all lung cancers, which corresponds to evaluations made by others. He said that data on the numbers of cases caused by other exposures, such as radon, asbestos, and occupational carcinogens, are not conclusive, adding that the effects of these exposures are strongest in combination with smoking.

Dr. Sydney Salmon asked whether the same metabolites were generated measurably by nicotine administered by oral or percutaneous routes as part of a smoking cessation program. Dr. Hecht said that his team had not analyzed the urine of individuals using the nicotine patch but stated that it is possible that these compounds could be formed endogenously from nicotine. He added that even if the nicotine patch does form small amounts of nitrosamines, it is still preferable to smoking because it does not contain the other carcinogens that smoke contains.

Dr. Lakshmi Mishra asked whether Dr. Hecht has studied any other nitrosamines. Dr. Hecht answered that his organization has in fact studied other nitrosamines, noting that there are seven tobacco-specific nitrosamines. The primary carcinogenic nitrosamines, he stated, are NNK and NNN, which appear to be involved in other cancers associated with smoking, such as those of the lung, oral cavity, esophagus, and pancreas. Dr. Hecht said that NNK and NNN are found in large amounts in smokeless tobacco, noting that there are as many as 10 million oral snuff users in the United States. These products are addictive, he added, because of the rapid absorption of nicotine.

Dr. Erwin Bettinghaus asked whether Dr. Hecht has studied foods or plants on which nicotine has been used as a pesticide. Dr. Hecht replied that his organization has only looked at tobacco plants themselves, in which nitrosamines were not found until after the leaves were cured. He speculated that nitrosamines would not be found in other plants treated with nicotine as a pesticide but agreed that this is an interesting question.

Dr. Sheila Newton asked how Dr. Hecht found the subjects for the experiment with sidestream smoke, considering the fact that some were members of groups considered at high risk. Dr. Hecht explained that all of the subjects were volunteers from his laboratory, including himself, and that all participants signed consent forms and received information on the results of the experiment.

Dr. Broder asked whether Dr. Hecht feels that there might be any common type of lung cancer in the United States that is not associated with smoking. Dr. Hecht said that he has not heard of one. Dr. Broder pointed out that statements have been made to the effect that adenocarcinomas are not associated with smoking. Dr. Pelayo Correa noted that these statements were based on studies generated in the 1950s based on data available at that time on

bronchial alveolar carcinoma. Dr. Broder agreed but stressed the fact that old and erroneous stories have a life of their own. He reported that in the previous week he was told that certain forms of lung cancer were not associated with smoking; while he knew this was not true, Dr. Broder stated, he needed information such as that provided by Dr. Hecht to be sure that the record is clear on this point.

Dr. Walter Lawrence asked whether the association with smoking is as strong for adenous squamous carcinoma. Dr. Correa said that studies show the rarer squamous carcinoma is only rare in comparison with adenocarcinoma. He added that in his own study of passive smokers, the most prevalent type was adenocarcinoma.

Dr. Broder emphasized the fact that virtually all types of lung cancer are lethal, noting that the incidence is approximately equal to the death rate.

Dr. Adamson pointed out that smoking, as well as exposure to passive smoke, is synergistic with other lung carcinogens.

Dr. Charles Wilson asked for further information on the association between changes in ratios of lung cancer types with changes in cigarettes. Dr. Hecht replied that the nicotine content of cigarettes has increased, partly as a result of efforts to decrease levels of polycyclic aromatic hydrocarbons. The increase in nicotine has resulted in increases in nitrosamines. Dr. Hecht also noted that most cigarettes now have filters, which means that smokers are inhaling more deeply in order to get the same amount of nicotine. This, he suggested, could change the balance of carcinogens.

XIV. RECENT STUDIES OF THE COMMUNITY CLINICAL ONCOLOGY PROGRAM (CCOP) PROGRAM—DR. ARNOLD D. KALUZNY

Dr. Arnold Kaluzny, member of the Lineberger Comprehensive Cancer Center and Cecil Sheps Center for Health Services Research and professor at the University of North Carolina School of Public Health, discussed recent studies of the Community Clinical Oncology Program. Unfortunately, Dr. Richard Warnecke was unable to attend, Dr. Calabresi explained.

Dr. Kaluzny said the main topics of his discussion would include a brief review of the Community Clinical Oncology Program, evaluation of the program, background analysis of some of the CCOP's findings, and strategies to improve the performance of the CCOP.

Dr. Kaluzny reported three fundamental findings concerning the CCOP Program. First, he noted that CCOPs have clearly demonstrated their ability to accrue patients to both treatment and prevention control trials. In fact, approximately 25 percent of all patients in the ongoing National Surgical Adjuvant Breast and Bowel Project (NSABP) tamoxifen trial have been enrolled through the CCOP mechanism. Second, CCOPs have affected the practice patterns of community physicians, which Dr. Kaluzny said he would discuss in more detail later in his presentation. Third, CCOPs are not undifferentiated but, rather, have distinguishing characteristics that present important policy implications related to the selection of CCOPs and their management over time.

The Community Clinical Oncology Program began in 1983 and entailed a systematic effort of involving community physicians in community treatment trials, building on the resources of research bases available within the NCI, to develop community networks. In

1987, the NCI mandated that CCOPs include cancer prevention and control as a requirement for the program.

Specific objectives of the program are to conduct treatment and cancer control research within the community and within an organized framework, improve community practice patterns of primary health care providers, and increase accrual of minority and underserved populations. Dr. Kaluzny noted that improvement of community practice patterns was particularly critical in the 1987 movement to expand the scope of the Program to include the areas of prevention and control. Realizing that it would be difficult for the CCOP, as originally conceived, to increase accrual of minority and underserved populations, NCI initiated the Minority-Based Community Clinical Oncology Program (MBCCOP) in 1988. Dr. Kaluzny stated that the MBCCOP has been able to demonstrate the ability to accrue patients in the areas of treatment, prevention, and control as well as to accrue patients from minority communities.

The organization of the CCOP involves an alliance among the following organizations: National Cancer Institute, which is responsible for overall direction, funding, and management of the program; research bases (e.g., Eastern Cooperative Oncology Group (ECOG), NSABP, North Central Cancer Treatment Group (NCCTG), and the Southwest Oncology Group (SWOG), which focus on various treatment areas and are responsible for developing protocols for data management and quality assurance; and the individual CCOPs, which accrue patients to protocols and manage the studies locally within the participating communities. Dr. Kaluzny related that these local organizations vary in size and complexity. The basic organization has a core set of activities, with a principal investigator, co-principal investigator, and data manager. A number of components within the community, such as hospitals or health maintenance organizations, are affiliated with this core. Most structures, Dr. Kaluzny explained, are not extremely elaborate, but the CCOP initiative was designed to handle high levels of complexity. He added that the cancer prevention and control effort added to the CCOP initiative in 1987 was most often implemented with a cancer control committee.

Dr. Kaluzny explained that there are 52 CCOPs that involve 30 States, 253 hospitals, 103 group practices, and more than 1,000 physicians. Evaluation of the CCOPs began in 1987, at which time 13 new programs were added to the original 39. There were 17 research bases in 1987, comprising eight cooperative groups, eight cancer centers, and the Minnesota State Health Department (although the Department was never an active participant in the program). The MBCCOP includes 12 research bases, 9 States and the District of Columbia and Puerto Rico, as well as 31 hospitals, 209 physicians, and 75 "type B" physicians. Dr. Kaluzny stated that most of the CCOPs are located in the Midwest and Northeast. He observed that the absence of CCOPs in the Rocky Mountain States is the result of the peer review process that all proposed CCOPs must pass in order to participate.

The evaluation team included statisticians, an oncologist, and Dr. Kaluzny as the Principal Investigator from the Cecil Sheps Center for Health Services Research at the University of North Carolina at Chapel Hill. This group collaborated with Richard Warnecke at the Illinois Survey Research Laboratory and used the statistical services of Dennis Gillings at Quintiles Transnational Corporation in Research Triangle Park, North Carolina. Members of an oversight panel helped to ensure that the evaluation had practical clinical and program relevance to NCI. Dr. Kaluzny acknowledged the contributions of a number of clinicians, statisticians, and sociologists—including Frank Meyskins, Paul Engstrom, Dick Berk, Jerry Yates, Gary Cutter, and Brad Patterson, along with Jay Goldman, Dick Scott, and Jerry Hagi.

Dr. Kaluzny outlined three objectives of the evaluation: 1) to determine whether the CCOPs were able to accrue the required number of credits in terms of treatment as well as prevention and control; 2) to determine if the CCOP had any impact on practice patterns in the

local communities; and 3) to determine what organizational characteristics differentiated the more effective community-based networks from those that were less successful.

Dr. Kaluzny next discussed the evaluation design of the CCOP initiative, and explained that annual reports, provided by NCI, summarize data from all 52 CCOPs and 17 research bases, making it possible to assess yearly accrual rates. To gain knowledge about organizational and community dynamics, a key informant survey was instituted that was sent to key individuals in the CCOP and community. This questionnaire provided a rich source of information in terms of decision making, dynamics, conflict level, communication, and similar factors. Individual CCOPs were the unit of analysis in the area of implementation.

The evaluation team looked at changes in practice patterns in the community in terms of treatment of breast, colon, and rectal cancers. Dr. Kaluzny related that evaluators selected 20 CCOPs for extensive medical chart audits, and approximately 9,000 charts were examined. The evaluation team decided to track secular trends in these three disease sites in order to compare changes in practice patterns in the CCOPs with the larger SEER database. Two surveys of physicians within CCOP communities and primary care physicians in a national sample from the American Medical Association were conducted to assess physician readiness to participate in cancer prevention and control trials. Statisticians are still analyzing these complicated data.

Finally, because the actual dynamics of organizations can be quite different from the way they are described on paper, organizational characteristics were examined during site visits to 20 of the 52 CCOPs. These 1-1/2 day visits yielded the most revealing data and guided the analysis toward additional data collection.

Dr. Kaluzny then reported some of the findings of the evaluation of the Community Clinical Oncology Program. The CCOP, he said, plays a major role in the Cooperative Groups and the NCI Clinical Trials Network. During the evaluation period, the Program contributed 32 percent of total accrual for the five major cooperative groups. CCOPs clearly demonstrated their ability to accrue patients for treatment studies during the second generation of the organization, and there were significant increases in overall accrual. Dr. Kaluzny stated, however, that site visits revealed that it will take some time to assimilate prevention and control into the program. Accrual to cancer prevention protocols was in the early stage of development during the evaluation period, with 10 percent of the CCOPs meeting the credit standard in year one, and 35 percent in year two. Data indicate that many CCOPs had difficulty gaining access to prevention and control protocols that were relevant for their programs.

Dr. Kaluzny explained that the examination of practice patterns was intended to test the hypothesis that practice patterns would be diffused from CCOP physicians to non-CCOP physicians and, finally, into areas that did not have CCOP organizations. He related that practice patterns of CCOP physicians in treating breast, colon, and rectal cancer patients were significantly different from non-CCOP physicians in CCOP communities and SEER control communities for each of the three disease sites. There was no evidence of any diffusion from CCOP to non-CCOP physicians. However, non-CCOP physicians were referring patients to CCOP physicians. Thus, there was a fundamental change in referral patterns in the community, rather than in physician practice patterns. Dr. Kaluzny remarked that it is a significant and an encouraging finding that non-CCOP physicians viewed the CCOP as a center of excellence to which they referred their patients.

Dr. Kaluzny stated that the practice pattern study was being conducted when the 1988 NCI clinical alert was issued. The CCOP evaluation was able to assess the impact of this alert on breast cancer treatment patterns in the community and found that physicians significantly changed their practice patterns to comply with these guidelines.

Dr. Kaluzny then discussed the third objective of the evaluation—to examine organizational factors associated with accrual for prevention and control. CCOP staff hypothesized that the structure that had proven successful for accruing patients to treatment protocols would be equally effective in accruing patients to cancer prevention and control protocols. The key informant survey allowed evaluators to identify several program characteristics that affect treatment accrual, which, Dr. Kaluzny noted, focused on participation in research bases. The extent to which nurses were involved with the activities at the research base was a major predictor of whether the CCOP was accruing patients to treatment protocols. Size of the CCOP in terms of the number of components was also a factor in patient accrual, with the larger programs being more successful. Successful CCOPs also tended to dedicate resources to data management.

An additional set of factors affecting cancer prevention and control accrual emerged. A primary factor was the availability of protocols, which was controlled for at onset. Other critical factors were involvement in research bases and physician and nurse involvement. Three other important factors affecting accrual focused on past experience: 1) physicians' experience in the larger clinical trials network and the extent to which they were able to bring this experience to the CCOPs; 2) CCOP integration into the primary care network, particularly involving surgeons; and 3) the link between the principal investigator and non-CCOP physicians within the community.

Dr. Kaluzny related that the oversight committee was concerned that this evaluation not become an "academic exercise." Thus, evaluators collaborated with NCI to identify cross-cutting themes that affect the management of this program, such as strategies in light of budget constraints and Federal regulations, protocol availability, relationship between national and local environments, and NCI funding policies. It is important, Dr. Kaluzny indicated, for organizations that want to become CCOPs to have had previous involvement in research-based activity and to have physicians and nurses who are involved in the clinical trials network of the participating research base. Dr. Kaluzny cautioned that the number of participating components should be considered carefully, since many research bases have conflicting demands that could present challenges for CCOPs that have not developed adequate managerial sophistication.

Involvement of primary care physicians and selection of research bases with a strong commitment to prevention and control are important factors for the cancer control element. The research base serves as an important vehicle for introducing prevention and control by providing information on recruitment of primary care physicians into prevention and control trials and providing a forum for CCOPs to discuss activities and exchange solutions to problems. Dr. Kaluzny added that the MBCCOPs have benefited tremendously from such activity. Visibility of a CCOP within the community can affect its ability to function, and NCI assurance of high-priority protocol availability is also a central issue. Research bases should also be able to integrate the CCOPs into the clinical community. Several of the research bases, Dr. Kaluzny remarked, have worked aggressively to modify their strategies and involve the CCOPs in their policy-making process. He added that some hospitals have capitalized on implications of excellence by advertising that the project was funded by NCI.

Dr. Kaluzny commented that the evaluation did not address cost monitoring. The evaluation committee recommends, however, that it is important to address costs and resources, considering the fact that resources are limited and health care reform is imminent. Dr. Kaluzny emphasized that, while the CCOP is successful, other mechanisms and program initiatives should be considered and interfaced constructively.

Questions and Answers

Since Dr. Kaluzny chairs the Board of Scientific Counselors for the Division of Cancer Prevention and Control, Dr. Greenwald noted, he will follow up on recommendations.

Dr. Broder complimented Dr. Kaluzny on his presentation. He observed that one of Dr. Kaluzny's slides indicates that a large portion of the United States is not receiving the benefits of the CCOP. Given this fact, Dr. Broder asked if Dr. Kaluzny feels that the NCI can justify the support of CCOPs or an analogous clinical trial mechanism outside the United States. Dr. Kaluzny answered that, based on the NCI's mission to conduct research to resolve a problem with a specific disease, geographic boundaries should not be a factor in resource distribution. Dr. Broder asked if Dr. Kaluzny believes that the importance of science overrides the community-benefit issue. Dr. Kaluzny explained that the CCOP has always been a mechanism, or infrastructure, to better perform the science of cancer prevention, control, and treatment, not to regionalize health services.

Dr. Broder contended that Dr. Kaluzny's presentation dealt with the transfer and diffusion of knowledge into the community and acknowledged that there are barriers to knowledge transfer. In this context, he requested that Dr. Kaluzny help prepare him for Congressional inquiries about this issue. Dr. Kaluzny replied that the CCOP is a small program, while technology transfer is an ambitious program for which there are multiple vehicles. Diffusion and technology transfer, he continued, are a by-product of the CCOP's success. At the current time, Dr. Kaluzny suggested, it would be ambitious to expect the Program to conduct technology transfer as a primary function, in addition to conducting good science (i.e., accessing patients for randomized clinical trials).

Dr. Kaluzny described the issue raised by Dr. Broder as a challenge to involve Rocky Mountain area clinicians in the peer review system, rather than a need to specify that there should be a CCOP in that area. Dr. Bettinghaus commented that geography can be and has been considered a factor for awards. Dr. Broder indicated that, with the advice of the NCAB, the NCI has the discretion to use geographical diversity as an issue. He pointed out that one reason for establishing the CCOP, in addition to conducting scientific research, was to ensure the performance of state-of-the-art treatment and prevention protocols that will benefit communities. Dr. Broder suggested that if a section of the country does not appear to participate in such a program, the Institute should be prepared for inevitable questions on this issue.

Dr. Leslie Ford added that, while there are States without CCOPs, there are other vehicles for conducting clinical trials in treatment and prevention, including the outreach program, Cooperative Groups, and Cancer Centers. While there are still some sparse areas of coverage, she noted, there is no large area that is not served.

Dr. Broder repeated his request for a discussion of the rationale for providing community-based services in other countries—for example, in Canada.

Dr. Freeman observed that the CCOP was established with clinical trials as the primary driving force, with the prevention and control aspects added later. He suggested that treatment protocols may be dominating the cancer control aspects of the program and suggested the possibility of creating another concept in which cancer control would be the driving force.

Dr. Kaluzny expressed the belief that the structure of the CCOP has been successfully adapted to handle prevention and control protocols. Thus, he suggested, creating a new and different mechanism would not be cost-effective.

Dr. Freeman said that he was not suggesting replacing the protocol-based efforts described by Dr. Kaluzny but, rather, that some cancer control strategies could be established and studied in communities that have excess mortality.

Dr. Peter Greenwald, Director of the Division of Cancer Prevention and Control, observed that such an effort could be described as a cancer control research unit targeting minority or underserved populations rather than a CCOP, noting that protocols could eventually be incorporated into such a study rather than starting off with a protocol-driven plan. He stated that NCI should continue to promote minority-based CCOPs and explore new approaches because achieving effectiveness in some populations is still a formidable challenge. Dr. Freeman added that it is important to consider new approaches if the Institute is under criticism for not reaching certain communities.

Dr. Sidney Salmon asked whether the lack of penetration of cancer prevention and control protocols into some areas could be related to the intellectual interests of individual investigators. He suggested that more interest might be created in prevention and control if medical oncologists worked with co-investigators whose interests went beyond treatment or if prevention protocols could be based in mammography units instead of surgeons' offices, for example. Dr. Kaluzny agreed, citing the example of tamoxifen trials, in which CCOPs became involved because clinicians expressed interest in participation. Asked by Dr. Salmon about the role of the principal investigator, Dr. Kaluzny remarked that while the individual investigator is still the key person, many of the CCOPs are now looking to the committees that were involved in their original proposals to provide more organizational guidance in the utilization of the structure, resources, and interests within the CCOP.

XV. CONFIDENTIAL STATEMENT OF EMPLOYMENT AND FINANCIAL INTERESTS—MS. ANNE E. HALL

Dr. Calabresi introduced Ms. Anne Hall, Assistant Special Counsel for Ethics in the NIH Office of the Special Counsel for Ethics, to discuss the mandatory new confidential financial disclosure form.

Ms. Hall explained that NIH employees are obligated to use the new SF450 form until an alternative is developed and adopted by both the Office of Government Ethics (OGE) and the Department of Health and Human Services (DHHS). She said her talk would include a brief history of the form and a discussion of current trends and future implications.

Ms. Hall related that the SF450 form was developed as the result of an Executive Order and the Ethics Reform Act of 1989. Then President George Bush charged the Office of Government Ethics, an independent executive agency, with creating a uniform executive branch-wide confidential financial disclosure form. All individual executive branch agencies had their own forms before this time. Ms. Hall noted that the HHS 474 was developed for use by DHHS Advisory Committee members. Presidential appointees and other senior-level officials use the public financial disclosure form SF278.

In 1992, OGE established regulations describing the content of the financial disclosure form and its required use. These regulations gave no discretion to agencies in terms of required content and paralleled the requirements of 18 U.S.C. 208, the criminal conflict of interest statute, which prohibits Government employees from participating in matters that would affect their financial interest or a financial interest imputed to them (e.g., interest gained from the employee's, a spouse's, or a dependent's stock in a company or membership on the board of directors of an outside organization). Ms. Hall stated that section 208 is a broad

prohibition on participation in certain kinds of activities, but holdings that are not considered problematic can be waived.

Ms. Hall then acknowledged the Board's concerns about the relevancy and intrusiveness of some of the information that is requested on Form SF450. She explained that the OGE requires specific information to protect employees from prosecution, which, she said, the Department of Justice has recently been pursuing more aggressively, and to ensure that NIH Advisory Committee decisions are not tainted by outside interests.

The SF450, which officially replaced the HHS474 in October 1993, allows agencies very little discretion about who should file the form; all SGE Advisory Committee members are required to file the SF450. Ms. Hall announced that the OGE recently issued new regulations that no longer require the disclosure of savings and checking accounts, Treasury bills, bonds, Government securities, and Government liabilities in general. She expressed hope that even less disclosure will be required in the future, noting that NIH has received permission from OGE to waive the requirement for Advisory Committee members to file annually. Advisory Committee members will file the form once and, in subsequent years, before each meeting, indicate any changes in assets, liabilities, or membership in outside organizations on either a single-page attachment or photocopy of the original form that is received and returned by mail. Other agencies are still required to complete the form every year.

Ms. Hall related her hope that the NIH will develop an alternative to the financial disclosure form. Not only is the form intrusive, she continued, but it does not collect enough relevant information (e.g., laboratory support from an outside organization received by a member's institution). The Public Health Service has been charged with examining its concerns and considering an alternative form. The Food and Drug Administration has an alternative form, but Ms. Hall indicated that it requests a tremendous amount of detailed and confidential information, including information about products in the "thought stage."

Ms. Hall concluded by noting that impediments to development of an alternative form include the need to obtain OGE approval and undergo a rulemaking process. The creation of another form, she stated, could conflict with Vice President Gore's initiative to "reinvent" Government. Ms. Hall thanked the Board for complying with the form and commented that elimination of the annual filing requirement is just one step toward minimizing this burden.

Questions and Answers

Dr. Salmon asked why information on financial liabilities, such as a home mortgage, is requested when it seems that this information is irrelevant to the mission of the PHS, NIH, or the Government in general. He questioned whether an inquiry about this information is an invasion of privacy, since commercial liabilities linked to professional activities are not included. He also inquired about a guarantee of confidentiality of these forms, and asked whether the Office of the General Counsel has a liability to make this information public, since he recalled that confidential information about a prominent scientist appeared in scientific journals a few years ago.

Ms. Hall first addressed the issue of confidentiality. Confidentiality of the SF450 is protected by statute and regulations for 6 years; after this time, the form is destroyed. The public financial disclosure report is available to the public upon request. Conversely, the confidential financial disclosure form can only be released by court order. Ms. Hall noted that the court has requested all of these forms in the Health Care Reform Task Force and Working Group litigation, but the Office of the General Counsel is arguing that the forms are not relevant to the litigation. Release of confidential information can result in a reprimand or

termination of employment; however, the statute does not mention criminal prosecution or penalties.

Ms. Hall agreed with Dr. Salmon that some information requested in the form seems irrelevant to personnel in science-based agencies. She pointed out that one problem with a "uniform" form is that it contains information that is important to some agencies and inapplicable to others.

Dr. Broder asked if someone could challenge the vote of an advisory member if that member was accused of failing to file the form or filing the form improperly. Ms. Hall replied that there have been such challenges. Dr. Broder assured Board members that an NCI employee who released a form improperly could be dismissed without warning. A Congressional oversight committee, however, can lawfully request such forms. Dr. Broder added that an individual member of Congress would be denied access to these forms.

Dr. Ghosh stated that he is on active duty in the United States Navy and asked if he is required to fill out the SF450. Ms. Hall explained that, as an employee of the Navy, Dr. Ghosh probably is required to fill out a form for the Navy, and, if so, should forward a copy of it to the NCI.

The issue of spousal and children's income was discussed. Dr. Yodaiken commented that the form clearly states that it is not necessary to disclose information on mortgages. Ms. Hall clarified that it is not necessary to disclose information about a primary residence, but information must be provided about homes used for income-generating purposes.

Dr. Sigal indicated that this requirement to disclose confidential information could prevent the NIH from attracting quality people to its advisory committees. Ms. Hall replied that the NIH is aware of this problem and has expressed this concern to the Office of Government Ethics. Dr. Calabresi agreed that the forms could discourage many talented people from accepting advisory committee positions.

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

Dr. Calabresi announced that the Board would first vote on new business items and then hear the subcommittee reports and his presentation on the Subcommittee to Evaluate the National Cancer Program.

Motion

Dr. Salmon reread his motion of the previous day: "Inasmuch as cancer research is the primary mission of the National Cancer Institute, the NCAB recommends that the NCI not involve itself directly in the setting of health care policy, including the development of formal guidelines." Dr. Calabresi then opened the floor for discussion.

Dr. Sigal expressed concern about the word "directly." She interpreted the motion as suggesting that the NCI can make, but not officially mandate, recommendations. Dr. Salmon affirmed her interpretation and indicated that consensus conferences or clinical alerts are not problematic, as long as they are accompanied by references and detailed information. An agency, he continued, should release information along with supporting material and be held responsible for the recommendation.

Dr. Bettinghaus stated that he had intended to vote for the motion, but decided to vote against it for several reasons. First, he said, the public regards statements made by senior NCI officials as guidelines. Although Drs. Broder, Greenwald, and Sondik made statements to Congress that the NCI was not changing the existing guidelines but, rather, discussing the state of the science, Dr. Bettinghaus related, the media reported that the statements were changes in guidelines. Because of the credibility and stature of the NCI and the nature of the media in this country, scientific statements are regarded as guidelines, he continued. Second, the NCI does not have a process for establishing guidelines. Dr. Bettinghaus stated that, in the interest of cooperation, the Board of Scientific Counselors set guidelines in 1987 (when he was chair of the BSC) without a process for doing so. He added that he feels the science is too weak at this time to make statements on either side of the issue.

Dr. Bettinghaus also commented that he would not object to setting guidelines if the NCI were to develop a rigorous procedure to be followed, as it has for consensus conferences. He suggested that the NCI should set guidelines in areas where there is established scientific knowledge, such as tobacco and some treatment protocols. He strongly recommended that the NCI develop a process for establishing guidelines.

Dr. Calabresi remarked that the statement made by Drs. Broder and Greenwald was misinterpreted by all the newspapers.

Ms. Brown asked what the NCI would use as a definition for "guidelines" to avoid confusion between NCI-mandated guidelines and Congressionally mandated guidelines—for instance, for minorities and women in clinical trials. Dr. Broder clarified that there is an operational funding regulation to accrue women and minorities to clinical trials. This, he emphasized, is the official policy of the NCI, which is not open to debate.

Dr. Salmon reiterated that he made the motion because a mechanism for establishing guidelines does not exist, and the Board should recognize this issue at the present time.

Dr. Calabresi asked if Dr. Bettinghaus or Dr. Salmon would like to add an amendment to the motion. Dr. Bettinghaus answered that if he were to write up a motion stating that the NCI should move expeditiously through its advisory mechanisms to set up procedures for establishing guidelines, it would be an alternative to Dr. Salmon's motion.

Dr. Broder commented that the core function of the NCI is to generate knowledge at a basic and clinical level. He pointed out that the NCI has not always been in concordance with the guidelines of other Government agencies. Dr. Broder recommended that, in this time of health care reform, the NCI should be cautious in its role and focus on generating and disseminating knowledge in a scholarly format. The process of issuing guidelines has a regulatory component, he stated, in addition to a scientific basis; thus, the NCI should reassess its role and adjust it according to what it does best, based on science.

Dr. Calabresi asked Dr. Broder if the motion, as written, is helpful. Dr. Broder answered that the motion gives the NCI the flexibility to carry out its mission during this time of health care reform.

Dr. Mishra remarked that guidelines are sometimes construed as rulemaking. He explained that the Consumer Product Safety Commission has a rulemaking process in its statute. Unless an agency creates guidelines through a rulemaking process delineated by its statute, he asserted, the guidelines are merely an Institute policy.

Dr. Sigal addressed the issue of funding mechanisms for minority and female accrual to clinical trials and mammography. She emphasized that it is the NCI's responsibility to

synthesize and report information and make recommendations to the public, although the Institute does not have to formulate strict policies or guidelines for interpretation by other agencies.

Dr. Lawrence stated that the NCI has a tremendous mission and it is not equipped to expand the mission to include regulatory functions. Dr. Broder's words, he added, persuaded his support of the motion.

Dr. Broder stated that it is appropriate for other organizations to make policy statements, since they have slightly different perspectives and mandates from the NCI. He emphasized that grantees should not submit applications to the NCI if they cannot assure gender and minority equality in their investigations. The NCI clinical trials process must be open to all populations. Dr. Broder suggested that it would be unwise for the NCI to produce its own health care reform agenda. Health care reform, Dr. Broder proposed, will resolve many issues that prompted the guidelines. He related that President Clinton's health care reform plan includes a board that would make decisions about appropriate medical care delivery and preventive and treatment services. Dr. Broder recommended that the Institute consider the future direction of society.

Dr. Freeman asked if the Board is suggesting that the NCI not give advice to the public if the information involves a monetary cost. Dr. Broder clarified that money is not involved in this issue. If information is based on facts that are unanimously supported (e.g., a therapy works), Dr. Broder demonstrated, the NCI should impart this information. However, the NCI should not regulate the individual practice of medicine between doctors and patients and should not conflict with other Government agencies that are charged to address certain issues. The real issue, Dr. Broder specified, centers around the NCI trying to arbitrate information for which there is no consensus and no results based on clinical trials. A similar debate on making a statement about the role of mammography in women between the ages of 40 and 50 occurred with the Breast Cancer Demonstration Project in the late 1980's. Although there was inferential data based on case-control studies, the Project decided to postpone a decision pending clinical trials results. Dr. Broder commented that an NCI statement that is not based on a consensus or the results of clinical trials is essentially a policy statement.

Dr. Wilson suggested that there is a clear distinction between health policy research and science and Dr. Salmon's motion succeeds in making this delineation. Dr. Wilson used prostate-specific antigen (PSA) as an example to show that health policy research would involve defining the population for which the treatment would be most effective and determining the frequency with which the tests should be administered.

Dr. Chan asked for clarification on the difference between smoking and mammography in terms of regulatory implications. Dr. Broder emphasized the fact that smoking is harmful to health and is supported by a tremendous amount of scientific data. The issue of smoking and health is incomparable to debates on PSA, flexible sigmoidoscopy, or mammography. Dr. Broder explained that the NCI will not make a recommendation or statement about PSA until the ongoing clinical trial is complete. If the trial fails to show any mortality improvement, this information will be made public; findings about flexible sigmoidoscopy will also be released when they are definitive. Dr. Broder suggested that the mammography debate has been particularly difficult because mammography is a vehicle for entry into the medical system for underserved and minority women. The NCI, he stressed, must inform the public that there is controversy over this issue.

Dr. Bragg pointed out that a motion recommending a delay in changing the guidelines, although it was not acted upon, was supported by a majority of NCAB members at the last meeting. He stated that he would find Dr. Salmon's motion more acceptable if it could be modified to focus on specific issues of concern to Board members.

Dr. Salmon explained that he created this motion to delineate the NCI's charter and mission. Health policy is not part of the NCI's mandate, he stressed. If the NCI attempts to be a "quasi-policy-creating body" without a mandate or the authority or resources to do so, resources will be taken from research.

Dr. Yodaiken suggested that this debate centers around the semantics of three words: guidelines, policy, and regulation. He stated that the NCI does not have the authority to regulate, the means of implementing or ensuring compliance, nor does it have penalties. Dr. Yodaiken questioned the term "formal guidelines." He remarked that "policy" refers to NCI's internal policy, and anyone can issue "guidelines." Dr. Yodaiken recommended that the NCI explain and comply with its mission as well as set appropriate guidelines.

Dr. Bettinghaus commented that three terms in the motion that concern him are "health care policy," "formal guidelines," and "not involve itself directly." He suggested that the NCI cannot simply deliver scientific information but will be required to cooperate with other agencies in developing guidelines, which he interprets as direct involvement. Dr. Broder assured Dr. Bettinghaus that this motion would not prohibit the NCI from involvement in this type of cooperative activity. Dr. Bettinghaus repeated his concern that the language in the motion indicates that NCI will not be involved in these issues. Dr. Salmon replied that his use of the word "directly" was meant to indicate that NCI should not unilaterally formulate guidelines. Dr. Bettinghaus suggested changing the word "directly" in the motion.

Dr. Bettinghaus stated that "formal guidelines" is a confusing term; Dr. Kaluzny's presentation on CCOPs showed that an alert had been perceived as a guideline and had impacted health care practice. Dr. Broder emphasized that the alert had been strongly objected, because many felt it would interfere with the practice of medicine. He also expressed his own rejection of this view, because the NCI can educate but should not instruct doctors on their private practice or warn them about noncompliance. Dr. Bettinghaus reiterated that issuing such a statement has a significant effect on health care in the clinical community. He proposed that Dr. Salmon delete the phrase ". . . including the development of formal guidelines" from the motion, because informational statements are likely to be considered guidelines. Facts, Dr. Bettinghaus continued, can have policy implications.

Dr. Greenwald stated that the Board's concerns would probably not be problematic if the motion should pass, since the NCI currently collaborates with several other agencies to create policy related to dietary guidance and smoking education and prevention.

Dr. Salmon suggested that the word "directly" be substituted with "independently" and agreed with Dr. Bettinghaus' amendment to end the sentence after the word "policy." Dr. Bettinghaus agreed with these changes. The amended motion, which reads as follows, was seconded: "Inasmuch as cancer research is the primary mission of the National Cancer Institute, the NCAB recommends that the NCI not involve itself independently in the setting of health care policy." The amendment passed the Board's approval, with one abstention. The motion also passed, with one abstention. Dr. Broder thanked the Board for passing this motion, and Dr. Calabresi thanked Dr. Salmon for his time and effort and the Board for contributing to this meaningful discussion.

New Guidelines for NCI Staff for Adjusting Grant Awards and Terms

Dr. Kalt asked Board members to turn to the New Business tab in their notebooks. The first item of new business related to "Guidelines for National Cancer Institute Staff in Negotiating Desirable Adjustments in Grant Amounts and Terms." Dr. Kalt explained that these guidelines list the circumstances in which NCI staff may make minor changes in amount or terms and conditions of grant awards when there must be adjustments between NCAB meetings to permit the uninterrupted flow of research. The guidelines, he said, have not been

changed since the Board approved them last year. The Board offered no changes to the current document, giving their approval to keep the guidelines; thus, they will be in effect for another year.

New R01 Grants Policy

Dr. Kalt next discussed an article that appeared in the *NIH Guide* on November 26, 1993, which describes the new NCI (and major NIH Institutes) policy on R01 grants. The policy requires that unsolicited R01 grants for prevention or other trials that total more than $500,000 a year in direct costs be awarded as cooperative agreements. This policy will not change the current peer review process, Dr. Kalt said. Conversion to cooperative agreement status will only take place when an application is actively being considered for funding. These applications will be identified for the Board. Also, Dr. Kalt noted, an additional level of Institute approval—the NCI executive committee—is needed prior to review of R01 applications requesting more than $1 million in direct costs. This approval ensures that no study will be proposed that cannot be considered within the expected extramural research budget of the Institute for a particular year. Dr. Kalt emphasized that potential applicants are invited to contact himself or the appropriate Institute program staff member to facilitate the consideration of such applications.

Dr. Sheila Newton asked how people can obtain information on the appropriate program staff to contact. Dr. Kalt replied that his office will make referrals to the appropriate staff, including co-referrals, if there is overlap with other agencies within the Public Health Service. The Division of Research Grants, he added, will still make the final determination on where a particular application will fall.

Federal Reinvention Laboratory

Dr. Kalt informed the Board that the Vice President's Reinvent the Government Initiative has designated the NIH Extramural Program an official Federal reinvention laboratory. This allows the Initiative to conduct experiments and streamline the review process, evidence of which the Board will begin to see at the next Board meeting.

The Division of Research Grants is currently testing the concept of triage of applications in four of its study sections to expedite the review of noncompetitive applications. Dr. Kalt explained this process, which will expand the time that reviewers spend in differentiating among more competitive ideas. If preliminary reviewers concur that an application is noncompetitive (i.e., in the lower half of applications of that nature submitted), discussion of the application can be expedited at the meeting. A motion for designation of the new term "noncompetitive" will be made, similar to the "not recommended for further consideration (NRFC)" motion. The Board will see these applications only by listing, unless there is a special request. This experimental action affects only four study sections and is not likely to affect many applications at the May meeting, but the experiment may be replicated if successful.

Dr. Kalt noted that the Division of Extramural Activities may apply similar methodologies to selected high-response RFAs, where the number of applications far exceeds the potential for paying awards. This type of experiment, he explained, is part of an effort to focus reviewers on discriminating among closely ranked, good applications and to continue to prioritize efforts as staffing levels are reduced across the NIH.

Dr. Chan asked if the initial classification of "noncompetitive" is based on the area or science. Dr. Kalt explained that these applications have been assigned for regular review in the DRG study sections; thus, the classification will be based completely on the science. The

three individuals who read applications prior to the meeting will inform the scientific review administrator of the study section when they have identified an application that they feel is noncompetitive. When general consensus on this decision is attained, the application will be expedited at the review meeting and a truncated summary will be prepared.

XVII. SUBCOMMITTEE REPORTS

Cancer Centers

Dr. Salmon related that Dr. Holmes and her staff produced a preliminary draft report from the Cancer Centers database, including information on clinical trials activities of 41 of the Clinical and Comprehensive Cancer Centers, along with an overview of the use of resources according to shared resources, senior leadership, and other aspects of overall use of core grant funding.

Dr. Salmon referred to individual reports from about 12 of the 54 Cancer Centers, currently issued as administrative confidential reports, that will be used as a basis for producing a report covering all 54 Centers.

Dr. Salmon said that the Subcommittee passed a resolution regarding the OMB circular A21, which directs that certain administrative costs may not be charged as direct costs for the purpose of core grant expenditures. Dr. Salmon stated that indiscriminate enforcement of the OMB circular would be damaging to the work of the Cancer Centers' programs and Cancer Center core grants. He elaborated that certain administrative functions associated with coordination and integration of cancer research are critical to the conduct and coordination of the research itself and are, in fact, also subject to peer review.

Dr. Salmon stated that the Subcommittee passed a motion requesting that the NCI review grants where administrative core activities are a critical component of research procedures, and that specialized administrative functions be a direct cost function subject to peer review.

Dr. Calabresi suggested that the Board should see the motion in writing before taking action because of its complexity.

Dr. Kalt emphasized that the NCI cannot take independent action in this type of situation. Rather, the NCI could propose that the NIH, which, like NCI, is part of the Public Health Service, define activities involved in high-interdisciplinary, multiproject assistance instruments and very clearly state which costs are associated directly with research.

Dr. Salmon indicated that the institutions need assistance on this matter. Dr. Broder commented that the NCI will be very sympathetic to the needs of the institutions in areas where it has some control and discretion. He stated that in the case of gene therapy, for example, NCI strove to have special regulatory requirements covered within the core grants. He emphasized that if a particular function can be linked to the actual execution of the science or clinical trial, NCI will do everything possible to interpret the Executive order in a way that will promote the science. Dr. Broder added that when committees or institutions feel that NCI interpretation is unfair or inappropriate, the NCI will try to defer as much as possible to the institutions. The Public Health Service, not the NIH, actually has grants-making authority.

Dr. Kalt then recommended that applications continue to include requests for costs and positions that are considered to be justifiably direct costs and let the grants management process take its course, rather than try to "self-censor" what is submitted.

Dr. Calabresi suggested that a presentation on this issue be planned for the May meeting rather than voting at the present time; Dr. Salmon agreed.

Environmental Carcinogenesis and Women's Health and Cancer

Dr. Becker noted that this was the first joint meeting of the two Subcommittees, and it focused on the Long Island Breast Cancer Study Project (LIBCSP). The NIH Revitalization Act, P.L. 103-43, directed that a study be done of the reasons for high breast cancer incidence and mortality rates in Suffolk and Nassau Counties on Long Island, New York, and two other small counties in New York and Connecticut. Dr. Brenda Edwards, Associate Director, Surveillance Program, Division of Cancer Prevention and Control, gave an excellent overview of the breast cancer epidemiology data sources for Long Island and other parts of New York State and of currently available data. She also described a surveillance action plan to collaborate to evaluate and improve data quality and comprehensiveness.

Dr. Becker pointed out that Allegheny County in rural western New York had a higher incidence of breast cancer than either Nassau or Suffolk County. Dr. Becker also noted that Dr. Bettinghaus had questioned whether increased mammography screening rates were a contributing factor to the reported increase in breast cancer. Dr. Edwards agreed that increased screening might play a role, but suggested that it is not the sole cause.

Dr. Becker reported that Dr. Iris Obrams, Chief of the Extramural Programs Branch, Epidemiology and Biostatistics Program, Division of Cancer Etiology, who heads the LIBCSP, presented a detailed overview of the collaborating institutions in the New York metropolitan area, NCI interactions with area advocacy organizations, and the specific environmental factors to be studied as enumerated in the statute. He explained that Dr. Obrams reviewed some of the methodologies to be used to attempt to define the role of specific environmental exposures. For some factors, such as aircraft emissions, assessment methodologies do not currently exist and the project will support an effort to develop them. Dr. Obrams also stated that NCI funds a number of independent studies, such as those on electromagnetic forces, that pertain to the LIBCSP.

Dr. Becker emphasized that although the study is just beginning, it should provide some interesting models for research on other purported foci of environmentally caused cancers and may also provide new methodologies for measuring and assessing the impact of various exposures.

Dr. Becker concluded his report by noting that Dr. Peter Greenwald had given the Subcommittees an update on NCI activities related to mammography screening guidelines and the statement released by the Institute in December. Dr. Greenwald also reviewed the NCI research portfolio to develop improved technologies for breast cancer early detection. Dr. Arnold Kaluzny, Chairman of the DCPC BSC, attended the meeting and expressed support of the BSC for the NCI actions on screening mammography.

Questions and Answers

Dr. Sigal inquired whether the Long Island Study has received extra funding. Dr. Broder replied that it has not. Dr. Bettinghaus commented on the complexity of the study in terms of the potential number of variables. Dr. Freeman expressed his concern that research

decisions are being driven by political concerns. He suggested that New York City has been shown to have a greater breast cancer problem than the areas being studied.

Information and Cancer Control

Mrs. Malek stated that the Information and Cancer Control Subcommittee did not meet.

Minority Health, Research, and Training

Mrs. Brown reported that the Minority Health, Research, and Training Subcommittee discussed four issues, including: new directions for the Cancer Education Program; the minority recruitment plan for T32 grants; minority enhancement awards; and minority health training initiatives.

During the meeting, she said, Dr. Cairoli summarized an announcement in the *NIH Guide* regarding minority recruitment on institutional training grants. The announcement states that principal investigators must report statistical data on the number of minority applicants recruited, trainees retained, and the number who graduate from the program. They must also explain any lack of progress and describe changes in the minority recruitment plan that might result in more successes. Mrs. Brown added that the Subcommittee's summary statement will contain a more detailed description and evaluation of the minority recruitment efforts in progress to date.

Mrs. Brown said that Dr. Cairoli made a brief presentation on the new guidelines and objectives of the Cancer Education Grant Program. A discussion followed concerning possible joint ventures with institutions with large pools of minority patients.

Mrs. Brown reported that the Subcommittee received an update on the Minority Health Professional Training Initiative; the enhancement awards, which were formerly administered through several Cancer Centers, will now be funded as RO1s through the more recently announced RFA. She stated that two new minority faculty development programs have been awarded to the University of the Virgin Islands and Meharry Medical College, making a total of six awards.

Mrs. Brown said the Subcommittee discussed the critical need for very early science orientation and education programs such as the NCI Science Enrichment Program implemented by Dr. Baquet. The Subcommittee suggested pursuing an interdepartmental agreement with the National Education Association and the Departments of Education and Agriculture, which have established similar training programs.

Mrs. Brown noted the Subcommittee's announcement of the first Minority Breast Cancer Awareness Day on April 28th for members of the Congressional Black and Hispanic Caucuses. The purpose of this event is to promote understanding of current developments in research and to express concern about costs and other issues related to regulations requiring the recruitment of additional minorities into clinical trials.

She also summarized the Subcommittee's discussion of a recommendation made at the September NCAB meeting to consolidate the Subcommittees on Aging, Women's Health and Cancer, and Minority Research, Health, and Training. She said the Subcommittee expressed concern about losing the focus and momentum of the Minority Training and Education Program, even though they were assured in a subsequent meeting that this would not happen. She concluded by saying that the Subcommittee will continue to consider the feasibility of consolidation.

Planning and Budget

Dr. Bettinghaus called the Board's attention to two elements of the Subcommittee report—the presentation on the President's Budget and the 1995 Bypass Budget. The 1996 bypass budget, he said, will be going to press sometime between May and July.

The 1995 bypass budget, he suggested, is a considerably improved document, compared with some from previous years because of its improved readability and redesign of some sections by Dr. Judith Karp. He indicated that Dr. Karp has asked the NCAB for assistance in quickly carrying out some other suggestions for improvements in the document. Dr. Bettinghaus asked members of the Board to review the document and provide Dr. Karp their comments by March 1st. He suggested that the document needs a complete executive summary at the front of the Bypass Budget, which includes and replaces chapter summaries.

Background materials on the influence of the various research project grants (RPG) mechanisms on success rates were distributed. Dr. Bettinghaus called the Board's attention to a letter from Dr. Frederick Becker concerning paylines, percentiles, and success rates. He said that the Subcommittee recommends in its minutes that a short journal article be published in *JNCI* or *Science* that explains percentile and success rates.

Minority, Women, and Aging

Ms. Mayer reported that this Subcommittee held an organizational meeting on the logistics of merging the three subcommittees—Aging and Cancer; Minority Health, Research, and Training; and Women's Health and Cancer—the results of which will be reported at the May NCAB meeting.

Resolution Honoring Mrs. Barbara Bynum

Ms. Mayer then read a resolution that she and Dr. Bragg drafted, with input from Dr. Paulette Gray, on behalf of the NCAB, honoring Barbara Stewart Bynum:

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

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

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

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

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

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

After accepting a change in wording from Dr. Chan (to transpose "NCI" and "Division of Extramural Activities" in the first line), Dr. Calabresi called for a vote, and a motion to

accept the resolution was passed. Dr. Calabresi said the resolution will be properly enscrolled and presented to Mrs. Bynum at the May meeting.

Dr. Calabresi inquired about another resolution honoring Dr. Howard Temin, which Dr. Bettinghaus said is in the process of being written. Dr. Calabresi suggested circulating this resolution to Board members for voting by mail so that it can be presented at the May meeting.

Dr. Broder mentioned that a memorial service for Dr. Temin will be held on Sunday, March 13th, in Madison, Wisconsin.

A motion was made and passed to accept the minutes of the Subcommittee meetings as written.

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

Dr. Calabresi began by stating that he was presenting an interim report from the Subcommittee to Evaluate the National Cancer Program (SENCAP). He explained that Congress, in its appropriations report for fiscal year 1993, requested a review of the National Cancer Program to assess its achievements, reinvigorate the program, and develop a plan of action to carry the program into the next century. He explained that this was an extensive mission that review involved consulting a broad constituency with various views and insights. Six to 8 months were allotted to complete this review.

Dr. Calabresi described the three-phase review process approved by Congress. Phase I, called Measures of Progress Against Cancer, convened six panels of outside experts to identify cancer research advances over the past decade, assess the potential of these advances to reduce the cancer burden, and identify challenges for the future. Phase II involved several meetings of the President's Cancer Panel and the report of the PCP Special Commission on Breast Cancer. Phase III, which will continue through September 1994, involves the development of a report to be submitted to Congress. Dr. Calabresi then went on to discuss each phase of the evaluation in detail.

In Phase I, expert panels discussed the following topics: Molecular Medicine, chaired by Dr. John Niederhuber; Mechanisms of Cancer Induction and Progression: Endogenous and Environmental Exposures, chaired by Dr. James Felton; Cancer Prevention, chaired by Dr. Alfred Haynes; Early Detection and Diagnosis, co-chaired by Drs. Noel Warner and George Bosl; Cancer Treatment, chaired by Dr. Paul Carbone; and Cancer Control, chaired by Ms. Helene Brown. Dr. Calabresi explained that these six panels identified cancer research advances over the past decade, assessed the potential of these research advances to reduce the cancer burden, and identified challenges for the future. Their findings were consolidated into six panel reports and a consolidated report.

Dr. Calabresi stated that in Phase II, information was collected and testimony heard through the framework of the President's Cancer Panel, and through site visits and presentations to the SENCAP. Previous PCP meetings were reviewed and several additional PCP meetings focused specifically on the evaluation. The final report of the PCP Special Commission on Breast Cancer Report also will be used as source material.

The first of these meetings, which occurred in September 1993, was attended by members of the SENCAP. Dr. Calabresi explained that along with supporters of the Program, a number of people who were highly critical were also invited. Topics of discussions included

alternative medicine, protection from environmental factors, and cancer prevention. A notable statistician questioned the National Cancer Program's progress in the battle against cancer. Dr. Calabresi stated that the second meeting, held in November 1993, discussed cancer statistics in "chronic disaster areas." The third meeting, which took place in January 1994, involved the role of government in the cancer research mission. A report on the President's Special Commission on Breast Cancer was also received during Phase II.

Dr. Calabresi stated that the SENCAP was established in August 1993 to undertake Phase III of the evaluation of the National Cancer Program. The SENCAP's mission is to assess progress against cancer, define gaps and shortfalls, and identify opportunities for improvement that may exist in research, prevention, treatment, control, and rehabilitation. Dr. Calabresi stated that the Committee has sought to define barriers to further progress and provide recommendations for future directions of the National Cancer Program. Once these barriers have been identified and recommendations defined, he explained, a report outlining these findings will be transmitted directly to Congress with the approval of the NCAB.

Dr. Calabresi also explained that the integration of information from Phases I and II and the comments of outside experts are essential. He stressed to all members of the NCAB, that because of their roles in approving the report, and to all the divisions of the NCI that feedback will be necessary for incorporation into the final report to Congress.

Dr. Calabresi expressed his gratitude for the opportunity to chair the SENCAP and expressed his appreciation to the committee for their devotion to its mission and goals. He explained that the committee is composed of members of the NCAB, outside experts in cancer research, and public advocates representing various constituencies. Dr. Calabresi acknowledged the individual committee members:

- Dr. Karen Antman, medical oncologist and President-elect of the American Society of Clinical Oncology.
- Dr. Erwin Bettinghaus, NCAB member and representative for cancer control, outreach, and communications.
- Dr. Norman Coleman, Chief of Radiation Oncology at Harvard.
- Dr. Pelayo Correa, NCAB member and representative for epidemiology, pathology, and prevention.
- The Honorable Joseph D. Early, former Congressman from Massachusetts.
- Dr. Margaret Kripke, representative for molecular medicine and President of AACR.
- Dr. LaSalle Leffall, surgical oncologist from Howard University.
- Dr. Deborah Mayer, NCAB member and representative for oncology, clinical nursing, geriatrics, and rehabilitation.
- Dr. John Niederhuber, representative for molecular medicine and surgical oncologist from Stanford.
- Dr. Charlie Sanders, President of Glaxo and representative of the pharmaceutical industry.
- Dr. Ellen Sigal, NCAB member and representative for environmental cancers.

- Dr. Ellen Stovall, President of the National Coalition for Cancer Survivorship and representative for patient advocacy.
- Dr. Mimi Yu, from the Kenneth Norris Comprehensive Cancer Center and representative for environmental, occupational, epidemiology, carcinogenesis, and prevention.
- Dr. Harold Freeman, Chairman of the President's Cancer Panel.

Dr. Calabresi acknowledged the dedication and contributions of Cherie Nichols, executive secretary of the SENCAP, and the logistical staff who provided all the essential support necessary to prepare the meeting agendas and material for the SENCAP members. Dr. Calabresi also expressed his appreciation to Dr. Broder for providing the resources of the NCI and his staff while simultaneously restraining from providing input that could potentially connect the NCI directly to the committee's final report.

Dr. Calabresi explained that the SENCAP has met at least once a month since it was first established. In September 1993, the first organizational meeting took place. In October 1993, the SENCAP met in Chicago to review the "Measures of Progress Against Cancer" reports and other resource material. Following the President's Cancer Panel meeting on cancer statistics that took place in November 1993, there was a working meeting of the SENCAP to identify the recommendations. In January 1994, two meetings were held—one in San Diego to identify the framework for the report and draft an introduction and another in conjunction with the President's Cancer Panel meeting involving the role of government in the cancer research mission.

Dr. Calabresi stated that the next working meeting is scheduled to take place in March 1994 on the west coast to finalize recommendations and solicit outside review and comments for the final report. In April 1994, a final meeting in Research Triangle Park in North Carolina has been scheduled to take place where presentations from the pharmaceutical and biotech industry will be scheduled. Dr. Calabresi also stated that the final draft of the report will be prepared at this meeting and presented at the NCAB meeting on June 1st, at which time comments and final input will be solicited.

Dr. Calabresi explained that extensive research is involved in preparing the final report to present to Congress. It requires the integration of information that has been collected, development of recommendations for where the National Cancer Program ought to be going in the next century, and a review of the expenditure of $20 plus billion dollars over the last 20 years.

Dr. Calabresi stated that three areas of emphasis have been developed for the future direction of the National Cancer Program: research application, translational research, and basic cancer research. He stressed the importance of the application of current research benefits to the entire population. Dr. Calabresi noted that 37 million Americans lack any type of health care and approximately two or three times as many receive deficient care. He suggested that this misuse of available health care resources may be a major contributor to loses currently being felt in the war against cancer .

Dr. Calabresi alluded to the idea that translational research or clinical investigation is a necessary area for future development. Bridging the gap between the basic science laboratory and the patient would be essential to the development of cancer treatments and cures. He added that this transfer of knowledge must be reciprocal—from laboratory to patient and patient to laboratory.

Finally, Dr. Calabresi pointed out that it would not be possible to save all the people who have or will get cancer even if all available information on cancer was applied. Therefore, Dr. Calabresi explained, basic research must continue to advance, facilitating progress and maintaining the productivity and excellence that have been seen in the last 20 years.

Dr. Calabresi concluded his presentation by stating that the SENCAP report will contain an executive summary that will provide a recapitulation of all pertinent points and recommendations, so that Congress and the lay public can obtain the salient material. The report will be composed of a preamble introduction and a detailed analysis of research application, translational research, and basic cancer research for future development. In addition, the final report will include a summary, appendices, the Measures of Progress reports, any additional information generated, and a breast cancer report.

Questions and Answers

Dr. Bragg pointed out that the preamble to the report contained no reference to detection and diagnosis. He suggested that someone with an occupational background in diagnostic radiology be invited to contribute to the evaluation.

Dr. Calabresi acknowledged Dr. Bragg's concern and expressed his appreciation for the feedback. Dr. Bettinghaus stated that the Division of Cancer Treatment created a document outlining recommendations and future areas of concern. This contribution, he commented, will be integral to the final report to Congress. Dr. Bettinghaus suggested that other divisions provide similar input.

In reference to Dr. Bettinghaus' request for feedback, Dr. Broder raised the concern that the suggestions provided by each division may overly influence the SENCAP committee in their recommendations to the National Cancer Program. Dr. Calabresi assured him that all input provided to the SENCAP would be taken into careful consideration, and only pertinent information would be integrated into the committee's final report.

Dr. Broder asked Dr. Calabresi if he would like the NCI to prepare a conventional bypass budget for the report. Based on the possible difficulty of dividing the report into financial categories, Dr. Bettinghaus proposed that the committee examine the report before making a decision. Dr. Calabresi related that a conventional bypass budget would be valuable, but suggested that it be prepared in September.

Dr. Calabresi then recognized Dr. Harold Freeman's involvement in Phase II and Phase III of the evaluation and asked for his comments. Dr. Freeman suggested that some criticism of NCI could have been prevented though improved application of the Institute's findings to benefit the American public. Dr. Freeman stated that this should be reflected in the final report.

Dr. Calabresi was asked to clarify if the National Cancer Program was envisioned to be a program of NCI or a program of the Federal Government; what percentage of the National Cancer Program's effort falls within the NCI versus other agencies; and the perceived level of future participation. Dr. Calabresi explained that the National Cancer Program involves the NCI as well as all other ongoing programs. Dr. Broder pointed out that, according to the original National Cancer Act of 1971, the NCI Director is also supposed to direct the National Cancer Program, representing and coordinating all government cancer activities. Dr. Freeman emphasized that a coordinated effort of all programs and government agencies, led by the NCI, will be necessary to win the war against cancer.

Dr. Broder stressed that the NCI is a component of the NIH and not greater than the NIH as an entity. He stated the importance of the entire biomedical research effort as it affects all diseases, as opposed to the importance of cancer specifically.

Dr. Calabresi recognized Dr. Norman Coleman, a member of the SENCAP, and Ms. Cherie Nichols for her support to the committee. He encouraged the Board to inform Ms. Nichols of any comments, suggestions, or ideas for the committee's review.

XIX. ADJOURNMENT

There being no additional business, Dr. Calabresi thanked the group for their participation and adjourned the 89th National Cancer Advisory Board meeting at 12:59 p.m.

May 17, 1994
Date

Dr. Paul Calabresi, Chairman