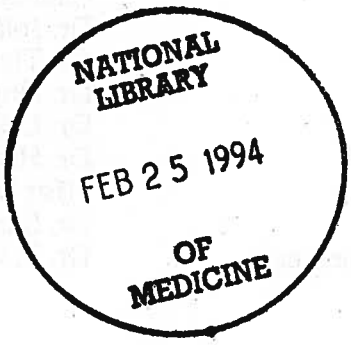
DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
September 20 and 21, 1993



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

Department of Health and Human Services
Public Health Service
National Institutes of Health
National Cancer Institute
National Cancer Advisory Board
Summary of Meeting[1]
September 20 and 21, 1993

The National Cancer Advisory Board (NCAB) convened for its 87th regular meeting at 8:00 a.m., September 20, 1993, in Building 31, C Wing, 6th Floor, Conference Room 10, National Institutes of Health (NIH).

NCAB Members

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

President's Cancer Panel

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

Alternate Ex Officio NCAB Members

Captain Bimal C. Ghosh, DOD
Dr. John Johnson, FDA
Dr. Theodore Lorei, DVA
Dr. Hugh McKinnon, EPA
Dr. Lakshmi C. Mishra, CPSC
Dr. Harold Mungin, DOL
(for Dr. Ralph Yodaiken)
Dr. Sheila Newton, NIEHS
Dr. P. C. Srivastava, DOE

Members, Executive Committee, National Cancer Institute, NIH

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

---

[1] For the record, it is noted that members absented themselves from the meeting during discussion of 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. Eve Barak, National Science Foundation
Ms. R. Davilene Carter, American Association for Cancer Education, Inc.
Mr. Alan Davis, American Cancer Society
Dr. Robert W. Frelick, Association of Community Cancer Centers
Dr. Edward Gelmann, American Society of Clinical Oncology, Inc.
Ms. Linda L. Johnson, Oncology Nursing Society (for Ms. Carol Curtiss)
Dr. Thomas King, American Association for Cancer Research
Dr. Marston Linehan, The Society of Urologic Oncology
Dr. Edwin A. Mirand, Association of American Cancer Institutes
Mrs. Yvonne Soghomonian, Candlelighters Childhood Cancer Foundation

In addition to NCI staff members, meeting participants, and guests, a total of 22 registered members of the public attended.

TABLE OF CONTENTS

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

Dr. Calabresi called the 87th meeting of the National Cancer Advisory Board (NCAB) to order and introduced several guests representing medical, research, and professional organizations. He welcomed members of the public and informed them that they could express their views on issues discussed during the meeting by writing to the NCAB Executive Secretary, Mrs. Barbara Bynum, within 10 days of the meeting. The proposed 1995 NCAB meeting dates were confirmed. Dr. Calabresi called for approval of the minutes of the previous meeting, which were unanimously approved without change.

Dr. Calabresi explained that, as part of the National Cancer Institute's (NCI's) response to a Congressional mandate, the NCAB has been asked to establish a new subcommittee whose mission will be to assist and advise the NCI Director in evaluating the National Cancer Program. The subcommittee will assess progress against cancer; define gaps and shortfalls in this progress; identify new opportunities in areas such as basic research, prevention, treatment, and rehabilitation; define barriers to further progress; and provide recommendations for future directions. Because the Congress specified that groups of experts involved in the evaluation should include individuals from outside the "cancer community," this subcommittee will be composed of five members of the NCAB plus selected representatives from the scientific community and the public at large.

Dr. Calabresi stated that he will serve as chairman of the subcommittee and listed the following subcommittee members: Dr. Karen Antman, professor of medicine and Chief of the Division of Medical Oncology at Columbia University and president-elect of the American Society of Clinical Oncology, Inc. (ASCO); Dr. Erwin Bettinghaus, NCAB member; Dr. Norman Coleman, Chairman of the Joint Center of Radiation Therapy at Harvard University; Dr. Pelayo Correa, NCAB member; the Honorable Joseph B. Early, former Congressman from western Massachusetts; Dr. Margaret Kripke, professor and Chairman of the Department of Immunology at the M. D. Anderson Cancer Center and president of the American Association for Cancer Research (AACR); Dr. LaSalle Lefall, professor and Chairman of the Department of Surgery at Howard University; Ms. Deborah Mayer, NCAB member; Dr. John Niederhuber, Chairman of the Department of Surgery at Stanford University; Dr. Ellen Sigal, NCAB member; and Ms. Ellen Stovall, Executive Director of the National Coalition for Cancer Survivorship. He added that one or two additional members may be selected for the subcommittee if assistance in additional areas of expertise is needed. Ms. Cherie Nichols, Chief of the Planning, Evaluation, and Analysis Branch in the Office of the NCI Director, will assist the subcommittee.

Dr. Calabresi announced that the subcommittee's first organizational meeting would take place during the second day of the current NCAB meeting and that members would also attend the President's Cancer Panel meeting on the following day. He explained that the President's Cancer Panel has been involved in Phases I and II of the evaluation project and that the new subcommittee will contribute to Phase III of the project. Phase I entailed the establishment of six expert panels that reviewed progress against cancer during the past 10 years in the areas of molecular medicine, mechanisms of cancer induction and progression, diagnosis and early detection, treatment, cancer control, and cancer prevention. The chairs of these six panels, Dr. Calabresi added, would present outlines of their reports at the President's Cancer Panel meeting.

Phase II of the evaluation project, he continued, will consist of a series of hearings and informational meetings conducted by the President's Cancer Panel. The new subcommittee's role in Phase III will be to coalesce and unify all of the information gathered during Phases I and II, hold additional hearings if necessary, and produce a final report to the NCI Director and to Congress within 6 to 8 months. This report will present an overview of progress against cancer and a blueprint for the future of the National Cancer Program. Dr. Calabresi noted that

the subcommittee hopes to have a preliminary report ready for review at the February 1994 NCAB meeting.

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

Dr. Freeman began his report by noting a change in the Panel's membership. He thanked Mrs. Nancy Brinker for her service on the Panel and her continuing service as chair of the Panel's Special Commission on Breast Cancer. Dr. Freeman then welcomed the panel's newly appointed member, Ms. Frances Visco, a partner in the law firm of Cohen, Shapiro, Polisher, Sigmund, and Cohen and the first president of the National Breast Cancer Coalition. Ms. Visco, he added, is a member of the Special Commission on Breast Cancer, the Board of Directors of the Linda Creek Breast Cancer Foundation, and the Consumer Advisory Board of the Temple University Comprehensive Cancer Center.

Dr. Freeman reported on two meetings held by the President's Cancer Panel during 1993. The Panel met at the University of California Special Program of Research Excellence (SPORE) to discuss the program's relationships with breast cancer organizations. The meeting focused on translational research, loosely defined as the application of basic research to human problems. The University of California SPORE is taking a comprehensive approach to encouraging investigator-initiated research and ensuring the provision of state-of-the-art prevention and treatment services. The laboratory and the clinic, Dr. Freeman explained, are linked through ongoing dialog to achieve a harmony among basic research, clinical investigations, and epidemiological studies, which facilitates a diverse socially and economically sensitive breast cancer research program. Dr. Freeman added that the SPORE also provides a model for interacting with patient advocates in the planning and evaluation of clinical trials and reviews related to research funding.

In July 1993, Dr. Freeman continued, the Panel held a meeting that coincided with the American Cancer Society (ACS) conference on psychosocial and behavioral research, which marked the 10th anniversary of the ACS extramural program on these topics. He noted that the meeting provided a unique opportunity for clinical and laboratory personnel to learn directly from patient representatives about the impact of cancer on families. Topics included the psychosocial impact of cancer on the patient's spouse; the impact of breast cancer on the family; the effects of childhood cancer on families; counseling options to enhance early diagnosis; the psychobiological aspects of the family with cancer; the value of cancer risk counseling; and the role of cultural, ethnic, and socioeconomic influences on family adaptations.

A major theme that developed during the meeting, Dr. Freeman observed, was the need for more research on the impact of psychosocial factors on cancer patients and their families. Participants stressed the fact that the two elements combined in the concept of "psychosocial" factors—psychological and social elements—are, in fact, two very different areas and suggested that those involved in psychosocial research should endeavor to disentangle the influences of class, race, ethnicity, income, and education to make social and psychological services more accessible to the public.

Dr. Freeman stated that three additional Panel meetings are scheduled for the remainder of 1993. The first is the meeting on evaluation of the National Cancer Program described earlier by Dr. Calabresi. Dr. Freeman noted that this will be the first open meeting held for the purpose of acquiring testimony on the achievements of the National Cancer Program and to identify gaps in the research agenda. In November, a special Panel meeting will examine what he called "chronic disaster areas"; the Panel will hear testimony regarding parts of the United

States in which mortality rates from cancer parallel those of Third World countries. In December, he continued, the Panel hopes to host a meeting of government and quasi-government organizations to explore the role of government in the research mission of the National Cancer Program. Dr. Freeman added that the Panel feels that the war against cancer should be fought by the entire government, not just the NCI.

Dr. Freeman noted that the Panel's Special Commission on Breast Cancer has finished its investigations after holding 11 meetings in a period of just over 1 year. He thanked Mrs. Brinker, the chair of the Commission; Iris Schneider, the Executive Secretary; and the members of the Commission for their outstanding work. The Commission is in the process of preparing a final report on a wide range of issues affecting breast cancer in the United States.

Dr. Calabresi added that Dr. Freeman will serve as an ex officio member of the NCAB subcommittee on evaluation of the National Cancer Program. He then turned the floor over to Dr. Broder for the NCI Director's report.

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

Dr. Broder joined Dr. Freeman in welcoming Ms. Visco as a new member of the President's Cancer Panel. He also noted that President Clinton has nominated Dr. Harold Varmus to serve as Director of the National Institutes of Health (NIH). Dr. Broder described Dr. Varmus as a very distinguished scientist who, along with Dr. J. Michael Bishop, was awarded the 1989 Nobel Prize in medicine for their research on oncogenes. He added that Dr. Varmus has been an NCI grantee, and suggested that he will be among the strongest possible advocates for the NIH in an era of fiscal constraints. Dr. Broder stated that the Institute looks forward to Dr. Varmus' confirmation and will invite him to speak to the NCAB at the earliest opportunity.

Another noteworthy event, Dr. Broder noted, was the April 7th appointment of Dr. Frances Collins as Director of the National Center for Human Genome Research, which manages the NIH role in the Human Genome Project. He added that Dr. Collins will also head the Center's new intramural research program, which will be an investigator-initiated effort comparable to the intramural programs of other NIH components. Dr. Broder described this as a very positive step and said the NCI looks forward to an effective collaboration. Dr. Collins, he explained, pioneered a gene-finding technique known as positional cloning; codiscovered the genes for cystic fibrosis, neurofibromatosis, and Huntington's disease; and is currently pursuing a key gene for familial breast cancer.

Dr. Broder briefly announced recent honors achieved by NCAB members and NCI staff, referring Board members to a printed handout for more details on these awards. Board member Ms. Zora Brown has been awarded the first Making the Difference Award; Ms. Deborah Mayer has been elected as a fellow of the American Academy of Nursing; Mr. Leo Buscher, Chief of NCI's Grants Administration Branch, received the 1993 Newton Lifetime Achievement Award from the National Grants Management Association; and Dr. Joseph Fraumeni received the 1993 Linlienfeld Award from the American College of Epidemiology and the Wick Williams Memorial Award from the Fox Chase Cancer Center.

Dr. Broder then announced recent staff changes. Dr. Peter Howley, Chief of the Laboratory of Tumor Virus Biology in the Division of Cancer Etiology (DCE), has resigned to become Professor and Chairman of the Department of Pathology at Harvard Medical School, and Dr. Carl Baker has been appointed acting head of the Laboratory of Tumor Virus Biology;

Dr. Takis Papas, Chief of the Laboratory of Molecular Oncology in the DCE, has retired to become Director of the Center for Molecular and Structural Biology at Hollings Oncology Center at the Medical University of South Carolina, and Dr. James Lautenberger has been appointed as acting chief of the Laboratory; Dr. Stuart Aaronson, Chief of the Laboratory of Cellular and Molecular Biology in the DCE, has retired to become Director of the Ruttenberg Cancer Center at the Mount Sinai School of Medicine in New York City, and Dr. Steve Tronick has been appointed as acting chief of the Laboratory; Dr. Steven Brown, Associate Director of the Radiation Research Program in the Division of Cancer Treatment (DCT), has resigned to become Corporate Medical Director at the Oncology Services Corporation in State College, Pennsylvania; Dr. Steven Ettinghausen of the DCT Surgery Branch has resigned to join the staff of the Washington Hospital Center; and Dr. Michael Stellar was appointed on August 8th to head the Surgery Branch's Gynecologic Oncology Section. Dr. Broder congratulated all those receiving awards or going to important new positions, thanking those leaving the intramural program for their contributions.

Dr. Broder reported that on September 13th, Dr. Peter Greenwald, Director of the Division of Cancer Prevention and Control (DCPC), testified on the subject of NCI's diet and cancer program at a House Subcommittee on Human Resources and Intergovernmental Relations hearing chaired by Representative Edolphus Towns (D-NY). Also on this topic, Dr. Broder added, NCI has released the results of a population-based nutritional study in China. Participants received a supplement with beta-carotene, alpha tocopherol (a form of vitamin E), and selenium. Results indicated a 13 percent decreased risk of dying from cancer and an overall reduction of about 9 percent in risk of death from all causes. Deaths from esophageal cancer were reduced about 4 percent, from all types of stomach cancer by 21 percent, and from stroke by about 10 percent. Dr. Broder noted that, while this is a substantial advance in the field of bionutrition, the study population had certain baseline nutritional deficits and, thus, the findings may not generalize to the American public at large. Nevertheless, the information from this trial will be incorporated into the design of new studies and may be taken into consideration for the modification of existing trials.

Dr. Broder reported that NCI testimony was recently given before the House and Senate Appropriations Committees, whose hearings were held relatively late this year. He stated that while the NCAB and NCI staff are primarily interested in supporting and defending the National Cancer Program, it is impossible to benefit any Institute through decreases in the resources of any other Institute. Thus, he suggested, the philosophy of the NCAB and NCI should be to demonstrate concern about the resources available to all of the components of NIH. Dr. Broder said that from his point of view, both the House and Senate Appropriations Committees were as supportive of NCI and NIH as could be expected considering current fiscal realities.

An NCI symposium was recently held at the Frederick Cancer Research and Development Center (FCRDC), Dr. Broder noted, in memory of Dr. Werner Kirsten, who was the Director of that Center until his untimely death in December 1992.

Dr. Broder reported that Dr. Daniel Ihde, Deputy Director of NCI, addressed the National Coalition for Cancer Survivors as part of their observation of Cancer Survivors' Day, reaffirming NCI's commitment to the activities of this important organization.

The General Motors Cancer Research Foundation, Dr. Broder stated, presented its research awards on June 23rd, and several individuals with close ties to NCI were honored. Drs. Bernard Fisher and Gianni Bonadonna shared the Charles F. Kettering Prize for advances in cancer treatment; Dr. Carlos Croce received the Charles S. Mott Prize for achievements in understanding the causes of cancer; and Dr. Hidesaburo Hanafuso received the Alfred P. Sloan, Jr. Prize for basic science contributions to cancer research. The GM Cancer Research Foundation International Biomedical Journalism Prizes were given to Diane Sawyer and Chris

Whipple for a story on mammography on *Prime Time Live*; to Penny Stewardson of the *Sunday Tribune* in Durban, South Africa, for a series of columns on her personal battle with breast cancer; and Dr. Douglas Daly of *Audubon* magazine for a story on the harvesting of Yew trees to produce Taxol.

Dr. Broder announced that the first international SPORE Investigators' meeting was held at NCI on July 19th and 20th. He explained that there are three levels of SPORE grants—full-fledged SPOREs and two levels of programs in various phases of development. At the July meeting, each SPORE presented a program overview and highlighted areas of scientific promise. Dr. Broder expressed the belief that the SPORE program will serve as a catalyst to shorten the time required for the translation of future basic research findings into clinical applications in prevention, diagnosis, and treatment. The program, he added, provides an effective forum for communication between scientists of many disciplines.

Dr. Broder described the recent emergence of a novel approach to possible cancer vaccine development, noting that one vaccine developed by this approach has actually been administered to patients with colon and breast cancers. This approach involves the combination of the recombinant vaccinia virus vector, which has long been used for smallpox vaccination, with carcinoembryonic antigen (CEA), a tumor-associated antigen, for potentially treating established tumors or, perhaps, in the long run, to prevent recurrence of tumors.

A high percentage of gastrointestinal cancers, Dr. Broder related, as well as about 50 percent of breast cancers, express CEA on the cell surface. When the entire recombinant vaccinia CEA genome is expressed, CEA is coexpressed with the immunogenic, but noninfectious, virus. In theory, he explained, immunogenic peptides of CEA, properly processed in an intracellular basis, will be expressed in association with relevant Class I histocompatibility antigens. This approach could enhance the development of relevant cytotoxic T cells, and is potentially applicable to many other tumor types. Dr. Broder added that an interim report on this topic would be presented during the second day of the current NCAB meeting.

Dr. Jay Bersofsky and his colleagues, Dr. Broder continued, are leading another cancer vaccine project that involves the use of small portions of a patient's own mutated *p53* as a novel anticancer vaccine. Point mutations on *p53*, he noted, are exceedingly common in a diversity of cancers; in theory, it is possible to develop an immune response targeted against the patient's own autologous mutation. While the project has not yet reached the point of human administration, Dr. Broder said that this approach is expected to be used in the treatment of breast, lung, and gastrointestinal malignancies, and possibly in others, in the not-too-distant future. When point mutations can be identified before an individual has cancer, he stated, then it will be possible to talk about true prevention—primary prevention—through a vaccine approach.

Dr. Broder reported that the President's Cancer Panel's Special Commission on Breast Cancer held two meetings since the May NCAB meeting. On June 25th, the Commission focused on information dissemination; the Commission's final meeting on July 21st concerned public policy and legislation. Dr. Broder noted that the Commission is currently developing its final report; the target date for the report's release is October, during Breast Cancer Awareness Month. The Commission, Dr. Broder stated, collected information from a wide diversity of the American public, having received testimony from more than 190 speakers since May 1992.

Dr. Broder, referring to Dr. Calabresi's earlier description of the evaluation of the National Cancer Program, expressed his hope that the NCAB will work with NCI to develop an effective plan to take the Program into the next century. He suggested that the response to the Congressional mandate for an evaluation and plan should focus on specific goals rather than general programs.

Moving on to the topic of NCI's budget, Dr. Broder noted that a more detailed presentation would be provided by the Budget and Planning Subcommittee. He used two slides to present a brief introduction to budgetary issues. In fiscal year (FY) 1992, the NCI actual obligations were approximately $1.948 billion; in 1993, the estimated obligations are approximately $1.978 billion. For 1994, the President's budget for NIH as submitted to Congress included approximately $2.142 billion for NCI, an increase of about 8.3 percent. However, this budget included a seldom-used mechanism for prepayment of the full obligation associated with multiyear grants in specific areas, particularly breast cancer, instead of the usual process of budgeting at an annualized level of effort. The House and Senate did not endorse this approach, and the approximately $101 million intended for this prepayment were subsequently removed from the budget. This left a total of $2.041 billion, for an increase of about 3.2 percent, in the President's budget. The House, however, added about $41 million, and the Senate version is expected to have a similar addition.

Dr. Broder called attention to some specific points listed in the House report. The House asked NCI to expand all facets of breast cancer research; make prostate cancer research one of its top priorities; emphasize other gender-related diseases, such as cervical and ovarian cancers; give basic research equal emphasis with disease-specific research; continue development of research in leukemia, lymphoma, and related cancers; and continue proton beam research. He said that a similar breakdown of specific requests in the Senate report will be provided as soon as it is available.

Dr. Calabresi introduced Ms. Dorothy Tisevich, Director of NCI's Office of Legislation and Congressional Activities.

IV. LEGISLATIVE UPDATE—MS. DOROTHY TISEVICH

Ms. Tisevich reported that the NIH Revitalization Act of 1993 was signed by President Clinton on June 10th as Public Law 103-43. She noted that a summary of the major provisions of the act appear in the "Legislative Update" handout distributed as part of the Board members' meeting notebooks. Ms. Tisevich explained that this authorization bill requires NCI to spend a fixed percentage of its appropriation on cancer control: 7 percent must be spent on control activities in fiscal year 1994, 9 percent in FY 1995, and 10 percent in FY 1996. Since the House and Senate have not addressed specific earmarks for cancer control in their appropriation reports for FY 1994, she added, it is expected that NCI will be bound by this statutory requirement.

In two high-priority areas—breast and other women's cancers and prostate cancer—NCI has been instructed to expand and intensify efforts to develop a research plan to address these issues and report periodically on progress in implementing the plan. Ms. Tisevich stated that drafts of research plans for these two areas have been developed and would be discussed later in the meeting. She explained that when the plans have been finalized, they will be routed through departmental clearance channels and then submitted to Congress.

A third stipulation of the reauthorization bill requires NCI to conduct a case-control study to assess biological markers of environmental and other potential risk factors contributing to the incidence of breast cancer in four Northeast counties: Nassau, Suffolk, and Schoharie Counties in New York and Tolland County in Connecticut. The latter two counties, she added, have the highest age-adjusted breast cancer mortality rates in the Northeast among counties with no less than 30 deaths during the 5-year period between 1983 and 1987. NCI is instructed to monitor current exposure and estimate cumulative exposure to the following: contaminated drinking water; sources of indoor and ambient air pollution, including aircraft emissions; electromagnetic fields; pesticides and other toxic chemicals; hazardous wastes,

including municipal wastes; and other factors. The study is to be completed and a report submitted to Congress by December 1995 (within 30 months of enactment of the bill).

Ms. Tisevich reviewed three recent legislative mandates regarding breast cancer. First, in its FY 1993 appropriations report, the Senate urged NCI to undertake a study of elevated breast cancer rates in the Northeast and Mid-Atlantic States; the report language indicated that $1 million had been included for this purpose. Secondly, several months later, Ms. Tisevich stated, the Cancer Registries Act mandated virtually the same study. The third mandate, she continued, was the four-county study of risk factors previously described. A provision in the House FY 1994 appropriations bill would prohibit the expenditure of appropriated funds to undertake the second and third studies. The Senate bill includes appropriations for the second study but does not refer to the third. Ms. Tisevich explained that NCI has the discretion to proceed or not to proceed on the first study, regarding elevated breast cancer rates, based on scientific merit; she added that the prohibition of the second study does not affect the Institute's ability to fund the first, even though it is an identical study. Regarding the third study, Ms. Tisevich stated that clarification will be provided by House and Senate conferees, since the two appropriations bills differ.

Questions and Answers

Dr. Bettinghaus noted that the Legislative Update handout mentions testimony on June 24th concerning alternative medicine, specifically calling attention to Senator Harkin's interest in NCI's evaluation of Dr. Stanislaw Burzynski's antineoplasm therapy. He asked whether the Institute has completed an evaluation of that therapy. Dr. Chabner reported that the Institute is waiting for a drug shipment from Dr. Burzynski before initiating a clinical trial. Dr. Friedman added that NCI has successfully filed an Investigational New Drug Application (INDA) with the Food and Drug Administration for an evaluation of a mixture of chemicals specified by Dr. Burzynski for patients with primary brain tumors. Two approved protocols, from Memorial Sloan Kettering and the Mayo Clinic, will evaluate its use with patients who were refractory to other standard forms of therapy.

Dr. Lawrence referred to a resolution passed by the NCAB at a previous meeting in support of increased excise taxes on tobacco, and asked whether any information was available on progress in this area. Ms. Tisevich observed that the lay press has reported on Administration efforts to introduce increased taxes on tobacco products to finance health care reform, which would at least in part address the Board's concerns as expressed in its resolution. Dr. Lawrence expressed concern that the tax increases reportedly being considered as part of the health care reform plan fall short of those recommended by the NCAB. He suggested a new resolution based on the following language:

"The NCAB reaffirms its earlier resolution strongly supporting a $2.00 per pack excise tax on cigarettes, and hereby urges the Administration to propose this level of taxation rather than the current $1.00 level being considered. The basis for the specific concern is that the purpose of said tax is not only that of raising revenue, but is also that of producing a significant deterrent to a significant cause of cancer."

Dr. Lawrence presented this resolution in the form of a motion, which was seconded, and Dr. Calabresi opened the floor for discussion.

Dr. Salmon asked where the $1.00 figure came from. Dr. Lawrence said that it was an estimate based on general statements reported by the media. Dr. Devra Davis explained that the actual figure proposed by Congress is likely to be lower—probably between 50 and 75 cents. Dr. Calabresi suggested a change of wording from "the current $1.00 level" to "the current much lower level."

In the absence of any further discussion, Dr. Calabresi put the motion to a vote. The resolution was passed unanimously.

Ms. Mayer suggested further discussion of the possible impact of the Administration's health care reform plan on cancer care and cancer research. Dr. Broder stated that this was an excellent idea, and that once the plan has been made public, the issue will be placed on the agenda for a future NCAB meeting.

Breast Cancer Screening Guidelines—Discussion

Dr. Calabresi asked Dr. Broder to begin a discussion on the topic of potential modifications in breast cancer screening guidelines, adding that he would then call on Dr. Lawrence for additional comments and the possible introduction of a resolution.

Dr. Broder noted that this topic was recently the subject of a workshop organized by the Division of Cancer Prevention and Control. He stated that the importance of mammography, particularly in conjunction with clinical breast examination, is well established and that mammography screening in women over the age of 50 can lead to a one-third reduction in the death rate from breast cancer. Most European countries, he observed, offer mammography as screening for asymptomatic women over 50. Recent discussions, he stated, have focused on the issue of mammography among women 40 to 49. A number of studies, all of which were summarized at the DCPC workshop, have examined whether mammography has a comparable benefit for women between the ages of 40 and 49. Dr. Broder suggested that such a benefit has not been demonstrated.

The advice given to asymptomatic individuals between 40 and 49 should be seriously examined from a public health perspective, Dr. Broder stated, and informed by the results of the studies that have been conducted. He cautioned that such studies must be evaluated carefully and that recommendations must be formed on a factual basis, without withholding information concerning any level of uncertainty or failure to demonstrate an effect. He noted that guidelines are dependent upon the facts available at a given time, not written in concrete. As new data become available in the future, they might be revised accordingly.

Dr. Greenwald, Dr. Broder added, would be at the DCPC workshop during the meeting of the Subcommittee on Women's Health and Cancer, and he invited Board members to review the draft guidelines that had been distributed and attend this meeting. He stated that another open meeting will be planned, under the auspices of the DCPC's Board of Scientific Counselors (BSC), to invite comments from all interested parties, including the general public. Dr. Greenwald added that interested parties are welcome to attend the DCPC BSC meeting on October 21st.

Dr. Calabresi turned the floor over to Dr. Lawrence, who noted that those who are involved in other organizations with an interest in this issue are concerned about the problem of NCI and other groups presenting mixed messages. He gave as an example the public concern over the fact that the American Cancer Society reported a lifetime risk of breast cancer of one in nine, while NCI cited a risk of one in eight. He stated that he has outlined a resolution, which he would like to bring before the Board at the appropriate time, to address the issue of preventing the development of guidelines that do not have a consensus.
Dr. Greenwald related that he recently met with an ACS committee on breast cancer treatment and detection; he reported that the group unanimously voted to try to achieve a consensus with NCI. He added that the Institute, in agreement with other Federal agencies, hopes to involve other groups, including advocacy groups.

Dr. Broder agreed that consensus is desired, but suggested that a lack of consensus among people of good will should not be withheld from the public. He argued that the public realizes that science cannot always achieve precise answers and understands that at times the best answer is that "we are not sure." The public, he added, would rather not receive artificially precise statements that are not supported by facts.

Dr. Lawrence observed that a consensus of 12 organizations, including NCI, has already been reached. He said that the key question is whether new information has been produced or the minority view of the 12-organization meeting has been resurrected. New facts, he argued, would justify and require a new statement on guidelines, but a new statement designed to account for vagueness in existing information would be a mistake. Dr. Broder stated that the guidelines are being reconsidered because of legitimate disagreements in interpreting the data.

Dr. Salmon suggested tabling the discussion until after the Subcommittee's meeting and report to the full NCAB. Dr. Calabresi agreed and asked that Board members be prepared to discuss the issue further.

V. ENVIRONMENTAL SENTINELS: TUMORS IN FISH—DR. JOHN HARSHBARGER

Dr. Adamson introduced Dr. Harshbarger, Director of the Registry of Tumors in Lower Animals at the Smithsonian Institute, and explained that the National Cancer Institute supports this registry because it is believed that tumors found in lower animals are potential sentinels for human cancer.

Dr. Harshbarger began his presentation by reviewing the history of lower animal tumor studies. He noted that tumors in fish were first documented in the scientific literature in 1853, when Henry David Thoreau wrote of catfish inhabiting the Acabet and Concord Rivers that had velvety black masses on their bodies. Even today, fish from these rivers exhibit such masses, which have been determined by Fish and Wildlife Service biologists to be large melanotic tumors. Between 1853 and 1900, Dr. Harshbarger continued, there were more incidents of tumors in cold-blooded animals, including reptiles, clams, amphibians, and more fish. In the following 65 years, several examples of specific gene-induced tumors in lower animals were discovered, leading to the formation of the Registry of Tumors in Lower Animals. One of these discoveries, made by geneticist Calvin Bridges in 1916, involved a tumor mass found in a drosophila. Dr. Bridges and his student, Dr. Mary Stark, found the drosophila to be a specific mutant strain of insect that expresses the tumors. The insects died in the larval stage when the tumor was homozygous for the specific gene, which was subsequently named Lethal-7.

Some 20 years after the discovery of Lethal-7, the laboratory incubator overheated and the drosophila strain was lost. After much controversy, the gene was rediscovered in 1968 through the observation of dying drosophila larvae by Dr. Elizabeth Gaiteff. Dr. Gaiteff noticed abnormalities in the larvae which, when transplanted into normal adult drosophila, grew like cancer in the adult flies and killed them. She reasoned from this discovery that other gene tumors may exist, and, using mutagens, has been able to induce a total of 20 gene-specific cancers in drosophila. Because of her observations, Dr. Gaiteff has been honored by *Cancer Research* as one of the first to recognize recessive genes as a regulator for tumor formation.

Dr. Harshbarger mentioned the work of Dr. Meschler involving genes on the second chromosome of drosophila. He pointed out that the sequences of the specific genes recognized by Dr. Meschler to involve tissue overgrowth could be potentially useful for future work in the determination of gene activation in human tumors.

Another example of gene influence in fish tumors occurred in the 1920s. Dr. Harshbarger described an experiment in which swordtails, which have no pigment spots, were crossed with platyfish, which do have pigment spots. By selectively eliminating the regulator genes for the pigment genes, malignant melanomas were induced in some of the strains. This process can be elevated by chemical exposure, suggesting that exogenous factors that interact with the genome can act through several potential points of genetic vulnerability to initiate the formation of pigment cell tumors.

Dr. Harshbarger next discussed the occurrence of skin tumors in fish found in polluted areas surrounding the Delaware River. These tumors were first reported during the 1940s, and a survey completed during the 1980s by the New Jersey Department of Natural Resources found identical tumors present in fish in the Delaware River.

In the 1950s, Dr. Harshbarger continued, lip papillomas were found in fish near sewer jet falls off the coast of California. These tumors, however, were not present in the fish of the nonpolluted waters off Catalina Island. Also in the 1950s, the first evidence was observed indicating that the herpes virus might be responsible for causing some tumors. Bilateral renal adenocarcinomas were found in high numbers of leopard frogs, along with intranuclear occlusions. Using electron microscopy, researchers identified herpes virus particles, and subsequently, it was demonstrated that the virus could, in fact, cause the tumors.

Dr. Harshbarger reported that, around 1960, the development of pelleted plant food for hatchery rainbow trout seemed to be linked to a pandemic of liver cancer in this fish. Investigators determined that the mold *Aspergillus flavus* was growing on the pelleted trout feed. This observation, coupled with the knowledge that *Aspergillus* produces aflatoxin, led to the discovery that the mold is highly carcinogenic for rainbow trout, producing large liver masses that kill the fish. The early 1960s also marked the first experimental carcinogenesis with fish tumors. One of those involved, Dr. Harshbarger noted, was an NCI researcher, Dr. Merle Stanton, who induced liver cancer in small fish by feeding them diethylnitrosamine.

Dr. Harshbarger emphasized the importance of these examples, which, he said, demonstrate that specific genes can cause cancer—chemical carcinogens in the form of aflatoxins, and viral carcinogens in the form of herpes virus. He also stressed the association of both skin and liver tumors with polluted environments. These findings, he concluded, were the main contributing factors to the formation of the Registry.

The Registry of Tumors in Lower Animals was started in 1965 and was contracted to the Smithsonian in 1966, where it has since remained. Dr. Harshbarger reviewed the rationale for the Registry, stressing the value of investigations concerning potential vectors of tumor viruses, such as mosquitoes and ticks; potential reservoirs for carcinogens that are present in the food supply; effective animal models for studying human tumors; and the possibility that tumors in fish could serve as sentinels for environmental carcinogens.

The functions of the Registry are primarily to collect, identify, characterize, and preserve specimens with neoplasms and related disorders from the natural habitat that are used in core and laboratory experiments. The Registry is primarily a diagnostic service that also collaborates with field survey experimental studies to help with the diagnosis of lesions. Dr. Harshbarger pointed out that the Registry collects literature on tumors in cold-blooded animals, abstracting both the specimen database and the literature database on the same

parameters. At present, he noted, each of these databases contains approximately 6,000 units; the information is analyzed and disseminated in response to specific inquiries.

Dr. Harshbarger then reviewed the geographic distribution of epizoic tumors in North America, noting that the most thorough study on this subject has been done in the areas of the Puget Sound, Tacoma, and Seattle by the National Fishery Service. Studies have been completed involving the epidemiology of different species of fish at differing runs of these polluted sites. Tests have examined the uptake of chemicals by the invertebrates that live in the sediment and are eaten by the fish, and analyses of the sediment and fish have been performed as well. Attempts have been made to induce tumors in the fish using extracts taken from the sediment, and studies have been performed to examine the physiology in the liver and determine how the chemicals are metabolized by the enzyme system. Results have shown the reactive intermediates to be in the bile.

The distribution of reported tumors in the United States was then presented. Dr. Harshbarger referred to his earlier mention of lip tumors in the fish along the coast of California, noting that hepatocellular carcinoma has been observed there as well. Few tumors, he continued, have been reported in the southern United States, although the Registry has recently received specimens from the Tennessee Valley and more material has been promised from that region. A high incidence of hepatocellular carcinoma has been found in the polluted areas of the Northeast. Dr. Harshbarger cited the mummichogs in the Elizabeth River that have a very high incidence of cholangiocellular and hepatocellular liver cancer. This epizootic is especially significant, he stressed, since approximately 33 percent of mummichogs located near a creosote plant along the Elizabeth River were found to have an extremely aggressive and destructive form of liver cancer, compared with none of the mummichogs along the opposite riverbank. Dr. Harshbarger concluded that the mummichog appears to be a good environmental sentinel.

Dr. Harshbarger discussed an experiment completed by the Environmental Protection Agency that demonstrated the movement of liver cancer within the food chain. Sediment from the Long Island Sound was fed to bivalve mollusks, which then developed tumors. When these mollusks were fed to the winter flounder, the flounder developed tumors as well.

Examples were presented of fish tumors in specimens found in several regions around the United States. In a significant study off the coast of Maine involving three separate sites, clams from all three sites were shown to have developed gonadal tumors called germanomas. Dr. Harshbarger indicated that the only common denominator among the sites was the presence of herbicides. He also presented information from an area of the Midwest, where the walleye in a chemically polluted lake have demonstrated liver tumors.

Dr. Harshbarger then discussed his own studies conducted in the Black River near the USX plant in Lorraine, Ohio. He discussed the 80 to 90 percent liver tumor occurrence in bull head catfish that were more than 3 years of age. He also pointed out that although there is usually little metastasis in fish tumors, he found metastatic tumors in the fish from the Black River area. The USX plant was closed following disclosure that cancer had been found among the fish, and studies have continued since that time. Levels of chemicals in the river sediment have decreased, as have levels within the tissues of the fish. The shutdown of the plant also resulted in decreased severity and prevalence of fish tumors. The subsequent dredging of the river by the Corps of Engineers, however, brought the settled material back into the water, once again raising the prevalence of cancer in the fish.

Experiments were performed in which sediments from the Buffalo River and the Black River were either painted on or fed to mice and fish. Skin tumors resulted in the mice and fish that were painted and liver tumors resulted in the fish that were fed the sediment. These findings are consistent with experimental carcinogenesis data showing that established

carcinogens induce liver cancer in fish. It is also an indication that the enzymes in the livers of fish are effective metabolizers of indirect-acting carcinogens with the production of electrophilic intermediates that adduct DNA and activate oncogenes. Finally, these results indicate that fish liver cancer is an excellent indicator of the presence of carcinogens in the environment.

Dr. Harshbarger mentioned experimental work using approximately 30 species of fish and 50 to 100 chemicals. He presented a slide on the original work done with zebra fish with diethylnitrosamine, aflatoxins and acetamidofluorene aflatoxins, MNMG, DDT, benzo pyrene, and nifurpirinol. He pointed out that the target area in the fish is almost always the liver, but there have been occasional occurrences of tumors in the GI tract and other sites. He presented documentation reporting that tumor development begins as early as 5 to 12 weeks in small fish. Based on these epidemiological experiments indicating that sediment extracts cause tumors in fish and the almost nonexistent occurrence of spontaneous liver tumors in fish populating wild habitats, conclusions can be drawn linking tumor occurrence to carcinogens within the habitat.

Dr. Harshbarger concluded with an overview of ongoing studies. He reported that follow-up studies concerning the dredging of the Black River are still being continued to determine whether the level of tumors will again decline as the sediment settles. He also stated that surveys are continuing in the Tennessee Valley and New York areas. Recent surveys on fish in the Potomac River have found liver tumors in 5 to 10 percent of the bull head catfish in the Woodbridge, Virginia area. In another preliminary study conducted along the Anacostia River, 16 of 20 catfish tested were found to have liver tumors, and, based on these preliminary findings, the survey is going to be extended. Dr. Harshbarger also discussed continuing studies of the clams in Maine, which demonstrate tumors appearing to be associated with herbicides.

In conclusion, Dr. Harshbarger mentioned that the National Institute of Environmental Health Sciences is supporting a project investigating the potential use of fish for carcinogen bioassays. Finally, he expressed his belief that fish can be extremely useful as sentinels for carcinogens in the environment and as bioassay agents.

Questions and Answers

In light of the problems that occurred after the Black River was dredged, Dr. Becker informed Dr. Harshbarger of his concerns regarding the Houston Ship Canal dredging project being done by the Corps of Engineers. Dr. Harshbarger expressed his support for a project in this area.

Dr. Calabresi commented on the number of shark tumors in existence, considering the publicity indicating that sharks do not develop tumors. He asked Dr. Harshbarger about the origin of this myth concerning tumor incidence in the shark. Dr. Harshbarger explained that there have been no definitive studies involving the incidence of tumors in sharks. The cases that do exist, he explained, have been anecdotal. Dr. Harshbarger cited knowledge of 36 examples of shark tumors, and explained that only 20 examples would remain if dubious examples and examples acquired from past literature were eliminated. Dr. Harshbarger also cautioned that these 20 examples cover several different organ systems. He added that although shark tumors have been viewed on occasion, there have been no definitive studies involving sharks and, as a result, no conclusions can be drawn that sharks do not develop tumors.

Dr. Calabresi mentioned the presence of cartilage in the shark. He commented that cartilage will not support blood vessel growth and, since tumors need blood vessels to grow, an antiandrogenic substance may suppress the tumor growth. Dr. Harshbarger commented that

three of the shark tumors were condylomas. Dr. Adamson added that sharks spend most of their time far out in the ocean, where there is a much lower incidence of tumors.

Dr. Freeman asked whether there is any correlation between cancer rates in people living in areas with high cancer rates in fish, indicating that the people living in those areas would be exposed to the same factors as the exposed fish. Dr. Adamson said cancer rates in humans and fish have been examined in two sites and no correlation has been found.

Dr. Freeman raised another question concerning the consumption of fish that contain cancer. He asked if there have been any studies indicating that there is a vehicle that could transfer the cancer gene. Dr. Adamson indicated that this phenomenon would be very unlikely. He explained that the tumors occur primarily in the liver, lips, and skin and that people generally consume muscle meat. Dr. Adamson did emphasize, however, that carcinogens can be acquired from the areas where the fish have been exposed, but most of the carcinogen deposited in animals is not in the muscle.

Dr. Calabresi thanked Dr. Harshbarger for his interesting presentation and called for a brief recess.

VI. *HELICOBACTER* AND CANCER—DRS. JOHN DONOVAN AND JERRY RICE

Dr. Adamson announced that the NCI will hold a workshop on *Helicobacter* on October 16, 1993. *Helicobacter*, he explained, is an emerging group of bacterial pathogens of which nine species have been identified thus far. Dr. Adamson related that Dr. Correa has researched *Helicobacter pylori* and associated the bacteria with stomach cancer; other studies have shown that the bacteria causes ulcers in humans. Dr. Adamson explained that Drs. John Donovan and Jerry Rice would both present on a new species of helicobacteria associated with a different type of cancer in animals. He then introduced Dr. John Donovan, Director, Office of Laboratory Animal Science, NCI.

Events Leading to the Identification of *Helicobacter*

Dr. Donovan began with a brief overview of the Frederick Cancer Research and Development Center at Fort Detrick, Maryland, which consists of a series of animal production, research, and administrative buildings. The animal production area (APA), he explained, is a series of 18 block buildings that are used to produce pathogen-free rodents for investigators at NCI and for extramural grantees and contractors. Dr. Donovan presented slides on which he identified specific areas of these facilities that are known to be contaminated with the *Helicobacter* species, noting that original observations of *Helicobacter* were made in a self-contained animal facility within building 539. Veterinary pathologists reading slides from two 12-month carcinogenicity studies conducted by Dr. Lucy Anderson observed unique liver lesions in control mice in November 1992. Affected animals included A/J strain mice obtained from the animal production area, as well as hybrid mice bred in building 539.

Hematoxylin-eosin stained slides from animal health surveillance animals were retrospectively evaluated for the presence of similar lesions. Based on a small number of slides, the earliest appearance of the lesion in animals was in a pool of retired breeders from the animal production area in January 1992. Based on knowledge of the etiology and progression of the disease, Dr. Donovan suggested that the causative agent probably first appeared in mid-1991. Because of the lesion's similarity to those caused by chemical insult to

the liver and the lesion's distinction from commonly encountered mouse hepatitis virus or other known infections, Drs. Jerry Ward, Miriam Anver, and Diana Haines, veterinary pathologists working on the problem, decided to call the lesion toxic hepatitis in early 1993.

Dr. Donovan related other characteristics of the syndrome discovered in early 1993. The lesion appeared to progress in severity with age, and males were more severely affected than females. Also, no clinical signs had been observed, and reproductive performance at the APA had remained unchanged. Most noteworthy was the appearance of liver tumors in a high percentage of Dr. Anderson's control mice that were more than 12 months of age.

Surveys were conducted to assess the extent of the problem. Investigators began by examining livers from retired male breeders from the production colonies of A/J mice, which were also positive for the toxic hepatitis. The survey was expanded, Dr. Donovan stated, in January 1993 to examine the histology and necropsy of a small number of animals from other production buildings of the APA; extensive surveys with large numbers of animals were not feasible. The expanded survey revealed that 7 of 11 mouse production buildings had the characteristic lesion; no rats, hamsters, or guinea pigs were affected. Generally, lesions were found in animals older than 6 months of age. Later studies showed that SCIDs and A/J mice developed lesions as early as 2 months. Other susceptible strains of mice were the C3H and BALB/C, and resistant strains included the C57/BL6 mouse, B6C3F1 hybrids, and nude mice on various backgrounds.

Dr. Donovan reported that the FCRDC sent a notification of these preliminary findings to approximately 2,000 recipients of animals from the APA on February 4, 1993, describing the histological lesion and explaining that older animals and males were more severely affected and that known infectious agents had been ruled out. To further explore this issue, water, food, and tissue samples from infected animals were analyzed for the presence of toxic substances, with negative results; additional analysis of the slides could not rule out an infectious etiology. Pathologists examined histological slides prepared with special stains to look for evidence of microorganisms, performed electron microscopy studies on the lesion, and conducted direct transmission studies with liver homogenates. The first evidence found was a spirochete-like organism on a Steiner-stained liver section from an infected mouse; slide analysis indicated a high degree of association between the organism and the liver lesion. Scanning electron microscopy confirmed the presence of organisms in the bile canaliculi that were compatible with the observations on the Steiner-stained slides. Ten percent liver homogenates from affected SCID mice were then inoculated intraperitoneally into a strain of (A/J) mice obtained from Jackson laboratories.

Dr. Donovan reported that no clinical signs were observed, but animals sacrificed at 5.5, 10, and 18 weeks after inoculation had liver lesions similar to those seen previously. Spiral organisms resembling those seen in natural infections were seen in Steiner-stained liver sections from these animals. Dr. Donovan pointed out that although an infectious etiology was indeed suggested by these experiments, it was still necessary to show the cause-and-effect relationship between the organism and the lesion.

The next step was to attempt to culture and identify the organism. Dr. Joe Tully from the National Institute of Allergy and Infectious Diseases (NIAID) in Frederick observed helical, motile organisms on wet-mount impression smears using dark field microscopy and was able to culture the organism on blood agar. Dr. Jim Fox, an expert in animal helicobacters in the Department of Comparative Medicine at the Massachusetts Institute of Technology, was asked to identify the organism. Through standard microbiological techniques, he showed that the organism was phenotypically and biochemically consistent with the *Helicobacter* species. Using RNA sequence analysis, he also determined that the organism was a novel *Helicobacter* species.

Mice were injected both orally and intraperitoneally with the cultured *Helicobacter*. Results showed that the organism alone was capable of reproducing the characteristic lesion by both routes of administration. Dr. Fox was then able to reculture the same organism from inoculated animals.

A second notification was sent to recipients of animals from the APA on August 17, 1993. In addition to explaining the infectious etiology, the notice explained that the FCRDC's first priority was the development of a rapid diagnostic test to further define the extent of bacterial involvement that could be used as a tool during the eradication process.

Dr. Donovan explained that the plan for eradicating *Helicobacter* from the production and research colonies is still evolving. The process of caesarian rederivation and repopulation can begin once a diagnostic test with a high confidence level is available. Dr. Donovan expressed his hope that some of the barriers or isolators will remain truly negative and will not require a breakdown. Elimination of infection from NCI research colonies in Frederick and Bethesda will be a primary focus once the animal production area is confirmed to be free of *Helicobacter*. The FCRDC has begun the process of developing a facility and procedures to work with the organism in an animal model without posing a risk to other colonies, while simultaneously eliminating contamination from production and research colonies.

Dr. Adamson then introduced Dr. Jerry Rice, Chief, Laboratory of Comparative Carcinogenesis, Division of Cancer Etiology (DCE), NCI.

Important Implications of This Discovery for NCI's Animal Resources Program

Dr. Rice indicated that although the presence of *Helicobacter* has had a significant negative impact on carcinogenesis investigations, this organism is a novel research tool of significant potential value because of its association with the development of neoplasms in chronically infected animals.

Dr. Rice explained that his laboratory was originally established at the FCRDC because of the Center's high-quality research animal facilities and its reliable source of experimental, pathogen-free rodents. He noted that there was no evidence of infectious disease in animals produced by the animal production area during the period 1981 through 1991, except for occasional outbreaks of mouse hepatitis virus. Strain A mice were genetically resistant to infection prior to 1992; no form of hepatitis was observed and liver tumor incidence was measurable, but very low. Beginning in December 1992 and continuing into the present, virtually all strain A mice have had a persistent, morphologically distinctive form of hepatitis associated with liver cell tumors in most mice older than 1 year.

Dr. Rice presented a slide illustrating intrahepatic pericholangitis, which is the early morphologically distinctive aspect of infection in strain A and other susceptible strains of mice. The bile duct in the slide was shown to be surrounded by inflammatory cells of various kinds, and the lining of the duct was severely damaged. It is likely, Dr. Rice noted, that leakage of bile into the surrounding tissues is partly responsible for the inflammation. The chronic nature of the infection and its histological features illustrated in these slides (e.g., proliferation and dysplasia of bile ducts, hepatocytomegaly, hyperplasia of liver cells, and cell proliferation) originally suggested that the syndrome might be caused by some form of chemical intoxication. *Helicobacter* was originally designated as toxic hepatitis because of its morphological pattern. The pathologists at Frederick, Dr. Rice explained, fortuitously discovered Steiner's method, which illustrates the spiral organisms that can be seen within hepatic parenchyma, mostly at sites that are somewhat distant from major foci of inflammation.

Another slide showed the microorganisms visible through transmission electron microscopy. The organism was shown to be within a bile canaliculus between the liver cells; it preferentially locates within the site where inflammation occurs. Dr. Rice explained that chronic infection is associated with development of hepatocellular tumors, usually multiple, within the livers of mice about 1 year of age, and that these tumors develop without the administration of any known carcinogenic agent.

New Opportunities to Study the Association of *Helicobacter* Species and Cancer in Man

Dr. Rice emphasized that, similar to observations in mice, cancer might develop in humans as a late effect of chronic infection by certain pathogens. An example is clonorchiasis, an infestation by the Oriental liver fluke, which is a symbiotic affliction of dogs, cats, and humans. This organism, similar to *Helicobacter*, localizes in small and large intrahepatic bile ducts. It gives rise to chronic cholangitis, which eventually progresses to cholangiocarcinoma.

Dr. Rice stated that the association between cancer and chronic cystitis, resulting from infection by *Schistosoma haematobium*, is possibly better known. This bladder fluke causes chronic cystitis that progresses to squamous metaplasia and, ultimately, to squamous cell carcinoma of the urinary bladder.

There is also an association between chronic infection by the bacterium *Helicobacter pylori*, a relative of the organism found in mice at the FCRDC, and gastritis. This organism is the only human pathogen of the approximately six known members of the genus *Helicobacter*. It colonizes the gastric mucosa of the lower portions of the stomach in humans, leading to several forms of gastritis, including chronic atrophic gastritis—a known precursor of gastric adenocarcinoma. Infection by *Helicobacter pylori* in infancy or youth persists for life if untreated, and is associated with adenocarcinoma of the stomach in many populations. This association is especially high in certain populations, such as women and Black Americans.

The mechanism by which *Helicobacter pylori* infection in humans contributes to the development of gastric adenocarcinoma is unknown. There are two major schools of thought on this issue, one of which suggests that the organism produces a carcinogen. Dr. Rice listed several examples of such carcinogens that have been discussed in the literature. Aflatoxins, the product of a specific species of mold, represent one group of numerous potent mutagens (some of which are also potent carcinogens) produced by higher plants, molds, and other bacteria. Both cycasin and the aflatoxins are classic examples of metabolism-dependent genotoxic carcinogens that require mammalian metabolism to generate reactive, DNA-damaging metabolites that are responsible for biological effects. Dr. Rice also mentioned fecapentaenes, which are produced in the human colon by another unrelated genus of anaerobic bacteria, *Bacteroides*, which are potent mutagens under various circumstances, but appear to be noncarcinogenic.

Dr. Rice described the second hypothesis, documented in *Gastroenterology Clinics of North America* in March 1993, which suggests that the inflammatory process itself contributes to the development of carcinoma as a consequence of some toxic intermediate or intermediates produced by various inflammatory cells. This process, Dr. Rice explained, postulates that inflammation-related mutagens, possibly oxidative products, superoxide, peroxides, etc., may be the causative agents.

Another possibility is that nitric oxide, a potent bioregulatory agent, may be an important effector of carcinogenesis in this model. Nitric oxide is produced enzymatically from arginine in mammalian cells. Its production can rise dramatically during certain infections, and it can efficiently nitrosate secondary amines under oxidative conditions to produce N-nitrosamines, which as a group are notoriously carcinogenic in the liver. The

possible role of nitric oxide in the carcinogenic process would be through its involvement in chronic inflammation that occurs during certain infections, including murine *Helicobacter* infection.

Two lines of investigation on possible mechanisms by which the murine *Helicobacter* infection might result in liver tumors are being pursued at the FCRDC. The first involves identification of the putative carcinogenic metabolite using the Ames assay for bacterial mutagenicity as a screening system. The second approach focuses on nitric oxide. The generation of nitric oxide increases substantially in viral hepatitis in woodchucks, which is associated with the development of carcinoma in that species. As a result, it should be possible to determine whether exogenous secondary amines are nitrosated to form nitrosamines to a readily detectable extent. Dr. Rice commented that this hypothesis is especially attractive because those substances are extremely effective as hepatic carcinogens and the pathology of the lesions in mice is consistent with chronic administration of hepatotoxic agents.

Dr. Rice emphasized that several problems remain to be solved in planning systematic studies on the role of *Helicobacter* in carcinogenesis, including: 1) the organism is difficult to culture; 2) it is virtually anaerobic; 3) it does not form discrete colonies on any of the solid media on which it has been cultivated; and 4) it has not been adapted to mass liquid culture. Moreover, related organisms are known to lose pathogenicity if they are cultivated *in vitro* for prolonged periods. Those organisms must be maintained by successive inoculation into mice, which suggests that the same process may have to be followed to maintain virulence in the *Helicobacter*.

Dr. Rice concluded that the challenge, therefore, is to eliminate the organism from the production areas and other animal facilities where it interferes with research, while maintaining it for study as a valuable tool that may provide enlightening information on the pathogenesis of several kinds of human malignancy.

Questions and Answers

Dr. Chabner commented on two papers recently published in *Lancet* that concerned mucosal-associated lymphoid tumors found relatively infrequently in man. One paper showed that lymphoid cells, apparently malignant cells, responded *in vitro* to *Helicobacter* extracts by proliferation and antibody secretion. The other paper, surprisingly, showed that the tumors would regress when treated with antibiotics.

Dr. Correa agreed that these findings have relevance to humans. He added that *Helicobacter pylori* infection is considered one of the most common chronic infections in man. There are populations in which 100 percent of individuals are affected, Dr. Correa reported, and between 30 and 50 percent (depending on which group is studied) of Americans have chronic gastritis due to *Helicobacter pylori*. Thus, it is a serious infection with an unquestionable bacteriological relationship with cancer. Dr. Correa stated that about 60 percent of stomach cancers would disappear if *Helicobacter* were eliminated, according to some calculations of attributable risk. *Helicobacter* does not act alone; it is, rather, one of a complex family of bacteria that influence etiology. A great deal of information on the mechanism of carcinogenesis should be gained from this model, Dr. Correa stressed, because it is not known how *Helicobacter pylori* produces cancer.

Dr. Calabresi inquired about the involvement of *Helicobacter* in the etiology of duodenal ulcer. Dr. Correa explained that there are a variety of responses to *Helicobacter*. Some people develop diffuse antral gastritis, which is an inflammation appearing in the antrum of the stomach with hypersecretion of acid—these are the people who develop duodenal ulcer. The most frequent gastritis found in the populations of Columbia, the former Soviet Union,

northern European countries, and China is multifocal atrophic gastritis, a chronic gastritis with atrophy of the mucous membrane and glands of the stomach that leads to gastric ulcer at one point and, later, to cancer of the stomach in some individuals. The steps that occur in this process are completely unknown. For some time, Dr. Correa continued, duodenal ulcer was thought to have no relation to cancer, but it has been found that most people who have gastrocardius cancer frequently have peptic ulcer history, and most of them are heavily infected with *Helicobacter*.

Dr. Day asked Dr. Correa to speculate about the cofactors involved in stomach cancer and the relation of the infection to the temporal changes that have been observed. Dr. Correa explained that one hypothesis is that people are infected in childhood and the infection lies dormant for a long period of time, until stomach cancer develops. This hypothesis, he added, would explain the rise in stomach cancer that occurred 30 or 40 years ago; however, it is believed that most people in this country who are infected today were not infected during childhood but later in life. Dr. Correa explained that the other hypothesis depends upon the specific cofactors involved. He cited examples of populations in Africa and coastal Central America in which the infection is severe in early childhood, yet stomach cancer never develops.

Dr. Pitot asked if we should expect a gradual increase in the human incidence of stomach cancer in the United States because of *Helicobacter* infection. Dr. Correa answered that there is no new infection. It is suspected that the incidence and prevalence of infection is decreasing. The phenomenon of gastric cancer of the cardia is not due to increasing infection, but, rather, to unknown interactions. Dr. Pitot asked whether the incidence of *Helicobacter* infection was as high as approximately 100 percent 40 or 50 years ago in the United States and if it is now decreasing. Dr. Correa responded that the prevalence of *Helicobacter* is about 60 or 70 percent in high-risk areas of the world today, and that this level could have been present in the United States 40 or 50 years ago.

Dr. Pitot asked Dr. Rice how the mice developed hepatomas if no carcinogen was involved. Dr. Rice reiterated the two potential routes under investigation: 1) tumors occur as a result of some agent produced by the organisms themselves, in which case there may be a direct causal effect; or 2) they occur as a result of nitric oxide generated in large quantities by the inflammatory cells that are so prominent early in the disease process, such that the oxidative nitrosation of secondary amines may generate N-nitrosamines *in vivo* that may act as the causative agents. Dr. Rice pointed out that both of these ideas are directly testable.

Dr. Pitot then asked if the level of hepatocyte proliferation is higher in the animal with the current infection and, if so, by how much. Dr. Rice answered that the level is at least double, judging from the frequency of mitotic figures in the histological sections. Dr. Correa added that the same is true for humans; there is hyperproliferation that returns to normal after treatment.

Dr. Broder commented that one of the most important cofactors is the host immune response genes. Depending on which genes were involved, a certain type of response would be obtained in one setting, and another type of response in a different setting. He added that there are several precedents for this in various models.

Dr. Broder also stated that findings related to *Helicobacter pylori* represent an unexpected lead, and that this organism's role as an important carcinogen has not been sufficiently addressed. It has been a slow process, Dr. Broder continued, for researchers to come to terms with the fact that this bacteria causes peptic ulcer disease and that a definitive treatment may exist that is not dependent solely on antacids. Sister Institutes, he continued, have begun conducting special workshops and issuing RFAs to investigate why the scientific

community is not taking advantage of the fact that, in theory, bacterial eradication of peptic ulcer disease is possible.

Dr. Broder asked for the Board's advice on coming to terms with the emergence of convincing data that *Helicobacter*-related species can cause cancer. There is strong circumstantial evidence, he stated, that gastric cancer is caused by *Helicobacter*; it is possible that several cancers are caused by *Helicobacter*. Dr. Broder asked for the Board's advice in determining how much of a commitment should be made in this area. He asked whether the cancer program should be restructured to make an intensive advancement in this area, or whether the standard process should be allowed to take place. He also asked whether the Board recommends development of a bacterial cancer program.

Dr. Becker commented that a partial answer may lie in terms of the genetics of resistance to *Helicobacter* infection. He referred to a slide presented by Dr. Rice that suggested that the C57 mouse might express a form of resistance different than the one expressed by the B6 mouse strain. It would be interesting, he suggested, to examine the C57 strain resistance more thoroughly. Dr. Rice cautioned about making comparisons among the different strains until systematic, controlled, deliberate infection studies in all the strains are conducted. Dr. Becker commented that the other parental progenitor of the B6 strain is a C3H strain, which Dr. Rice showed to be highly susceptible to infection. Thus, Dr. Becker continued, an F1 strain that is resistant when one parent is susceptible to infection should be further investigated.

Dr. Calabresi asked whether Dr. Rice had examined the Barrett's esophagus and/or esophageal cancer in relation to *Helicobacter* infection. Dr. Rice explained that the FCRDC has not investigated esophageal carcinoma in humans.

Dr. Broder emphasized that advice is needed on whether a structured program would be useful relative to the level of information presently available. Dr. Wells suggested that additional basic research information (e.g., whether these bacteria transform human cells) is needed before a substantial clinical program in bacteriological oncology is started.

Dr. Salmon asked whether the Institute has examined its grants portfolio to determine whether it has adequate funding for such a program. Dr. Adamson replied that an analysis has been done; he added that, currently, there is one grant related to bacteriological oncology in the epidemiology area and none in the biological carcinogenesis area. He explained that a workshop will be held on October 16, 1993, to examine the nine species of *Helicobacter* that have been identified. It might be necessary, he continued, to issue an RFA on this topic—both basic studies and animal models. Dr. Adamson emphasized that it is important to recognize the existence of naturally occurring carcinogens in addition to synthetic industrial carcinogens.

Dr. Bettinghaus asked how the other Institutes are involved with this research. Dr. Broder answered that the NIAID and the National Institute of Diabetes and Digestive and Kidney Diseases are issuing an RFA for exploring *Helicobacter pylori* from their points of view, not necessarily regarding cancer. Dr. Adamson noted that the NCI has some cooperative agreements concerning adenocarcinoma of the esophagus and *Helicobacter* as a risk factor. These issues, he continued, will be explored further at the upcoming workshop.

Dr. Calabresi asked Board members to read the drafts of the reports on the NCI plan for research on prostate cancer and NCI's research in the breast and female reproductive tract, to be discussed during the new business section of the meeting on the second day. Mrs. Bynum clarified that the report on breast cancer would be discussed at the subcommittee on women's health.

VII. UROGENITAL CANCERS TASK FORCE REPORT— DR. W. MARSTON LINEHAN

Dr. Bruce Chabner, Director of NCI's Division of Cancer Treatment, observed that Congress has taken a special interest in the encouragement of research on prostate cancer in general and urologic cancer in particular. He introduced Dr. Marston Linehan, Head of the Urologic Oncology Section within NCI's extramural program, to provide an overview of the Institute's research program in this area.

To emphasize the burden of urologic cancers in the Unites States, Dr. Linehan stated that the three predominant urologic cancers—cancers of the prostate, kidney, and bladder—are expected to occur in more than 240,000 individuals in this country in 1993 and take more than 55,000 lives. He noted that NCI supports multidisciplinary genitourinary cancer research, including studies in epidemiology, biology, diagnosis, therapy, prevention, education, community outreach, and rehabilitation.

The Institute places a high priority on prostate cancer research, including the establishment of specialized programs of research excellence in this area. Through this mechanism and others, NCI supports research in basic biology, vaccine development, early detection and education trials, therapy for localized prostate cancer, multimodality clinical trials building on numerous preclinical studies such as the NCI cell line screen, and applications of three-dimensional modeling. NCI, Dr. Linehan added, has introduced novel cytotoxic agents for prostate cancer, employing antimetastatic and antiangiogenic approaches, as well as new strategies involving differentiation agents.

Dr. Linehan observed that the integration of intramural and extramural expertise in defining critical research questions and designing innovative treatment strategies is exemplified in NCI's approach to genitourinary cancer. The Institute recently convened an intramural task force to report on a broad spectrum of clinical and laboratory studies of genetic aspects, carcinogenesis, prevention, and therapy for genitourinary, as well as gynecologic, malignancies. Dr. Linehan noted that a summary of the task force's report had been distributed to Board members and explained that the remainder of his presentation would concentrate on one portion of the report—focusing on studies of the molecular genetics of kidney cancer—as a template for multigroup intramural collaboration and intramural/extramural integration. He added that the work he would describe on a tumor suppressor gene associated with von Hippel-Lindau (VHL) disease, as well as nonfamilial kidney cancer, can serve as a model for identifying genes associated with prostate and bladder cancers. The studies described in this presentation, Dr. Linehan added, are being performed in collaboration with Drs. Berton Zbar and Michael Lerman of the Laboratory of Immunobiology at NCI's Frederick Cancer Research Facility.

Dr. Linehan related that in 1973, Dr. Alfred Knudson hypothesized the role of tumor suppressor genes in carcinogenesis. In addition to resulting from activation of an oncogene, Dr. Knudson suggested, it could also result from the inactivation of a recessive oncogene, or tumor suppressor gene, whose normal function might be to regulate cellular growth. The development of cancer requires the inactivation of both copies of this gene, either through loss of DNA, DNA sequence deletion, or another mechanism such as mutation.

Dr. Knudson hypothesized that if this was found to be the case in a sporadic, nonhereditary cancer and a hereditary version of the same malignancy existed, the same gene might be involved in both. This was found to be the case in retinoblastoma, in which both copies of the retinoblastoma gene are inactivated in both the sporadic and hereditary forms of the disease. Abnormalities in tumor suppressor genes, Dr. Linehan stated, have been associated with a number of solid human tumors, including lung, colon, and breast. Sites

being examined for tumor suppressor genes include chromosome 9 for bladder cancer and chromosomes 8, 10, and 16 for prostate cancer.

Dr. Linehan explained that, as with retinoblastoma and colon cancer, kidney cancer has both sporadic and familial forms. One familial form of kidney cancer is inherited in an autonomally dominant fashion; the other is associated with VHL, an autosomal dominant disease. Both differ from noninherited kidney cancer in that they tend to be multifocal and bilateral; their tendency to occur at a younger age suggests a genetic predisposition.

The first study to suggest a location for a kidney cancer gene was published in the *New England Journal of Medicine* in 1979 by Cohen and colleagues. These investigators evaluated chromosomal abnormalities (i.e., germ line abnormalities) in lymphocytes from a kindred group of individuals with kidney cancer. In the lymphocytes of affected family members, there were balanced translocations from the short arm of chromosome 3 to the long arm of chromosome 8. All family members who had this translocation had kidney cancer, and none of those who did not have the translocation had the disease. Similar families have since been reported.

Dr. Linehan explained that the NCI investigators used the technique of restriction fragment length polymorphism analysis, which takes advantage of a normal property in the human genome: there can be small variations in homologous chromosomes, including variations in the restriction enzyme sites in an individual's two copies of a specific chromosome. This powerful technique provides a very fine resolution for detecting DNA sequence deletions, which would indicate the presence of tumor suppressor genes.

Polymorphic probes localized to the short arm of chromosome 3 were used to look for loss of DNA in kidney cancer. Dr. Linehan provided an example of a probe that recognizes the DNF15S2 region; there are two constant HIND III sites, he noted, and one variable site. When the DNA is cut with the HIND III restriction enzyme, there can be either a 2.3 or a 2.0 kb band. Using this probe, there are two bands in the patient's normal tissue, whereas one band is missing if there has been DNA loss. He then showed a Southern blot from initial studies using this probe, showing DNA from both normal and tumor tissues from several patients. He pointed out a consistent decrease in band intensity in the tumor DNA. Tumor tissue from 60 kidney cancer patients was analyzed for loss of allele at different ordered loci on chromosome 3. In 51 of 58 evaluable patients, there was a loss of heterozygosity at one or more of the 10 loci, independent of tumor stage. Further analysis identified the distal portion of chromosome 3p, bounded by the markers D3S2 and D3S22, as the most likely region of the kidney cancer disease chain.

Dr. Linehan summarized that in tumor tissue and cell lines from patients with sporadic renal cell cancer, consistent loss of DNA on the short arm of chromosome 3 has been found, suggesting the presence of a kidney cancer tumor suppressor gene. He noted that abnormalities of this location have also been detected in lung cancer, breast cancer, and invasive bladder cancer.

The existence of a gene whose loss is associated with cancer, Dr. Linehan continued, suggests the hypothesis that replacing this gene by introducing a chromosome that carries it would reverse the carcinogenic process. He stated that researchers have demonstrated this to be the case in somatic cell transfer studies in which a whole chromosome 3 was transferred back into kidney cancer cell lines, with the result that tumor cells no longer grew in soft agar and no longer formed tumors in nude mice. This is one of the techniques, he added, that is being used to evaluate potential tumor suppressor genes in, for example, prostate cancer cell lines.

To more precisely define the location of the renal cell carcinoma gene, Dr. Linehan continued, studies of the familial form of renal carcinoma, associated with VHL, were initiated. The goals were to determine whether Knudson's hypothesis fits with this cancer—that is, to learn if there were DNA deletions on chromosome 3 among patients with this form of kidney cancer, to determine whether there was evidence of an inherited disease gene at this location, and, if so, to identify that gene.

Dr. Linehan showed a Southern blot from these studies of VHL patients, which used the probe described earlier. He observed that the study of nonfamilial patients showed a random DNA loss, sometimes occurring in the top band and sometimes in the bottom band. In this study, the loss was not random; in each case, the wild type allele, that from the nonaffected parent, was deleted in the tumor. This, stated Dr. Linehan, is consistent with the hypothesis that the origin of this malignancy is associated with loss of the wild type allele and the retention of an inherited, inactivated disease gene. This has been found in 15 of 15 VHL kidney tumors, as well as in tumors in the adrenal gland, cerebellum, and spine. These findings, Dr. Linehan concluded, are consistent with the hypothesis that there is an inherited disease gene that is associated with the development of these multiple cancers in this familial cancer syndrome.

A clinical trial was initiated to study VHL patients and at-risk family members. Dr. Linehan stated that DNA has been extracted from the blood of more than 3,700 individuals; 419 have been screened at NIH for the presence of VHL disease. Patients underwent a full clinical evaluation, including history, physical examination, imaging, and metabolic studies.

Genetic linkage analysis was used to localize the kidney cancer gene. This technique takes advantage of the normal recombination of genetic material during meiosis; if there are two markers, Dr. Linehan explained—for example, a disease gene and a DNA probe—the closer these markers are, the more frequently they will travel together from generation to generation. The known location of the marker is the key to identifying the disease gene. In order to evaluate loci on chromosome 3, NCI researchers had to develop their own reagents (the detailed genetic maps now available from the Human Genome Project were not available at that time).

Dr. Michael Lerman, at the Laboratory of Immunobiology in Frederick, isolated more than 2,000 single copy inserts—small pieces of DNA—from chromosome 3. The single copy DNA fragments were sorted into locations on the short arm and the long arm of chromosome 3 and then regionally mapped. These single copy DNA probes, Dr. Linehan explained, formed the basis of the researchers' cloning strategy.

Dr. Linehan presented linkage data using a probe for the protooncogene CRAF 1; the data show that CRAF 1 is very significantly associated with VHL disease. This finding, he said, is consistent with previous reports showing that RAF links with VHL. However, because CRAF-1 has a 12 percent recombination with RAF, it cannot be identified as the disease gene. Multipoint linkage analyses using multiple probes were used to identify the markers that were closest to the familial cancer disease gene; these analyses demonstrated that the location was in a 6-centimorgan region between D3S18, which is distal on the short arm of chromosome 3, and CRAF 1.

Dr. Linehan explained that the identification of probes that flanked the disease gene meant that it should be possible to identify carriers of the disease gene by DNA polymorphism analysis. The feasibility of this approach was tested in 48 patients from 16 VHL families who underwent evaluation in the Surgery Branch of the NIH Clinical Center. In 42 of 43 evaluable at-risk individuals, DNA polymorphism analysis accurately predicted disease status.

To illustrate the intramural effort that went into this project, Dr. Linehan pointed out that almost the entire region of the VHL disease gene locus was cloned. He also stressed the critical role of cooperation between clinical and basic research, noting that one encouraging candidate for identification as the VHL gene was removed from consideration because, in one family, there were meiotic recombinations of the gene.

In parallel with the cloning efforts, Dr. Linehan stated, the physical map of the region was established and researchers began looking for gross rearrangements of this region. These efforts resulted in the discovery of constitutional deletions in three unrelated VHL kindreds. It was reasoned that the smallest of these three deletions should either encompass or interrupt the gene; a DNA fragment was identified in the commonly deleted region that was then used to isolate different cDNAs. The candidacy of these cDNAs, or expressed genes, was evaluated by analyzing expression in target tissue and, most importantly, in activation mutations segregating with the disease phenotype.

The G7 gene, Dr. Linehan stated, proved to be a strong candidate for the familial cancer disease gene. In studies by Northern blot of the expression pattern of G7, transcripts were observed in all human tissues tested, including the brain and kidney, which are tissues frequently affected by VHL. Further analysis showed that the G7 gene is highly conserved across species; this evolutionary conservation is indicative of a basic life function and compatible with the tumor suppressor role.

Next, Dr. Linehan related, researchers performed an extensive search for inactivating mutations in constitutional DNA derived from 221 unrelated VHL kindreds, using Southern blot analysis with the G7 probe. They found a high incidence of aberrant bands that correlated with occurrence of the disease phenotype.

Dr. Linehan presented an example of a family in which the parents did not have the disease, a daughter had the disease phenotype and an aberrant band, and a granddaughter for whom it was too early to detect the disease clinically also had an aberrant band. To identify germ line mutations in the disease gene, he continued, researchers looked for additional DNA alterations from VHL lymphoblastoid cell lines to detect germ line abnormalities in this family. They found a germ line base pair insertion that results in a frame shift and downstream stop codon. This mutation was detected in each affected individual in this family. Dr. Linehan noted that for this family, linkage analysis would no longer be needed—disease phenotype determination could be accomplished through mutation analysis in the DNA.

Dr. Linehan stated that a germ line stop codon in the predicted protein is considered to be the "smoking gun" evidence for the identity of a disease gene. He stated that the mutation has been identified in the germ line in 47 of 130 kindreds currently being studied.

Finally, this analysis was performed in tissue from patients with sporadic nonfamilial renal cell carcinoma. A strategy was developed of polymerase chain reaction (PCR) amplification and DNA sequencing using genomic DNA isolated from kidney cancer cell lines, tumors, and matched normal kidney tissue as templates. The cloned portion of the VHL gene contains three exons, and PCR primers were prepared so that each exon could be amplified individually and the entire coding region could be analyzed.

Dr. Linehan explained that somatic mutations have been identified now in more than 50 cell lines or tumors from patients with sporadic kidney cancer. Mutations have been identified in 68 percent of the nonpapillary kidney cancer cell lines developed in the Surgery Branch. Most were distributed equally among the three exons, but they were concentrated over a 414 nucleotide span. These results, Dr. Linehan stated, strongly support the conclusion that the G7 gene represents the VHL tumor suppressor gene and that it is involved in the origin of nonfamilial kidney cancer.

The compiled sequence of the G7 cDNA, Dr. Linehan continued, revealed an open reading frame of 284 amino acids. Neither the nucleotide nor the predicted amino acid sequence showed any significant homology to genes with proteins in the databases. However, he stated, there is an acidic tandemly repeated pentameter that shows 48 percent homology to portions of the trypanosome procyclic surface membrane protein. This protein belongs to a novel class of membrane proteins that may function in signal transduction and intracellular targeting. The presence of this domain in the putative VHL protein suggests, Dr. Linehan stated, that it may be localized on the cell membrane and may be involved in signal transduction when establishing cell-to-cell contacts.

Currently, NCI researchers are working intensively to complete the analysis of this gene in cell lines and tumor tissue from patients with sporadic nonfamilial kidney cancer to develop antibodies for performing structure function and cell cycle studies and evaluation of the diagnostic potential of this disease gene. The identification of the VHL gene, Dr. Linehan stated, will have wide-ranging applications for the diagnosis and management of VHL disease and for understanding the fundamental abnormality associated with sporadic kidney cancer. This work, which Dr. Linehan said should lead to significant improvements in the prediction, diagnosis, and treatment of genitourinary malignancies, is the result of a 9-year communal effort. Dr. Linehan expressed appreciation for the work of many NCI colleagues and collaborators at Baylor, Cambridge University, and in Paris.

Dr. Linehan closed by stating that if these tumors are reached early, patients have a 93 percent 10-year survival rate, whereas those whose disease has spread have an 8 to 12 percent survival rate. The ability to detect this mutation, he said, could make it possible to diagnose the disease years before it develops into a large tumor.

Dr. Calabresi thanked Dr. Linehan for a very interesting presentation and opened the floor for questions.

Questions and Answers

Dr. Wells asked if he were correct in understanding that not all VHL families have the same mutation, and whether there is any phenotypic difference among the families. Dr. Linehan confirmed that not all families have the same mutation. He stated that most of the familial mutations are segregated to exon three, with some in exon one. Many of the mutations in sporadic tumors, he added, are in exon two.

Dr. Pitot asked if Dr. Linehan's group has been in contact with researchers working with the Eker rat, and whether those researchers are working with the same tumor suppressor gene. Dr. Linehan said scientists in his group are working with Dr. Knudson and others, adding that it is not clear whether the same gene is involved. He suggested that it will probably turn out to be a different gene.

VIII. NCI INVOLVEMENT IN CHERNOBYL—DRS. BRUCE WACHHOLZ AND JOHN BOICE

Dr. Adamson introduced Dr. Bruce Wachholz, Chief of the Radiation Effects Branch in the Division of Cancer Etiology, and Dr. John Boice, Chief of the Radiation Epidemiology Branch.

Dr. Wachholz began by explaining that he would discuss NCI's studies of populations in Russia, Belarus, and Ukraine that were exposed to radiation from the Chernobyl nuclear

power plant accident in 1986. Chernobyl, he continued, was a major nuclear facility in Ukraine comprised of four reactors supported by a large common building that linked the support facilities for all four reactors. This was the most severe nuclear power accident that has occurred to date, releasing massive quantities of radionuclides into the atmosphere. Millions of people were exposed to fallout as a result, and hundreds of thousands of workers were exposed to radiation at the facility in attempts to control the calamity, which required tremendous cost and effort. Seventy percent of the fallout occurred in the area of Belarus, with heavy concentrations also around Chernobyl in Ukraine and in the Bryansk area of the Russian Federation.

Dr. Wachholz explained that the damaged reactor currently is entombed in a large structure called the sarcophagus, which, unfortunately, contains large holes that allow birds and animals to go in and out of the structure freely. The government of Ukraine presently is negotiating with firms in Western countries to entomb the reactor in a second, more stable, sarcophagus.

The former Union of Soviet Socialist Republics (USSR) initially was not receptive to offers of Western assistance at the time of the accident, but Presidents Reagan and Gorbachev agreed on the need for joint studies in the field of civilian nuclear reactor safety in late 1987. A formal memorandum of cooperation between the United States and the former USSR was codified in 1988 under the auspices of the Peaceful Uses of Atomic Energy Agreement of 1973. The Nuclear Regulatory Commission served as the U.S. signatory on this agreement, while the USSR State Committee for the Utilization of Atomic Energy signed for the USSR. This led to the formation of a Joint Coordinating Committee for Civilian Nuclear Reactor Safety. This joint coordinating committee identified 12 areas of research, encompassing such issues as reactor design, construction, materials, etc. Working Group Seven addressed research on environmental and health issues, including Chernobyl. The Department of Energy (DOE) was requested to assume responsibility for Working Group Seven; DOE formed two task groups—one on the environment and one on health, each consisting of about 10 individuals. Andre Bouville represented the NCI on the environmental task group, and Gilbert Beebe and Robert Miller served as NCI representatives on the health task group.

The groups traveled to the former Soviet Union in September 1989 and returned with numerous recommendations for research in various areas. Two research recommendations concerning cancer focused on thyroid disease, especially cancer in children, and leukemia among the cleanup workers of Chernobyl—particularly those who were present in 1986 and 1987. Dr. Wachholz elaborated on the U.S. interest in these two issues, primarily because of the uniqueness of the population exposed and the conditions of the exposure. First, the risk of thyroid cancer in humans resulting from exposure to I-131 is unknown, although studies have shown that children are more sensitive than adults following x-ray exposures to the thyroid. Second, if large numbers of the public were to be exposed to radiation, it is likely to be the result of a reactor or reprocessing accident (such as the Chernobyl accident), in which case I-131 is one of the radionuclides most likely to be released.

Dr. Wachholz compared past accidental reactor releases of I-131. In 1957 in Windscale, England, about 20,000 curies of I-131 were released, and in 1979 at Three Mile Island, about 15 curies were released. In contrast, at Chernobyl in 1986, approximately 30 million curies of I-131 were released. There was, therefore, a factor of roughly 2 million between Three Mile Island and Chernobyl releases. More than 1 million children were exposed to radiation from Chernobyl; of those, approximately 130,000 to 150,000 children had their thyroids measured for radioactivity content at the time of, or shortly after, the accident. Dr. Wachholz commented that the validity of these measurements is questionable and that they will need to be assessed. He emphasized also that it is incumbent upon the U.S. to obtain as much information as possible from the Chernobyl tragedy so that risk coefficients can be

estimated for thyroid cancer resulting from exposure to I-131 so that public health authorities might be better informed should such an accident occur in this country.

In addition, Public Law 97-414 mandates that NIH conduct research and analyses to determine: 1) the risk of thyroid cancer associated with thyroid doses of I-131; 2) methods to estimate thyroid doses of I-131 received from fallout; and 3) the amount of exposure to I-131 that the American people received from atmospheric nuclear weapons testing in Nevada. The NCI formed an advisory committee to assist in implementing this mandate. The advisory committee examined data related to both medical and environmental exposures to I-131 up to that time and concluded that there was insufficient data on which to assess the risk of thyroid cancer. The committee was considering the usefulness of conducting large-scale animal studies to further investigate this issue when the Chernobyl accident occurred; thereafter, it focused on the possibility of obtaining information from the exposed populations.
Dr. Wachholz explained that, over the last several years, the NCI has reconstructed exposures and doses to the thyroids of the American people that were received from atmospheric nuclear weapons tests in Nevada, and that these methodologies are directly relevant to the situation in Chernobyl.

Dr. Wachholz described various routes by which people are exposed to radioactive iodine from fallout. Based on previous experimental work and on studies of populations in Utah, the dominant exposure route is the deposition of I-131 on vegetation, consumption of the vegetation by cows, concentration of the iodine in cow's milk, and subsequent ingestion by people. Dr. Wachholz emphasized that children are particularly vulnerable because of their increased ingestion of milk. Other exposure routes include the ingestion of leafy vegetables, inhalation, and aquatic pathways.

Dr. Wachholz indicated that there are gaps in our knowledge about the occurrence of leukemia, particularly following whole-body exposure to radiation received at low doses or dose rates. Most of our information, he continued, comes from studies in Japan following the bombings at Hiroshima and Nagasaki, which involved acute exposure. There are some occupational data regarding whole-body exposure, but these data relate to extremely low exposures (perhaps less than 1 to 2 rad per year) in limited numbers of workers. Dr. Wachholz commented that the effect of the dose rate on the occurrence of leukemia is unknown. Since the population of cleanup workers at Chernobyl were exposed to a variety of doses and dose rates over a period of days, weeks, and sometimes months, they might provide considerable information in this matter.

Dr. Wachholz provided several reasons for NCI's involvement in this study. Three NCI staff members were involved in the original task groups established by the Department of Energy. The NCI's experience in the fallout studies and its epidemiological expertise were also factors, as was the participation of NCI staff in the International Chernobyl Project carried out by the International Atomic Energy Agency in 1990. As a result, the Department of Energy requested that the NCI assume responsibility for working with Soviet counterparts to develop protocols for and implement long-term follow-up studies of thyroid disease, especially cancer among children, and to develop protocols for the study of leukemia. The Department of Energy provides financial support, particularly for equipment and supplies to the countries and institutions involved, and contributes a major portion of NCI's internal expenses in developing these programs.

A DOE-NCI interagency agreement was signed in 1990, and two working groups were formed—one focusing on thyroid and one on leukemia—which provided the major portion of scientific, medical, and technical advice. Approximately half of the members of these groups are experts from outside of the government and half are from the intramural staff at NIH, including Dr. Jacob Robbins, head of endocrinology at the Clinical Center; Dr. Gilbert Beebe, an epidemiologist, NCI; Dr. John Boice, NCI; and Dr. Andre Bouville, NCI.

Dr. Wachholz explained that interaction with the Soviets initially began in 1990. The disintegration of the USSR also occurred in 1991 and, thus, the NCI subsequently negotiated the development of the project with three newly formed governments that were organizing themselves politically and economically. A renegotiation of the initial agreement with each of the three government was conducted by the Nuclear Regulatory Commission, the Department of Energy, and the State Department.

Dr. Wachholz reported that none of the three countries involved has reported an increase in leukemia as a result of the Chernobyl accident. Increases in thyroid cancer in children, however, have been reported in both Belarus and Ukraine, although not in Russia.

Thyroid Cancer

Data on thyroid cancer in children from Belarus have been published, but information from Ukraine can only be considered preliminary. Starting in 1990, possibly 1989, the increase in cases is apparent, although it is not yet clear whether this is a real increase or if it may be, at least in part, a function also of other factors. The significance of radiation from Chernobyl has not been clarified with certainty, although circumstantial evidence has led many to attribute the increases in thyroid cancer to exposures from the accident. Dr. Wachholz explained that the x-ray studies to which he referred earlier in his comments have shown a 5- to 6-year latent period for thyroid cancer in children while the Byelorussian and Ukrainian data presented indicated a latent period of about 4 years; it also is not known to what extent more extensive and intensive screening has contributed to this observation, and no individual dosimetry has been conducted on any of these cases.

Dr. Wachholz then presented preliminary data on thyroid dose distribution from the Chernobyl accident among Ukrainian children with measured doses. Based on a total of approximately 67,000 children who were measured, Dr. Wachholz indicated that about 40,000 received 0 to 30 rad and 27,000 received in excess of 30 rad; approximately 9,500 received in excess of 100 rad. In contrast, studies of children in Utah exposed to I-131 from the atmospheric nuclear weapons tests conducted in Nevada have shown that, of several thousand children studied, approximately 10 children were estimated to have received doses of 100 rad or more.

Dr. Wachholz related that the NCI has been negotiating with Ukraine and Belarus to conduct both case-control and cohort thyroid studies. He noted that the studies in Belarus and Ukraine would be so similar that the data might be combined at some point. Case-control studies would be conducted in a limited timeframe of 18 to 24 months and would provide staff an opportunity to work with their counterparts in medical, scientific, administrative, and political settings.

One hundred and nineteen cases of children with thyroid cancer were identified in Belarus in the spring of 1992 for the case-control study. Approximately 50 cases were identified in Ukraine in early 1993; this number is expected to increase. Dr. Wachholz noted that there are essentially equal numbers of males and females in the case-control studies. NCI and West European pathologists have reviewed the pathology of the Byelorussian cases and essentially have verified the diagnoses. NCI is currently assisting Belarus and Ukraine to identify control subjects in each country and will begin reconstruction of doses for both the cases and the control subjects in terms of residence history, diet, sources of food, amounts consumed, etc.

The major focus of NCI's efforts, however, is on the cohort studies; the study group will consist of children who had thyroid measurements taken at the time of the accident—about 15,000 in Belarus and 60,000 in Ukraine. Dr. Wachholz indicated that the NCI hopes to

develop risk estimates for thyroid cancer in nodules and hypothyroidism as a function of dose, age at the time of exposure (including *in utero*), and gender.

Dr. Wachholz presented a slide with a more detailed listing of the type of studies included in the protocol. He mentioned that pathology and cytology review training began about 1-1/2 to 2 years ago with experts from Belarus and the Ukraine in various medical and scientific disciplines. The study, he continued, would involve on-site U.S. representation in Minsk and Kiev, with frequent expert interchange. A binational oversight group would be established in each country to monitor ongoing study activities.

The final form of the protocol in Belarus was agreed upon in early 1993 and submitted to scientific peer review. Results of the review are pending, but Dr. Wachholz indicated that there is strong support and encouragement to proceed with this potential study. He added that the NCI will be meeting with Ukrainian representatives in the near future to finalize that research protocol.

Leukemia Studies

Several hundred thousand workers participated in the cleanup of the Chernobyl accident—approximately 10,000 in Belarus, 140,000 in Russia, and 140,000 in Ukraine. There were another approximately 20,000 cleanup workers from the Baltic states, with the remainder of the workers scattered in other areas of the former Soviet Union. Although all of these workers may potentially be involved in studies of leukemia, Dr. Wachholz reported that NCI efforts have focused on the Ukrainian group, and that the U.S. Working Group has completed a draft of the research protocol that is being translated into Russian and will be the basis of a binational workshop early next year.

The proposed leukemia studies would consist of two phases. Phase I would be approximately 18 months long and would consist of several components related to sampling, dosimetry, and leukemia. Sampling would involve identification of cleanup workers and the review of existing registries in Ukraine. There are at least three of these registries in the country: 1) the Chernobyl registry, which includes people who were associated with or evacuated as a result of the accident; 2) cancer registries; and 3) dosimetry registries. Dr. Wachholz emphasized that it will be necessary to examine both physical and biological dosimetry. The most common physical dosimetry, he noted, is radiation badges, which are "notoriously unreliable"; therefore, efforts would be made to reconstruct radiation fields and to carry out dose reconstruction efforts based also on questionnaires and interviews. Biological dosimetry would potentially involve cytogenetics, somatic cell mutation, and electron paramagnetic resonance. Phase I would include the ascertainment of about 50 or 60 of the leukemia cases that have occurred between 1986 and 1992, and these cases would be examined for diagnostic review and consistency in terminology. Phase II would be a longer epidemiological design, the specifics of which would be dependent upon the findings in Phase I.

Dr. Wachholz concluded with a list of other domestic and foreign organizations and countries that are interested in working with Russia, Belarus, and Ukraine on health issues, including the World Health Organization, the Commission of European Communities, Japan, France, Germany, Italy, the Netherlands, and Switzerland. He emphasized that the NCI tries to maintain communication and interaction with all of them, particularly the Commission of European Communities.

Dr. Adamson then asked Dr. John Boice to continue with his portion of the presentation.

Dr. Boice reported on ongoing activities in the Baltic countries of Estonia, Latvia, and Lithuania, where 20,000 Chernobyl cleanup workers have been identified. The NCI is contacting the cleanup workers via questionnaire to obtain information on work histories and other cancer risk factors. Blood samples are also being collected to better estimate radiation exposure.

Dr. Boice presented an article that appeared in the *London Guardian* in the summer of 1993. Several hundred thousand workers were sent from 15 republics of the former Soviet Union over a period of 3 years to help in the cleanup effort. Workers on the roof of the reactor during the cleanup activities could receive as much as 25 rads of radiation within 90 seconds. Thus, if one were on the roof for 3 minutes, he would receive 50 rads of radiation. Dr. Boice explained that workers initially wore lead suits while on the roof, but the suits were cumbersome and were soon discarded. Americans who visited Chernobyl, he noted, more seriously considered the potential for radiation exposure.

For the past 2 years, the NCI has been collaborating with colleagues from Finnish and Estonian cancer registries on a study of the Estonian cleanup workers. Activities have recently been expanded to Latvia and Lithuania as well. Dr. Boice reported that, to date, nearly 5,000 Estonian workers have been identified, mailed questionnaires have been completed by 2,000 workers, and blood samples have been collected from 1,000 workers. A successful pilot study was recently completed in Latvia, where 8,000 cleanup workers were enrolled, and an ongoing feasibility study in Lithuania should track an additional 10,000 cleanup workers for investigation. Dr. Boice referred to these countries' nationwide cancer registries, which he said have been maintained for the past 20 years and serve to facilitate follow-up and cancer detection. He explained that the Baltic studies supplement the large-scale efforts presented by Dr. Wachholz and provide useful methodological information.

Dr. Boice noted that many Chernobyl cleanup workers were issued "passports," which recorded their time at Chernobyl and the radiation dose received. Preliminary tabulations of reported exposures in Estonia indicated a distribution that ranged up to about 35 rads of radiation, or .35 gray. Nearly 25 percent of those sent to Chernobyl had no record of their radiation exposure. Moreover, the accuracy of recorded doses is dubious. Thus, extensive biological dosimetry evaluations have been incorporated into the ongoing studies.

The glyco 4NA mutational assay, one of the evaluations being performed, is a somatic cell assay used to identify defects in certain blood alleles and red blood cells. Dr. Boice explained that radiation is thought to damage a stem cell by "knocking out" one of two glycoprotein alleles, M or N, that express on the membrane surface. The cells are dyed with monoclonal antibodies and 5 million of them are sent through a flow cytometer. The differences in light responses that are then observed, Dr. Boice continued, appear to be related directly to cumulative radiation damage and, therefore, provide a measure of lifetime exposures for the workers. This assay has been used successfully in studies of atomic bomb survivors in Hiroshima and Nagasaki, early accident victims at Chernobyl, and workers in the nuclear industry.

Dr. Boice explained that investigators are conducting chromosome translocation analyses using fluorescent *in situ* hybridization techniques as another indicator of Chernobyl's cumulative radiation exposures. There are plans to combine the personal interview information with the biodosimetry to estimate and assess radiation exposures at Chernobyl. Blood samples are being collected from all Estonian and Latvian workers, a portion of which are being stored for future evaluations.

Early returns of analyzed red blood cells indicate that exposures were higher than recorded. One hundred rads would have produced about 30 aberrant cells per million. Evaluations have revealed that exposures at Chernobyl were three to four times higher than

recorded estimates, and many workers received much more than 100 rads of radiation. Dr. Boice suggested that study of such workers has great potential for providing new knowledge about radiation effects of whole-body exposures received over a period of several months.

In addition to the cancer and biodosimetry studies, Dr. Boice noted that a study of approximately 1,000 Estonian cleanup workers is planned to determine the possibility of detecting radiation-induced thyroid nodularity in this group of relatively healthy young men. Scientists who participated in the international Chernobyl project from the International Atomic Energy Agency are willing to collaborate on this particular project.

Dr. Boice stated that ongoing record linkage activities are being used to identify cancers in Estonia, and preliminary linkage in Latvia has identified four leukemias to date, where less than one was expected. These record linkage capabilities are being incorporated with data obtained from the questionnaires, blood evaluations, and physical examinations. Dr. Boice concluded that the comprehensive evaluation of approximately 20,000 Chernobyl cleanup workers from the Baltics will be completed in about 3 years.

Dr. Calabresi thanked Drs. Wachholz and Boice for their presentation and opened the floor for discussion.

Questions and Answers

Dr. Becker inquired about the results of a study of Marshallese Islander children for thyroid carcinoma. This study looked at the accidental exposure of native populations in the South Pacific resulting from the firing of a U.S. hydrogen bomb. Dr. Boice acknowledged this 30-year study, in which the population is still being monitored and followed up. There were excess thyroid cancers and thyroid malignancies, he added, related to exposure to various iodines from the fallout. In addition to I-131, there was exposure to short-lived isotopes, which appear to be more carcinogenic because of their shorter dose rate. The minimum latent period there, Dr. Boice continued, was 9 years—longer than the latent period in the areas affected by Chernobyl. He concluded that the latency period in Belarus is questionably short. Dr. Boice proposed that the discrepancy is attributable to screening.

Dr. Salmon asked, based on dose exposure estimates, if Dr. Boice could provide projections of the incidence of thyroid cancer over the next 10 to 20 years in the populations in the areas surrounding Chernobyl. Dr. Boice explained that the incidence of thyroid cancer in these populations depends on dosimetry. If the children indeed received the amounts of radiation that Dr. Wachholz presented, there will likely be an outflow of thyroid cancers in that population. However, I-131 has an 8-day half-life and releases its dose very slowly to colloid cells and not necessarily to follicular cells. If the doses received were entirely from I-131, the incidence may be much lower. Dr. Boice reported that in studies of more than 35,000 adults exposed to radioactive iodine (diagnostic dose average of 1 gray), no excess thyroid cancers have been detected. He suggested that the adult thyroid gland may be less sensitive to the carcinogenic effects of radioactive iodine or any other radioactive exposures. Dr. Boice stated that it is, therefore, very difficult to estimate the incidence of thyroid cancers in these populations because it is based on so many qualifiers.

Dr. Wells asked if these thyroid tumors in children are much worse than what is normally observed. Dr. Wachholz answered that pathologists from the United Kingdom, Switzerland, Italy, and the United States have confirmed that these tumors, particularly those in Belarus, are unusually virulent.

Dr. Adamson commented that, in addition to its importance as a catastrophe, this issue is important to study for the potential provision of population-based data for the United States.

Dr. Calabresi concluded by mentioning that Dr. Adamson's picture appears on the cover of the September issue of *Cancer Research.* He then announced that subcommittee meeting times and locations would be posted. The open session of the meeting's first day was then adjourned.

IX. CLOSED MEETING—SPECIAL ACTIONS SUBCOMMITTEE

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 1,191 applications were received, requesting support in the amount of $288,706,550. Of those, 1,191 were recommended as being eligible for funding at a total cost of $261,722,386.

X. DEVELOPMENT OF RECOMBINANT VACCINES FOR CANCER IMMUNOTHERAPY—DR. JEFFREY SCHLOM

Dr. Alan Rabson provided a brief overview of the accomplishments of Dr. Jeffrey Schlom, Chief of the Laboratory of Tumor Immunology and Biology of the Division of Cancer Biology, Diagnosis, and Centers (DCBDC). Dr. Schlom is a virologist and performed his postdoctoral training with Dr. Sol Spiegelman, a pioneer in the study of reverse transcriptase. Dr. Schlom began working with retroviruses at the NCI and subsequently developed interest in diagnostic monoclonal antibodies. He has developed a major laboratory in immunodiagnostics. Dr. Rabson explained that in recent years, Dr. Schlom's interest has focused on viral vaccines, the subject of his presentation.

Dr. Schlom stated that he would discuss strategies for the development of recombinant vaccines for use in cancer therapy and potential prevention of the disease. He explained that the development of recombinant vaccines for cancer immunotherapy requires six steps: 1) identification of the appropriate tumor-specific or tumor-associated antigen; 2) cloning of the gene that codes for that antigen; 3) insertion of the gene in the appropriate vector (e.g., vaccinia virus) to amplify the antigen; 4) development of appropriate animal model systems to test immunogenicity, safety, and antitumor activity of the vaccine; 5) development of a clinical grade reagent; and 6) clinical trials. Dr. Schlom indicated that he would describe these steps in relation to three recombinant vaccines currently under development in his laboratory.

The first construct discussed was recombinant carcinoembryonic antigen vaccine. Dr. Schlom explained that the gene coding for the CEA was introduced into a plasmid. Cells were then coinfected with the plasmid and the vaccinia virus—the virus used for smallpox vaccine—and a recombinant vaccinia-CEA (rV-CEA) virus was obtained. The vaccine containing the rV-CEA virus was then administered to patients by skin scarification.

Dr. Schlom described the rationale for using the vaccinia virus as an expression vector. This virus has been used to eradicate smallpox worldwide and has been demonstrated to be safe and effective. The advantages of using vaccinia virus include: the potential for inserting a large amount of foreign DNA into the virus to generate a wide range of recombinant products; the accuracy of the replication; the efficiency of the posttranslational processing of the inserted genes; and, most importantly, the highly immunogenic properties of the

recombinant proteins. Dr. Schlom explained that the latter characteristic has been observed in some other viral systems with viral antigens and, recently, in his laboratory, with tumor antigens. He indicated that vaccinia proteins are among the most highly immunogenic proteins known to date. When a weak immunogen is combined with vaccinia, it becomes a stronger immunogen. Therefore, Dr. Schlom continued, the notion behind this strategy is to elicit a stronger immunogenic response—with release of cytokines and T-cell infiltration—than that produced by the tumor antigen itself, if the antigen elicits a response at all.

Dr. Schlom noted that CEA is the most widely studied human tumor antigen. It is a 180 kD glycoprotein, which is expressed in substantial quantities in 90 to 95 percent of colorectal, gastric, and pancreatic tumors, 70 percent of non-small cell lung cancers, and 50 percent of breast cancers. The fact that CEA is also expressed in high levels in fetal gut and in low levels in certain normal colonic mucosa may represent a problem in terms of potential cross-reactivity. Thus, in contemplating rV-CEA as a vaccine for cancer immunotherapy, several factors should be considered for potential failure. The first is tolerance to CEA. Since CEA is an oncofetal antigen expressed in normal tissue, the patient may express tolerance to CEA and an immune response may not be elicited with this vaccine. The second factor to be considered is the potential immune response to cross-reactive normal antigens such as normal cross-reactive antigen (NCA), a gene product that shares some homology with CEA. In addition, immune responses to certain normal colonic tissues may be elicited.

Dr. Schlom expressed that there is no way to know, *a priori*, whether there will be an immune response to the vaccine and what that immune response will be. He indicated that contrary to the failure rationale, there is a rationale for potential success with rV-CEA vaccines. There is no evidence of existence of tolerance to CEA. If tolerance does exist, however, it may be broken when the rV-CEA vaccine is administered. Dr. Schlom indicated that the main objective of incorporating the CEA gene into vaccinia is to avoid tolerance. He also maintained that in terms of cross-reactivity, there is evidence that the CEA epitopes are immunodominant over the normal antigens. Regarding the possibility of an immune response to normal colonic tissues, Dr. Schlom explained that the antigen density is substantially greater in colon cancer; it has been shown that antigen density is very important in terms of T-cell responses to targets. Therefore, normal colon may not represent an efficient antigen-presenting cell system.

Dr. Schlom explained that in order to test the efficacy of the rV-CEA vaccine, an experimental model in mice was used. Control animals were immunized with the New York City strain of vaccinia virus (V-NYC), the wild type vaccinia used in the smallpox vaccine, while the experimental group received the recombinant vaccinia CEA type of the same strain (rV[NYC]-CEA). The end result was to determine whether mice showed evidence of an immune response by stimulating T cells via a delayed type hypersensitivity (DTH) reaction. These studies indicated that mice required at least three immunizations with rV(NYC)-CEA in order to produce a T-cell response. Similar observations were reported in primate studies. Dr. Schlom stated that based on these results, it is expected that immune response will be elicited in patients after three immunizations.

Dr. Schlom expressed that there are no natural animal models to test for antitumor activity of the vaccine because there are no rodent tumors that express human CEA. An artificial model was, therefore, created in which the human CEA gene was transduced into a murine colon adenocarcinoma cell line. Dr. Schlom explained that an athymic mouse model could not be used because an immunologically intact animal was required. He indicated that the transduced cell line expressed CEA on the cell surface, and the CEA gene was not seen as a foreign antigen in this murine system, since tumors with the human CEA gene grew successfully in syngeneic mice.

To determine the effect of prior vaccination with rV-CEA on the growth of a transplanted murine adenocarcinoma cell line expressing human CEA, animals bearing CEA- and non-CEA-expressing tumors were immunized with the wild type vaccinia or with the recombinant CEA vaccinia construct. Dr. Schlom noted that both vaccines had no effect on the non-CEA-expressing tumors. Regarding the CEA-expressing tumors, animals preimmunized with the wild type construct exhibited tumor growth, whereas animals preimmunized with the rV-CEA construct showed no growth of CEA-expressing tumors. Dr. Schlom concluded that this study clearly indicated that the antitumor effect was due to the CEA gene inserted into the vaccinia virus.

Dr. Schlom explained that in order to determine whether the vaccine had any effect on established tumors, CEA- and non-CEA-expressing tumors were transplanted into mice. The tumors were allowed to establish and grow for 7 days. The animals were then immunized with the wild type or the recombinant CEA vaccinia construct. While there was no effect on CEA-negative tumors with either the wild type or the recombinant vaccine, there was substantial antitumor effect on CEA-positive tumors when the rV-CEA construct was administered. The antitumor effect was long lasting up to 105 days, at which time animals received another injection of tumor cells and were kept under observation for an additional 105 days. No tumors were reported to have developed in this period of time. Dr. Schlom stressed that these studies have demonstrated both prevention of and therapy for an established tumor in the rodent model.

Dr. Schlom indicated that Rhesus monkey studies were also performed. He explained that these studies were critical because they represented study of a higher species that is philogenetically closer to man and, most importantly, because Rhesus granulocytes express the NCA normal cross-reacting antigen that is also found on human granulocytes. Thus, the nonhuman primate could be used as a model to determine the effects of rV-CEA immunization in terms of immune responses to CEA and NCA, as well as toxicity. Dr. Schlom noted that there was no toxicity reported in these animals, which were observed for more than a year. In addition, substantial immune responses to CEA, but not NCA, were reported.

Dr. Schlom summarized the preclinical findings of the mouse and primate studies, indicating that in both experiments lymphoproliferative responses were observed and no toxicity was reported. Antitumor activity was demonstrated in the mouse model, both in terms of prevention and therapy. In addition, data have indicated that the rV-CEA construct is more efficient than the native CEA as a primary immunogen. Dr. Schlom cited other studies that have shown that anti-idiotype antibodies (antibodies against the anti-CEA antibody) can function as an efficient boost following primary immunization with recombinant vaccinia virus. Dr. Schlom explained that he is planning to use these anti-idiotype antibodies as a secondary boost in the clinic.

Dr. Schlom stated that the Phase I clinical trial has been initiated and is headed by Dr. Mike Hamilton. Dr. Schlom acknowledged Drs. Chabner and Rabson, and the Division of Cancer Treatment personnel for their collaboration in the joint effort being pursued between DCT and DCBDC.

Dr. Schlom presented a slide of the first patient immunized with the rV-CEA construct showing the vaccinia reaction and a substantial T-cell infiltration. He indicated that seven patients—breast, colorectal, and lung cancer patients—have received the first cycle of the first dose of the vaccine and will soon initiate the second cycle, while another group of patients is being treated with a second dose that is one log higher than the first dose administered. Dr. Schlom noted that analyses of immune responses in these patients are underway. He also stated that in addition to the anti-idiotype antibody, recombinant CEA protein and peptides are under clinical development and he hopes to have them in the clinic in approximately 1 year to use as secondary boosts for the rV-CEA vaccine. Dr. Schlom indicated that novel avian pox

viruses with potentially more immunogenicity than the vaccinia virus are currently being developed.

Dr. Schlom next referred to the second recombinant vaccine under development in his laboratory. He mentioned that the point mutated *ras* oncogene, probably the most widely studied oncogene, is being developed as a target for active specific immunotherapy. Studies have shown that the point mutated *ras* is a cofactor in many human tumors; it is not expressed on the cell surface but is processed in the cytoplasm and presented to the surface as a peptide in context with the major histocompatibility Class I or II (MHC) molecules and, therefore, may function as a target for T cells.

Dr. Schlom stated that 95 percent of the mutations in human tumors are at position 12, of which approximately 80 percent are represented by a few different mutations. For instance, when the glycine (GLY) at position 12 in the normal *ras* gene is changed to a valine (VAL), it becomes an oncogene. Dr. Schlom presented a table with the frequency of the point mutated *ras* oncogene in specific cancers, including pancreatic (86 percent), colon (33 percent), and endometrial (23 percent) cancers. He indicated that approximately 140,000 new cases of cancer with position 12 mutation are reported each year, and the current total number of cases is approximately 826,000.

Dr. Schlom summarized the data on the mouse model. He explained that the normal *ras* has never functioned as an immunogen in this system. Similar observations have been reported from human *in vitro* studies; there is no immune response to the normal *ras* oncogene. However, immune responses have been observed with the point mutated *ras* oncogene, including T-cell responses specific for the GLY-to-VAL mutation as well as other mutations. Dr. Schlom stated that T-cell lines and clones that are CD4 positive have been established. These cell lines have lytic immune reactions that are very specific to a particular type of mutation. Dr. Schlom mentioned that ongoing studies have revealed that human T cells recognize the point mutated *ras* oncogene as a foreign antigen, and these T cells are lytic to target cells. Several human T-cell lines have been established against the mutated *ras* forms. These T cells can induce secretion of interleukin-2 (IL-2), IL-6, and gamma interferon. They can also elicit a cytotoxic effect against target cells which express the corresponding point mutation. Dr. Schlom stressed that the point mutated *ras* oncogene represents, therefore, a potential target for a vaccine, either as a peptide in conjunction with an adjuvant, as a recombinant protein, or as a recombinant vaccinia construct. He observed that the three vaccine forms are being pursued.

Dr. Schlom concluded his presentation by stating that there are T-cell costimulatory molecules, such as B7 and cytokines, which have been cloned. The cytokine genes can be expressed in vaccinia virus. He indicated that a vaccinia virus construct containing both a tumor antigen gene and a cytokine gene (e.g., IL-2) has been generated. This combination of genes will elicit not only an extensive immune response, but also a burst of cytokine expressed by the vaccinia virus in the local reaction. The advantage is that there is no systemic toxicity of the cytokines while they are localized in the vicinity of the T cells attacking the vaccinia virus protein and the tumor antigen protein.

Questions and Answers

Dr. Wells asked Dr. Schlom whether point mutations occur with other cytoplasmic oncogenes. Dr. Schlom responded that Dr. Berzofsky has demonstrated that *p53* can function in a similar fashion to the point mutated *ras* oncogene with certain specific mutations. Dr. Wells asked Dr. Schlom whether it could be assumed that any point mutation would be suitable for immunotherapy. Dr. Schlom explained that there are basically three major mutations that can be identified very quickly by polymerase chain reaction techniques; patients can then be selected for a particular vaccine protocol on the basis of their specific mutation.

Dr. Wells asked Dr. Schlom if he knows why the point mutations are immunogenic. Dr. Schlom explained that the *ras* oncogene by itself is not really an oncogene, but is part of the neoplastic process and it just happens to be immunogenic. Dr. Schlom added that the real question is why tumors are not regressing if the *ras* oncogene is so immunogenic. He stated that since there are different degrees of immunogenicity, certain immune responses that were not evident before could be discernible if the immune system is propelled. He noted that this is the rationale behind the cytokine gene approach in vaccinia constructs.

Dr. Wells asked Dr. Schlom whether immune surveillance plays any role, since mutations might occur in several oncogenes. Dr. Schlom stated that immune surveillance might be taking place continuously and that the only evident immunogens are the weak immunogens that escape the immune response.

Dr. Broder stated that Dr. Schlom's vaccine approach might be adapted for almost any situation in which there appears to be a consistent mutation. He recommended that Dr. Schlom explore other potential molecular targets, such as *bcr-abl*, where there is some predetermined expectation of the specific kind of mutation. However, Dr. Broder continued, it will not be easy to adapt this approach to other situations. Dr. Broder also mentioned the issue of prevention; he noted that, for example, it would be a great contribution to reduce the colorectal cancer death rate in the United States by one-third. Dr. Schlom replied that the work of Dr. Bert Vogelstein at Johns Hopkins has shown that the *ras* point mutation is an early event in colon carcinogenesis; therefore, it can be identified and diagnosed at an early stage. Dr. Schlom indicated that there is a test presently available that can identify the point mutated oncogene from blood or gut cells by PCR, and a biopsy will probably no longer be required.

Dr. Salmon asked Dr. Schlom whether evidence exists that cytolytic immunity can act against intracellular targets such as the mutated *ras*. Dr. Schlom indicated that there is extensive evidence in various systems, including *ras*, that demonstrates that intracellular molecules can act as targets for immunity. He explained that the target is not the intracellular protein, but the peptides formed in the cytoplasm by cleavage of the protein, which are then transported in association with the MHC molecules to the cell surface.

Dr. Salmon asked Dr. Schlom whether the patient population for the rV-CEA vaccine clinical trial will be assessed by means other than the development of an immune response; he asked whether the patients have circulating CEA or tumors that can be evaluated. Dr. Schlom responded that there is no indication that circulating CEA is an important criterion. Dr. Hamilton then added that all 14 patients in the clinical study have measurable disease and all have circulating CEA; therefore, there will be measurable responses in these patients. He also mentioned that assessment will be performed after the third immunization is completed; there is no efficacy information available yet. However, four patients under treatment have developed new symptoms and their evaluation has revealed tumor progression, but these patients have not been assessed for immune responses.

Dr. Becker asked Dr. Hamilton what percentage of the cells in the human tumors stained negative to CEA. Dr. Hamilton replied that virtually 100 percent of the cells stained positive to CEA; he explained that CEA is a very homogenous antigen in terms of its expression, which is one reason CEA was selected as a target. Dr. Becker asked Dr. Schlom whether there has been evidence of downregulation of CEA. Dr. Schlom answered that there is no evidence of downregulation, but he has induced upregulation of CEA with human alpha and gamma interferons.

Dr. Chabner asked Dr. Schlom whether there is any evidence for inherent T-cell responses in patients who have CEA- or *ras*-positive tumors. Dr. Schlom indicated that the data available on antibody responses to CEA are controversial and that there are no data on T-cell responses. In terms of the *ras* oncogene, no *in vivo* human data are yet available.

Dr. Schlom explained that this information will be obtained as soon as the clinical trial is completed.

Dr. Calabresi commented that the NCI will follow this work with great interest and thanked Dr. Schlom for an excellent presentation.

XI. RECENT STUDIES WITH ANTI-B1 ANTIBODIES—DRS. MARK KAMINSKI AND OLIVER PRESS

Dr. Broder welcomed Dr. Mark Kaminski, associate professor of internal medicine at the University of Michigan Medical Center, and Dr. Oliver Press, associate professor of medicine at the University of Washington School of Medicine. Dr. Broder stated that his philosophy is that novel approaches to basic science are best induced through solid clinical observation. The purpose of the presentation, he continued, is to see the response rates firsthand, identify certain topics for future research and seek advice as to how the Institute should go about capitalizing on these discoveries, and discuss logistical problems related to the supply and availability of the approach.

Dr. Kaminski began by reporting that he and his colleagues have developed what could be a powerful weapon in the fight against non-Hodgkin's lymphoma. He stressed the impact of this disease in the United States, stating that this year, 40,000 new cases of non-Hodgkin's lymphoma will be diagnosed, resulting in approximately 20,000 deaths. The incidence of lymphoma is on the rise, and it now ranks fourth in terms of economic impact among cancers in the United States because it strikes people in their most productive years.

In describing why new therapies are needed, Dr. Kaminski said that there are two types of non-Hodgkin's lymphoma—low grade and intermediate/high grade—neither with a very good cure rate. There is no definitive curative treatment for low-grade lymphoma, and for intermediate- or high-grade disease, half of all patients either fail to achieve a remission, or relapse after remission. Bone marrow transplants have had some very promising results, but are limited to certain patient subsets.

Dr. Kaminski noted that more than 80 percent of non-Hodgkin's lymphomas are proliferations of malignant B cells, a fact that has driven many of the attempts to defeat this disease. Monoclonal antibodies have been developed that can bind various antigens expressed on the surface of both normal and malignant B cells, and these antibodies have been used to attempt to recruit the immune system to destroy the cancer; however, results have been brief and usually transient. To remediate this problem, investigators have tried to modify these monoclonal antibodies. One approach has been to tag them with lethal radioisotopes, because lymphomas are very radiosensitive. Thus, the field of radioimmunotherapy—cancer treatment using cancer-seeking radioactive antibodies—was developed.

Dr. Kaminski stressed three important concepts involved in this approach. First, the antibodies should home in on the specific target, a target not present on normal cells. Second, the radiation emitted by the particles must be energetic enough to damage cancer cells, yet have a limited range. Third, the antibodies must be able to recruit the immune system to destroy the cancer cells.

Dr. Kaminski observed that, over the years, many people have tried treating lymphomas with various antibodies and isotopes, but most responses have been of a transient nature with the accompanying side effect of pronounced myelosuppression. Dr. Kaminski stated that his group had experienced the same result, but then began to study the anti-B1

antibody. The anti-B1 antibody binds to the CD20 cell surface antigen expressed by more than 90 percent of normal and malignant B cells but not to anything else. Unlike other antibodies, it does not cause the antigen to disappear from the surface of the cell. In addition, it is of the IgG 2a isotype, which can promote immune cellular and complement-mediated lysis.

Anti-B1 is expressed on normal B cells, Dr. Kaminski continued, but not on stem cells, so there will always be a replenishing pool of unaffected stem cells. A slide was presented showing the structure of CD20, which spans the membrane outside and inside the cell, and is tethered within the membrane; therefore, it cannot come inside the cell and it cannot be spit out of the cell.

Dr. Kaminski next explained the objectives and design of his group's clinical trial, in which investigators hope to: assess the targeting potential of anti-B1 labeled with I-131; determine whether there is an effect of unlabeled anti-B1 pretreatment; determine the maximum tolerated radiation dose without bone marrow transplant support; and assess tumor responses. The trial, Dr. Kaminski continued, is designed with two phases for each patient entering the trial—a tracer phase and a radioimmunotherapy phase. In the tracer phase, anti-B1 is injected with no pretreatment of unlabeled antibody. One week later, patients are scanned to determine the location of the radiation and the clearance of the radioisotope. Another injection is then given of the trace-labeled dose, preceded by 135 milligrams of unlabeled anti-B1. Patients are then surveyed again and given a third injection in which the tracer dose is preceded by higher amounts of unlabeled anti-B1. The investigators then assess which dose results in the highest tumor-to-whole-body ratio, and then use that dose to scale up the dose for therapy. To be eligible for the trial, patients must be adults with any grade non-Hodgkin's lymphoma who have failed or relapsed after one prior chemotherapy regimen and have tumor bearing the CD20 antigen. To avoid excessive myelosuppression, they must also have less than 25 percent of their marrow involved by the lymphoma.

Dr. Kaminski next showed a gamma camera scan taken immediately after injecting 5 millicuries of anti-B1 into a patient. The radiation could be seen predominantly in the blood pool, heart, and lungs, but none in tumors. Twenty-four hours after injection, the radioisotope was clearing from the blood pool and traces could be seen in the lymph nodes, pelvis, and neck. By 72 hours, much of the radioisotope had disappeared from the blood and was retained by tumors in the pelvis, axilla, and neck. Dr. Kaminski stated that it has been possible to image any tumor greater than 2 centimeters in all of the patients in his study.

Through predosing, Dr. Kaminski said, they are trying to increase the tumor-to-whole-body dose. The theory is that the anti-B1 antibodies are trapped by the spleen, preventing most from getting to the tumor. If the spleen is saturated with unlabeled antibody, a bypass situation occurs in which labeled antibody will not be trapped by the organ and more will get to the tumor.

As an example, Dr. Kaminski discussed a patient with an enlarged spleen. The patient was administered 5 millicuries and, 1 hour after injection, it had all collected in the spleen; when 135 milligrams of unlabeled antibody was used as a pretreatment, however, the spleen became saturated and, 1 hour later, much more anti-B1 had gotten into the bloodstream.

Twenty three patients, Dr. Kaminski remarked, have been entered into the study, of whom 22 are fully evaluable. Thirteen of the 22 have low-grade histology; 9 have intermediate-grade histology. Of these patients, almost half have chemotherapy-resistant disease, and more than one-third have very high tumor burdens of more than 500 grams. Of the 22 patients entered, 16 have received the radioimmunotherapy dose. Of the remaining six, three developed a human antimouse antibody (HAMA) response and three were so sick that they fell out of physiologic status for a Phase I study. The whole-body dose administered to patients thus far has been between 25 and 65 centigrade and the radioactivity dose between 34

and 93 millicuries. The total antibody dose, including all tracer studies and the radioimmunotherapy dose, has been between 15 and 1,500 mg.

Dr. Kaminski then discussed treatment response. Fifteen of the 22 patients, nearly 70 percent, have had a complete or partial response. Of the 16 patients who actually received radioimmunotherapy, 13, or more than 80 percent, have had a dramatic response. Eight of these 13, or 60 percent, have had complete remissions after the radioimmunotherapy dose. Many of the patients have been followed for more than a year with no evidence of progression of disease.

Dr. Kaminski then discussed side effects, which he said are practically nonexistent. The hematological toxicity, which is the dose-limiting toxicity, has been extremely minor. Only three patients have had grade III toxicity and only for a very short period. Most patients have had either no toxicity or grade I toxicity, leaving significant room for dose escalation of the radioactivity.

Both histologies responded to this treatment, Dr. Kaminski reported, including four patients with more than 500 grams of tumor and seven who are chemotherapy-resistant. Important information can also be learned from the nonresponders, Dr. Kaminski noted. Most nonresponders had intermediate-grade histology, some had bulky disease, and some had resistance to chemotherapy, but in all nonresponders the targeting was clearly not as good as in the patients who did respond.

Dr. Kaminski then presented examples of some of the dramatic responses achieved. A CT scan of a patient prior to treatment showed a tumor that Dr. Kaminski said weighed approximately 1 pound. The same patient after just one treatment had a dramatic decrease in tumor size. Another example was that of a patient with a total body burden of more than a kilogram before treatment. The patient was chemotherapy resistant, growing through cis-platinum treatment, but showed much improvement after antibody treatment. Remarking that the treatment doesn't only work in one area of the body, Dr. Kaminski showed a patient with a huge abdominal mass obstructing his ureters. After treatment, the CT scan showed no signs of tumor.

Dr. Kaminski then discussed the importance of the tracer studies. A number of patients responded to tracer doses before receiving radioimmunotherapy doses. Many of these patients have had either a complete response or a major response prior to receiving the radioimmunotherapy dose. As an example of how quickly the therapy begins to work, Dr. Kaminski showed an example of a patient who, 1 hour after injection with unlabeled antibody began to have intense pruritus, swelling, erythema, and heat over each of his cutaneous B-cell lymphoma lesions. This patient went into a complete remission in his skin and has remained free of evidence of cutaneous B-cell lymphoma for 8 months.

In conclusion, Dr. Kaminski said that anti-B1 meets many of the criteria for a good radioimmunotherapy reagent, especially for lymphoma. It has wonderful radioimmunotherapeutic properties, can recruit the immune system, and can induce apoptosis potentiated by radiation. Radioimmunotherapy with anti-B1 radiolabeled with I-131 is a promising new treatment for lymphoma and may have diagnostic usefulness. This treatment is highly effective, with minimal toxicity when used at nonmarrow-ablative doses, and opens the door for combination therapy or for use on a repetitive basis if a patient should relapse.

Dr. Calabresi thanked Dr. Kaminski for his presentation and asked Dr. Press to begin, with questions for both speakers to follow.

Dr. Press began by saying that his group has been similarly encouraged by their studies with the same reagents Dr. Kaminski has been using, but through a different approach. Studies in the mid-1980s, he reminded the audience, with unmodified anti-CD20 antibody showed that some patients with non-Hodgkin's lymphomas could achieve partial temporary responses even without radioactivity. In unrelated studies, high doses of conventional chemotherapy have been able to cure a fraction of patients with otherwise incurable non-Hodgkin's lymphoma, but dose escalations have been prohibited by toxicity. Dr. Press said he and his colleagues hypothesized that selective targeting of radiation or chemotherapy to tumor sites with antibodies might allow dose escalation and improve cure rates. They used very high doses of antibody and radioactivity with bone marrow rescue to try to achieve the highest complete response possible.

Dr. Press stated that a Phase I study has recently been completed in patients with relapsed lymphomas to determine the maximally tolerated dose, the dose-limiting nonhematopoietic toxicity, the biodistribution, the pharmacokinetics, and the efficacy of radiolabeled anti-B-cell antibodies. Patients eligible were those who had B-cell lymphomas binding one of the antibodies, had relapsed after conventional therapy, had evaluable disease, and had less than 25 percent marrow involvement with lymphoma.

In describing the study design, Dr. Press stated that all patients initially underwent bone marrow harvesting and purging, followed by two phases of the study. Initially, patients underwent a trace-labeled series of studies during which, in successive weeks, they were administered .5, 2.5, or 10 milligrams per kilogram antibody trace-labeled with 5 or 10 millicuries of radioiodine. After each infusion, gamma camera imaging and tumor biopsies were used to assess the biodistribution of antibody in tumor and normal tissue, and observed doses were calculated that would be received by each normal organ and each tumor site. Patients were then labeled as having either a favorable or nonfavorable biodistribution. Patients with nonfavorable biodistributions were assigned to other therapies, while those with favorable distributions were eligible for the second phase of the study, and received the therapeutic infusions of B1 antibody.

Dr. Press next described the radiation doses. In all but three patients, he said, the limiting normal organ was the lung. Each patient started out receiving 1,000 centiGray (cGy) to the normal organ getting the most radiation, and doses were escalated until toxicity was observed. Patients were kept in the hospital until their activity was less than 30 millicuries and were readmitted if they needed bone marrow rescue.

Forty-three patients entered the tracer phase of the study, with a mean age of 47. Approximately 70 percent had low-grade lymphomas, and approximately 30 percent had intermediate grade; all had advanced stages of lymphoma. Seventy percent were poor-prognosis cases, as evidenced by their high lactate dehydrogenase levels, and all had been heavily pretreated, receiving an average of three prior chemotherapy regimens.

Dr. Press noted that his group studied five different types of antibodies before settling on the B1 antibody. Based on data obtained from gamma camera imaging and biopsies, the radiation to each tumor and normal site was calculated. Only those patients in whom each assessable tumor site was exposed to more radiation than any of the critical normal organs were eligible for radioimmunotherapy, because of the availability of potentially curative conventional transplants.

Dr. Press discussed the three main observations from the biodistribution trace-labeled studies. First, they found that a higher dose of anti-CD37 antibody than anti-CD20 antibody was necessary to achieve a favorable biodistribution. Second, the size of the spleen had a major impact. Five patients splenectomized before treatment all had favorable biodistributions, compared with 17 of 22 who had normal spleens. Only 2 of 16 patients with

massive splenomegaly had favorable biodistributions. Third, tumor burden, as assessed by tumor volumetrics, had a substantial impact on biodistribution. Twenty-three of 31 patients whose tumor burdens were less than 500 grams had favorable biodistributions, whereas only 1 of 12 patients with tumor burdens over 500 grams had a favorable biodistribution.

Twenty-four of the 43 patients met criteria for the therapeutic arm, and 19 patients were treated. In the upper-dose levels, 9,000 cGy were delivered to the tumor sites. Of the 19 treated patients, 16 had complete responses, two had partial responses, and one had a minor response of 40 percent reduction of tumor (which proved sufficient to alleviate his symptoms and prevent regrowth for a year and a half). The median response duration for all patients studied is more than 12 months, and for the patients treated with B1 antibody it is greater than 16 months.

Dr. Press then discussed the durability of the responses, noting that nine patients remain in continuous complete response without further intervention or relapse. One patient is 5 years posttreatment without further intervention and without relapse, and several others are 3 to 3-1/2 years posttreatment. Seven patients relapsed after remissions lasting 4 to 18 months; three relapsed and died.

Dr. Press next commented on the toxicity of the treatment. All patients had predictable myelosuppression, he said. All but four patients had nausea, and fever was mild in most patients. Asymptomatic transient elevations of transaminases were observed, as were infections, most of which were minor. One-third of the patients developed hypothyroidism, and one-third developed human antimouse antibodies. The dose-limiting toxicity was cardiopulmonary. One patient, 2 months after therapy, developed idiopathic pneumonitis and a cardiomyopathy. Both resolved, but resulted in termination of the study.

Dr. Press then reviewed the myelosuppression findings from the study. In the first two dose levels it took approximately 1 month for the white cell count to reach its nadir; many of the patients then recovered spontaneously. But in the other dose levels, myelosuppression occurred by day 10; then, after bone marrow reinfusion, reconstitution occurred over the next 3 weeks.

Dr. Press said that conclusions drawn from the study include: 1) 24 of 43 patients receiving trace-labeled infusions met criteria for treatment, with 18 of the 19 patients receiving treatment having either a partial or complete response; 2) myelosuppression was manageable with marrow reinfusion; and 3) the maximally tolerated dose appears to be about 2,725 cGy to the lungs.

Looking only at patients receiving B1 antibodies, Dr. Press continued, 26 patients were evaluated, 15 were favorable, and 12 were treated. Ten of the 12 had complete remission and eight remain in continuous complete remission. The median remission duration is greater than 16 months.

Dr. Press reported that a Phase II trial is currently being conducted and, at the maximum tolerated dose, seven patients have been treated and the results appear comparable. His group hopes, he said, to increase the fraction of patients eligible for the treatment by splenectomizing those with large spleens, administering cytoreductive chemotherapy to those with very large tumor burdens, and, perhaps, using cold B1 preinfusion.

Questions and Answers

Dr. Salmon asked whether the generation of HAMA could be related to the remission duration, failure to achieve complete remission, or to an unrelated phenomenon. Dr. Press

responded that no pattern in terms of duration or response could be discerned in those who developed HAMA after treatment. Dr. Kaminski added that two patients who developed HAMA went into partial remissions, showing that HAMA does not necessarily preclude a positive response.

Dr. Calabresi asked if external radiation had been tried. Dr. Press answered that because they are trying to determine the maximally tolerated dose, patients who had substantial prior radiation were ineligible. Dr. Kaminski also noted that they did not have the opportunity to look at radiation-resistant disease.

Dr. Ihde asked if the presenters knew why the majority of responders in both studies had low-grade lymphoma. Dr. Kaminski said that an answer would be pure speculation. He added that patients with intermediate-grade lymphoma can respond, but that it would take a larger number of patients to determine the benefit for each type of lymphoma. Dr. Press commented that they were referred more patients with low-grade lymphoma for the study than intermediate or high grades. There is no exclusion for histologic subtype, except possibly someone with Burkitt's syndrome whose tumor burden is doubling on a rapid basis.

Dr. Becker asked if patients who relapsed were given a second infusion of the radioactive antibody. Dr. Kaminski answered in the affirmative and noted that one patient who had relapsed and was retreated did not mount a HAMA response and did respond to retreatment.

Dr. Thomas Waldmann, commenting on possible improvement of the already impressive complete responses, said that the first issue would be choice of the isotope. Other than the fact that it can be used to directly label an antibody, he said, I-131 is not as attractive as yttrium, rhenium, or copper 67. I-131 is a strong gamma emitter requiring lead lining and long inpatient admissions and a short beta emitter. In comparing I-131 with yttrium 90, Dr. Waldmann said, researchers have been unable to effect a reduction of hepatoma tumor size with I-131 in mice, yet could get cures with yttrium 90.

Dr. Press acknowledged Dr. Waldmann's comments as valid, and noted that when these studies were begun several years ago, I-131 was clearly the gold standard. He added that the jury is still out on which, currently, is the best isotope.

Dr. Waldmann added that, in the future, the antibody should be humanized, various kinetic models should be studied, and the isotope should be switched.

Dr. Broder asked how this treatment could be generalized for breast, prostate, lung, or colon tumors—the cancers that are generating most of the morbidity in this country. Dr. Kaminski said that much can be learned from the experience with lymphoma, primarily the apoptotic mechanism and the identification of antigens that have transmembrane signals.

Dr. Schlom added that he believes the key in the solid tumor models is multiple administration, and noted that all of the trials that have been done thus far have been single or double injection only.

Dr. McKinnon asked about the rates of non-Hodgkin's lymphomas in children and potential contraindications for eventual use of this approach in children. Dr. Kaminski said that lymphoma is on the rise everywhere, and that this therapy should be entertained; however, with this approach one must be sure that the growth plates are not affected. There are also problems with potential sterility and long-term effects. Radiation is not totally benign, he remarked.

Dr. Salmon asked if splenectomizing patients would be helpful. Dr. Kaminski responded that splenectomy would improve distribution of antibody significantly. A second approach, he said, would be to give a nonmyeloablative radioactive dose to shrink the spleen sufficiently prior to administration of a radioimmunotherapy dose.

Dr. Chabner stated that if this treatment were given earlier in the course of the disease, splenectomy would not be necessary.

Dr. Calabresi asked about debulking patients with chemotherapy prior to B1-antibody administration. Dr. Kaminski responded that he has found that the bigger the tumor, the better the response, because of the cross-fire effect, so he would opt for using chemotherapy after B1-antibody therapy. Dr. Press noted that if the tumor masses get too big, there are penetration problems in delivering the antibody to the center of the tumor. He said that in two patients with unfavorable biodistribution, large tumor masses were cytoreduced and, after the reduction, they had favorable biodistributions and were treated with radiolabeled antibodies.

Dr. Kaminski concluded that there is room for combination therapy involving B1 antibodies.

XII. MINORITY CLINICAL TRIALS RECRUITMENT—DRS. OTIS BRAWLEY AND EDWARD TRIMBLE

Dr. Peter Greenwald introduced Dr. Otis Brawley of the Community Oncology and Rehabilitation Branch (CORB) and Dr. Ed Trimble of the Division of Cancer Treatment Cancer Therapy Evaluation Program (CTEP) to present an update on the accrual of minorities to clinical trials.

Dr. Brawley began with an overview of the Minority Community Clinical Oncology Program (MCCOP), which was started in 1990 as an offshoot of the Community Clinical Oncology Program (CCOP) begun in 1982. The MCCOP is a clinical group of physicians, hospitals, and health maintenance organizations that meet periodically, agree to work together placing patients into NCI-sponsored clinical trials, and, thus, apply to the NCI for a cooperative agreement that funds this effort.

The NCI funded 12 minority-based CCOPs in 1990 for the purpose of enhancing minority accrual to clinical trials. These CCOPs have also served as a basis for the Office of Cancer Communications (OCC) and the Division of Cancer Prevention and Control in the study of minority accrual to clinical trials and of the health care providers who care for minority patients. Today, minority-based clinical oncology programs accrue approximately 10 percent of all ethnic minorities in NCI-sponsored clinical trials.

A key aspect of the minority-based clinical oncology program is that more than 50 percent of the participating physicians' patients are minorities. A log of minority-based clinical oncology programs was initiated in 1991 to look at new cancer patients presenting for treatment. The patient log is used as a resource for studying characteristics of minority patients and identifying barriers that they encounter upon entering clinical trials; it also provides better understanding of the dynamics of minority accrual to clinical trial.

Each new cancer patient conveys basic information that is recorded and entered into a database. This patient data includes age, gender, race, medical care payment and source, primary cancer diagnosis and stage, protocol availability and eligibility, comorbid conditions, treatment disposition, and clinical trial activity. In the case of the CCOPs, protocol availability

consists of what the cooperative groups offer and what the principal investigators decide to activate through their Institutional Review Boards (IRBs). It is particularly important to determine whether there is an active protocol in the minority-based CCOP for a patient's particular type and stage of cancer and whether the patient is eligible for that protocol.

Dr. Brawley presented data from the patient log for 1992, indicating that 3,585 patients were seen by 151 physicians during that calendar year. Twenty-nine percent of patients were White, with over 70 percent of an ethnic minority; 43 to 44 percent of the patients were Black. Nearly 58 percent of these individuals were male, almost three-quarters were over the age of 50, and nearly half were between the ages of 50 and 60. A protocol was available matching the type and stage of disease for one-quarter (850) of this patient population, and nearly half (420) of those who had a protocol available were eligible for that protocol. Reasons for ineligibility were known for 296 of the 430 ineligible patients. Poor performance status, generally due to the effects of disease, was noted primarily, while comorbid disease was a factor in 13 percent, a second malignancy in 8 percent, and abnormal laboratory values in 7 to 8 percent of the cases. A protocol was thus available for 420 eligible patients; 247 (60 percent) chose to enter clinical trials, while 173 did not.

Eligibility decreased as the patient population increased in age. This occurrence was expected and is due to the effects of comorbid diseases of aging. Dr. Brawley noted, however, that in patients under the age of 70, approximately 60 percent of all eligible patients in each age group entered into a clinical trial. Also, as previously found in a number of other studies, a high level of eligibility and participation in clinical trials occurred among pediatric patients.

Dr. Brawley noted that there was no statistical significance related to race/ethnicity and eligibility in this study. Overall, no true statistical significance appeared among the 850 patients—200 White, 252 Hispanic, 373 Black, and 25 unknown—because, he believes, when racial minorities are offered the opportunity to participate in clinical trials, they choose to go into those trials in the same proportions as nonminorities. Dr. Brawley explained that the reasons why 173 of 420 eligible patients chose not to enter clinical trials can be separated into patient and physician concerns. For patients, the most common reason for failure to participate was concern regarding either toxicity or the experimental nature of the clinical trials. For physicians, on the other hand, preferences for alternative therapies and referral of patients to other physicians were the most common reasons for not placing patients in available trials.

Dr. Brawley closed his presentation with conclusions drawn from the Minority Clinical Oncology Program. Of the 12 minority-based CCOPs, 10 were eventually able to accrue patients into trials from a total of 31 hospitals. The fact that protocols were available for only 20 percent of the patients presenting for clinical trials indicates the need for program improvement. Other findings include: approximately 60 percent of eligible patients entered into clinical trials; race did not appear to influence the patient's decision to participate; patients' health status was the most common reason for ineligibility to participate in clinical trials; and minority patients with access to clinical treatment trials entered those trials at rates very similar to those of nonminority patients.

Dr. Brawley noted that the formation of the MCCOP required a great deal of work and cooperation from a number of individuals. He acknowledged the dedication of Drs. Leslie Ford, Karen Johnson, Claudette Varricchio, Susan Nayfield, Rosemary Padberg, Jeff Perlman, and Joan Pauley, and thanked Dr. Barry Kramer, the leader of this effort, and Dr. Carrie Hunter, founder of the MCCOP.

Dr. Calabresi thanked Dr. Brawley for his presentation and relinquished the floor to Dr. Ed Trimble.

Dr. Trimble began by explaining that the DCT complements the CCOPs in the funding of minority accrual to clinical trial through the Cancer Therapy Evaluation Program. Dr. Trimble asserted that some of the problems in recruiting minority and low-income individuals into clinical trials include inaccessibility of medical care, inadequate hospital and clinic resources, lack of family and social support, cultural and language issues, and transportation and other expenses.

A slide was shown illustrating the framework of cooperative groups sponsored by CTEP, including two pediatric groups, the Children's Cancer Group and the Pediatric Oncology Group; four specialized groups, including the Brain Tumor Cooperative, the National Surgical Adjuvant Breast and Bowel Project, the Gynecologic Oncology Group, and the Radiation Therapy Oncology Group; and four general adult groups—Cancer and Leukemia Group B, Eastern Cooperative Oncology Group, North Central Cancer Treatment Group, and the Southwest Oncology Group.

Dr. Trimble presented another slide showing numbers of patients enrolled on clinical trials in 1991 and 1992. More than 22,000 patients enrolled in treatment trials during that time, encompassing 1.7 percent of patients with newly diagnosed cancers. He then explained CTEP's funding mechanisms that support minority accrual to treatment trials, namely the Minority Accrual Initiative and the Minority Satellite Supplement, which was originally funded through the Department of Extramural Activities (DEA).

The Minority Accrual Initiative reimburses the cooperative groups via capitation for accrual over baseline. This may include increased time for physicians, nurses, and data managers, or additional expenses for mailings, consultants, translators, and local liaisons. Additionally, the operations or statistical offices may apply for funding for such items as quality assurance, increased patient volume, training for physicians and staff, or travel and per diem expenses for newly participating physicians.

Dr. Trimble then presented a slide illustrating funding levels, noting that the program was initiated in fiscal year 1990. From 1990 to 1993, Minority Accrual Initiative funding has increased from $959,000 to $1,204,000. The Minority Satellite Supplement, on the other hand, has gradually phased out during this period from $510,000 to $175,000, since it is being replaced by the Minority Accrual Program, which provides additional flexibility to both the CTEP and cooperative groups. Dr. Trimble pointed out a slight drop in funding for the Minority Accrual Initiative in FY 1991, which he said occurred because the program was not announced until April 1990. The monies were distributed in September 1990, with a large carryover from FY 1990 to 1991, but levels have remained relatively stable over the last 2 years.

Dr. Trimble asserted that the most important aspect of CTEP's role in the minority accrual program has been the effect of funding. In 1989, 20,088 patients enrolled, of whom 2,933 were minorities (14.2 percent), while in 1992, out of 22,700 patients enrolled, 3,768 were minorities (16.2 percent). This represents a 28 percent increase over baseline, thereby clearly substantiating progress achieved through the Minority Accrual Initiative.

A slide was next presented showing minority patient percentages for the 20 most common tumor sites during calendar year 1992. Generally, some variation is shown among tumor sites, reflecting incidence of cancer and referral patterns, as well as success in recruiting minority patients. The figures are distributed among the various minority groups—Black, Hispanic, and the combinations of Native American and Alaskan, and Asian and Pacific Islander. The figures vary among the cancer sites, with a high of 36.9 percent for cervical; 25.9 percent for head and neck; 26.6 percent, gastric; 22.9 percent, leukemia; 19.6 percent, prostate; 14.8 percent, breast; 9.5 percent, lung; 4.5 percent, bladder; to a low of 1.6 percent

for melanomas. The total, Dr. Trimble noted, is 16.2 percent, with only 6 percent of patients of unknown racial/ethnic status.

Dr. Trimble concluded that the DCT is pleased with the success of the Minority Accrual Initiative and will continue the program with the hope of increasing the number of minority patients accrued into clinical trials. The DCT plans to join forces with the Office of Cancer Communications, the Division of Cancer Prevention and Control, the American Cancer Society, and other professional societies in order to promote clinical trials throughout the minority population of the United States. Working with NCI leadership initiatives, the DCT will also focus on populations that have been underrepresented historically in NCI trials. Additionally, through a recently initiated analysis of accrual data, the DCT will examine the insurance status and residence of minority patients enrolled in clinical trials for future program recommendations.

Questions and Answers

Dr. Ellen Sigal asked whether the capitation over the baseline is considered sufficient to cover the incremental cost of the Minority Accrual Initiative. Dr. Trimble responded that the evidence of the program's success lies in the resulting heightened awareness of the investigators and cooperative groups as opposed to an increase in the absolute dollar amount. He further noted that $1.3 million is not enough to redress health care in the United States, but it can be used to increase program awareness.

Mrs. Barbara Bynum requested clarification of protocol availability and eligibility and expressed concern about whether unwarranted high expectations are instilled among eligible patients about entering into clinical trials. She referred to the 250 individuals out of 3,500 recruited patients who were actually eligible for trials. Noting the low 20 percent accrual figure, Dr. Brawley assured Mrs. Bynum that recruited patients are typically informed of the possibility of an available protocol for which they might be eligible. In any screening process, however, it is conceivable that a patient's eligibility for a given protocol may change, which, in turn, impacts the accrual percentage of the total recruitment.

Dr. Henry Pitot requested an update on the accrual for the tamoxifen trial and plans for the Proscar trial, noting that there has been a lack of minority enrollment. The overall goal, Dr. Brawley responded, is to advertise the existence and importance of the clinical trials, with the hope that this knowledge will encourage individuals to participate. He cited the finasteride trial as an example, for which the Southwest Oncology Group's outreach methods to provide screening via churches, union halls, and community organizations will be adopted on a national level. Dr. Brawley then recognized Dr. Leslie Ford to respond to the issue of the tamoxifen breast cancer trial.

Dr. Ford conveyed information on the tamoxifen breast cancer prevention trial, which began in September 1992. She noted that there was some concern about minority recruitment in the early stages of the trial. In the first 2 months, the majority of interest came from women who were self-referred, knew of the trial, and had a heightened awareness of their risk for breast cancer. Over the first few months, about 25,000 risk assessments were completed; 4 to 5 percent of these initial risk assessments were among minority women. There was a satisfying and major increase in the percentage of minority risk assessments over time, with a high of 14 percent in April and, again, in August of 1992. The group's efforts to increase minority accrual were realized through work with special compliance and recruitment committees and the development of public service announcements.

Dr. Ford emphasized that it takes about 3 to 4 months to convert a woman with an eligible risk assessment into an actual accrual because of the process of informing the women who are in baseline testing. Although uncertain why, she reported that 35 percent of minority

women, as opposed to two-thirds of White women, are actually eligible for the trial based on risk. Furthermore, only about 6 percent overall of the women with risk assessments performed between June and August 1992 have been randomized, as opposed to 25 percent in earlier periods.

Dr. Ford added that although the goal of minority recruitment of 10 percent of the overall population has certainly not been reached, efforts are continuing and the minority numbers are rising. She noted that funding is available in the cooperative agreement to provide tests and procedures needed by women with little or no insurance. The group's continuing efforts are focusing on minority accrual to the trial through additional recruitment centers and satellites which access large minority populations.

Dr. Calabresi thanked Drs. Greenwald, Brawley, and Trimble for an informative presentation and called a brief recess.

XIII. SUBCOMMITTEE REPORTS

Activities and Agenda Working Group

Dr. Calabresi reported that the Activities and Agenda Working Group met in Chicago, Illinois, at O'Hare Airport on September 1, 1993. The meeting was well attended and several recommendations were made.

The working group recommended that the NCAB meetings maintain a 2-day format, with the second day meeting beginning at 8:00 a.m. Dr. Calabresi noted that this change has been implemented. The subcommittee also recommended that subcommittee reports be scheduled earlier in the program on the second day of meetings, and that new business be conducted after lunch.

Dr. Calabresi related that the working group discussed the possibility of extending the program into the second day. Some people have suggested, he stated, that too much information is being packed into the first day of the meeting. Dr. Calabresi emphasized that the group did not unanimously agree on this issue, and encouraged the Board's recommendations. It was agreed that scientific presentations should be more focused, limited to 30 minutes, and allowed 15 minutes for discussion.

Dr. Calabresi explained that the working group had previously made several suggestions for the Director's report. He commented that Dr. Broder's written material prepared in advance has been very helpful. Dr. Calabresi noted the good balance between extramural and intramural program presentations in the Director's report and encouraged the continuation of this effort. On behalf of the group, he commended Dr. Broder for the quality of his presentations.

Dr. Calabresi stated that the subcommittee discussed the possibility of holding a confidential informational session during the closed session (e.g., to discuss certain aspects of the intramural program), at which time no actions would be taken and no votes or decisions would be made. The group believes this would provide the Director an opportunity to keep the Board informed of sensitive issues.

In the interest of saving time and money, the committee agreed that staff should communicate via fax and E-mail whenever possible and keep the use of Federal Express to a minimum.

Dr. Calabresi reported that discussion also centered around the annual program review meeting and the fact that only two Divisions are reviewed each year on an alternating basis, leaving a 2-year gap between formal presentations for each Division. The committee decided, therefore, that two Divisions will continue to present; however, prior to the meeting, all Divisions should submit brief outlines of their activities for the year. Nonpresenting Divisions will be allocated 30 minutes on the agenda to address questions from the Board, thereby preserving continuity of the review process.

Subcommittee members recommended that the Board receive a yearly update on trends in mortality and incidence, which, they felt, would help the Board keep abreast of tumors on the rise, tumors for which there is great progress, and new problems associated with mortality and incidence data.

Dr. Calabresi noted that the working group discussed future meeting topics, such as a presentation, preferably at the next meeting, from Dr. Harold Varmus, the new Director of the NIH. Dr. Broder clarified that Dr. Varmus would not attend a meeting of the NCAB until after his confirmation. Other topics of interest were a report of the Special Commission of the Breast Cancer Task Force, a presentation on the decision-making process of the breast cancer appropriation to the Army and ensuing deliberations at the Institute of Medicine, and a report from the NIH Office of Alternative Medicine.

Dr. Calabresi reported that this subcommittee discussed the lack of time for Board members to discuss new business, resolutions, motions, etc. The subcommittee suggested introducing motions and/or new business in a new business section on the first day after the NCI Director's report, so that Board members would have adequate time to discuss the issues before voting on the second day. Dr. Calabresi indicated that there will be an attempt to schedule subcommittee meetings immediately after the closed session to eliminate any waiting period.

Since it is difficult for the Board Chair and Dr. Broder to attend all of the subcommittee meetings, the working group recommended combining some subcommittees. For example, the subcommittees on Aging, Minority Health, and Women's Health could be combined to form the Subcommittee on Special Populations, which would have co-chairs and address minority health, aging, and women's issues. The working group also suggested combining the AIDS Subcommittee with the Environmental Carcinogenesis Subcommittee, so that the AIDS Subcommittee remains active during Dr. Temin's absence.

Dr. Calabresi related that there was also a discussion about holding an off-site meeting, possibly at a medical school or an academic medical center, with a particular theme. Working group members agreed that this meeting should not necessitate the attendance of all NCI staff. Dr. Broder suggested holding the November/December meeting off-site, since grants are not reviewed at that time. Dr. Calabresi suggested that this meeting could be tied in with the NCAB retreat, at which time participants could have in-depth discussions about specific topics and future directions.

Dr. Calabresi concluded that working group members felt that the orientation process for new Board members is helpful and well done; therefore, no changes to the process were recommended. He then opened the floor for comments or questions.

Dr. Adamson maintained that all Divisions—including those that are not formally presenting—provide the same supporting material for the program review meeting every year, and that no additional information should be required. Therefore, Dr. Calabresi proposed that no additional material should be requested from Divisions, but time for a 30-minute question-and-answer period should be reserved.

On behalf of the Board, Dr. Calabresi praised Dr. Wells for efficient operation of the closed session.

Dr. Becker expressed concern about combining the AIDS Subcommittee with the Environmental Carcinogenesis Subcommittee, since AIDS is a "significant entity of a specific etiology" and environmental carcinogenesis is a much broader topic. Dr. Adamson agreed, but suggested that, temporarily, AIDS-related topics could be discussed at alternate meetings of the Environmental Carcinogenesis Subcommittee. Dr. Calabresi emphasized that the working group did not want to necessarily combine the two groups, but thought it imprudent to have an inactive AIDS Subcommittee. Also, he noted, Dr. Temin's tenure on the subcommittee is scheduled to end this year. Dr. Adamson requested that a representative from the National Institute of Environmental Health Sciences be added to the committee.

Cancer Centers

Dr. Salmon reported that the major focus of this meeting was a presentation by Dr. Margaret Holmes on plans for implementation of a Cancer Centers Branch (CCB) annual report. He noted that the report will be presented to this subcommittee in February 1994. Dr. Salmon related that the Cancer Centers Branch has developed a program called cDATA, or Cancer Centers Data. The program will be distributed to Cancer Centers to aid them in collating the necessary standard information used in generating internal and annual reports. It would also allow individual centers to perform interactive readouts, or print or transfer files into a spreadsheet program, allowing each center to examine its own data with many specific sort capabilities. Dr. Holmes explained to the subcommittee that the CCB hopes to link the Cancer Centers by Internet in the future to allow them to share information in the areas of prevention and control. Dr. Salmon remarked that the subcommittee was pleased with the efforts of the CCB, particularly with the database program.

Based on the subcommittee's discussion, Dr. Salmon indicated that the core grant review for fiscal year 1994 will involve a greater workload than in past years. He estimated that there would be 16 or 17 competing applications, and possibly 1 or 2 new applications. Based on grant distributions, Dr. Salmon stated that the workload will be even heavier in FY 1995.

Clinical Investigations Task Force

Dr. Calabresi reported that he met with Dr. Jerome Green in July to discuss the possibility of setting up a separate study section and to identify problems related to clinical investigations. They decided to maintain a continuing dialogue on the subject. Thus, Dr. Green was invited to attend the Clinical Investigations Task Force meeting, along with his colleague, Dr. Anthony Dempsey.

Dr. Calabresi stated that Dr. Green offered an open invitation for the subcommittee or other organizations to submit names of qualified clinical investigators to facilitate the recruitment of more clinically oriented reviewers. Dr. Calabresi emphasized the fact that Dr. Green volunteered to investigate the problems associated with clinical investigation and expressed his desire to meet on a continuing basis. Dr. Calabresi pointed out, however, that Dr. Green is not in complete agreement with the Task Force.

Dr. Green, Dr. Calabresi stated, maintained that Institutes, not study sections or the Division of Research Grants (DRG), award grants, and that the NCAB is ultimately responsible for awarding NCI grants. More discussion, Dr. Calabresi continued, is needed on this issue, because it potentially offers the NCAB an alternative to the system of numerical

hierarchy provided by the study section. Dr. Calabresi asked Dr. Chabner to elaborate on this subject.

Dr. Chabner reiterated that the problem being discussed is the low percentage of clinical grants being funded. He explained that the Experimental Therapeutics 2 (ET2) study section, a recent creation of the DRG, reviews cancer grants related to the laboratory/clinical transition of basic research. Approximately equal numbers of clinical and laboratory grants are reviewed. The ET2 study section has received an increasing number of clinical applications in recent years. Although this increase has resulted in a larger absolute number of clinical grants funded, the funding rate (between 5 and 10 percent) for clinical grants is still significantly below the funding rate (between 15 and 20 percent) for basic science grants reviewed by the study section.

Dr. Chabner explained that all grants from the study section are considered together and ranked. According to policy, the NCI funds a certain percentage of grants from each study section; the funding rate is 14 percent this year. Dr. Chabner contended that while the study section does not make funding decisions directly, its rankings have a tremendous impact on eventual funding because the Board adheres to the percentiles and has limited flexibility to fund grants outside the pay line.

Dr. Chabner outlined two options that were considered at the Task Force meeting. The first is to create a new study section. Dr. Green did not support this recommendation because there are many requests for special study sections in other clinical areas, and he is concerned about setting a precedent for creating new study sections. Dr. Green prefers a mix of laboratory and clinical expertise on study sections, Dr. Chabner added. Dr. Chabner commented that because this arrangement results in a lower funding percentage for clinical grants, the Task Force does not entirely agree. Since he views clinical grants as a generic entity, Dr. Green suggested that the creation of a special study section should include a mix of cancer grants and grants of other clinical specialties. Dr. Chabner related that Dr. Green was most interested in creating a special emphasis panel, which would consist of a subpanel of the existing study section and additional expertise to review clinical grants. Dr. Chabner reiterated that this change would not improve the overall funding situation, although it might improve the actual review. Dr. Chabner reported that he also suggested shifting existing ET2 basic science grants into ET1, an existing basic science study section, and shifting clinical grants that are presently distributed among other study sections into ET2. He added that Dr. Green did not seem to favor this option. Dr. Chabner concluded that Dr. Green is contemplating several options and will make a progress report at the next Task Force meeting.

Dr. Broder explained that the Division of Research Grants is responsible for the assignment of all grant applications and has jurisdiction over any grant in the Public Health Service. The DRG also makes referrals to Institutes. Dr. Broder stated that many NCI funding instruments are determined by the policy of the DRG. He recommended that Dr. Calabresi discuss this issue at the NIH Director's Advisory Committee meeting, since it has NIH-wide implications.

Dr. Broder then discussed problems faced in clinical investigation. He observed that recommendations made to revise proposals or requests for preliminary studies are appropriate in the basic science arena, but can be great obstacles in the clinical research arena. One cannot begin a pilot clinical trial without a funding instrument—there is no opportunity to perform a preliminary study or perfect a proposal without having the resources available. However, basic science applications can be amended to obtain additional data or perfect a grant. Dr. Broder noted that it will be necessary to examine the issue of providing the same kinds of opportunities to conduct preliminary research in both the clinical and basic science areas. He described one solution created for the Cancer Centers and SPORE program, in which principal investigators assign developmental funds—which are part of all funding instruments—to staff

members (particularly young staff members) who use this resource until they can perfect the regular R01 application. Some suggestions for improving this situation, such as asking pharmaceutical companies to pay for pilot studies, have proven impractical.

Dr. Calabresi stated that the NIH Director's Advisory Committee has not been very active during the transition phase over the past 6 months, but assured the Board that he will communicate this important problem as soon as Dr. Varmus has assumed his new position.

Dr. Salmon expressed the Task Force's concern that clinical research is in a state of crisis, in which an "unlevel playing field" exists between grants (even basic science) assigned to ET2 and ET1. While Dr. Green proposed further studies before deciding whether action is needed, the Task Force preferred to discuss possible experimental approaches to the problem. Clinical research grants, Dr. Salmon continued, are by their very nature more complicated and receive poorer scores than basic science grants. A subcommittee member pointed out, he noted, that it is easier for basic science grants to benefit in ET2 than in ET1, since they are competing with clinical research grants. On the basis of Dr. Green's statement that Institutes and Boards—not study sections—form funding policies, Dr. Salmon suggested that the NCAB request that rankings of the basic and clinical research grants be reported separately by the ET2. The Board, Dr. Salmon recommended, could decide to fund 15 to 20 percent of the clinical grants if they were excellent or outstanding. The NCAB could use the scores in the given priority ranking, but divide them into two components. Dr. Salmon maintained that this method would not require a new study section and could be implemented on an experimental basis.

Dr. Broder emphasized that it would be inaccurate to say that the Institute has the final decision to fund grants. The NCAB votes on whether or not to fund a grant. This Board, Dr. Broder continued, has the statutory authority to prohibit the NCI from funding a grant over $50,000. However, the NCAB does not set pay lines or instruct the NCI to fund a grant. Rather than solve the problem of clinical investigation by creating special categories, Dr. Broder recommended using the RFA, program project, or R29 mechanism (the FIRST award). He mentioned that all of the Institutes have a liberal pay line for R29s; the NCI could deliberately seek clinical R29s to encourage individuals to make career commitments in this area. Dr. Broder indicated that reformulating the study sections' percentiles and rankings would contradict some NIH traditions.

Mrs. Bynum expressed support for Dr. Salmon's comments, and felt that Dr. Chabner had proposed a viable operating method for this problem. Dr. Salmon remarked that he proposed his alternative only if there was no progress otherwise. He offered his support for the option presented by Dr. Chabner. Mrs. Bynum suggested that Dr. Green views any kind of discipline-related segregation in the different study sections as an entitlement for a given area of research and is trying to be even-handed in his approach to this matter; however, she indicated that the Task Force would promote its preferred option.

Dr. Calabresi observed that one of Dr. Green's major defenses has been maintaining the fairness of review. The suggestion that the grant review process is not fair (i.e., that ET2 grants might have an advantage over ET1 grants), he continued, is a powerful indictment of the system and probably distressed Dr. Green.

Dr. Sigal stressed that it takes a great deal of time to organize a study section, write a report, and conduct a review of an issue. She expressed her disapproval of creating another study section to examine the problem and suggested that the Board issue a statement urging immediate action to this crisis situation. Mrs. Bynum clarified that Dr. Green was not proposing a study section to consider the problem; however, the suggestion, she added, represents a delaying tactic.

Dr. Calabresi indicated that a problem with the RFA mechanism is that there is no continuing study section to review the proposal and help the investigator to make improvements. Dr. Broder agreed that the purpose of a study section is to improve a grant through the wisdom provided in peer review. This process is beneficial for basic research applications, but in clinical studies it is impossible to respond to criticism, such as to prove the feasibility of the study, without first having a funding instrument. Thus, Dr. Broder stated, many clinical investigators never submit a second application.

Dr. Salmon emphasized the importance of the R29 mechanism to encourage careers in clinical research. He recommended that the NCI put great effort into the R29 for clinical investigation, so that investigators can hone their skills and, hopefully, develop better applications. Success in science, Dr. Salmon continued, is the foundation for a career commitment to science.

Dr. Calabresi stressed the need for a mechanism in addition to the R29. Many researchers, he noted, are discouraged to choose clinical investigation as a career because of the perceived difficulty in obtaining funding. Increasing training program funds, he added, will not revitalize careers in clinical investigation unless there is a clear future for it. Dr. Calabresi related the possibility of losing a generation of clinical investigators because of a lack of funding.

Dr. Bettinghaus suggested that the NCI conduct an audit of clinical investigation, commissioned by the NCAB, to document the number of rejected grants and the nature of the reasons why clinical research is rejected. This audit could be used as evidence to support changes in the current system, additional training for clinicians, or training for study sections to discern the differences between clinical investigation and bench science investigation. Dr. Bettinghaus proposed that actual data would be more convincing than arguments based on anecdotal evidence. Drs. Broder and Chabner contended that the percentages for clinical grants have been published.

Dr. Pitot agreed with Dr. Sigal's concern about the length of time needed to create a new study section. He related that it took between 4 and 5 years for the Board to start a new study section approximately 12 years ago. Thus, Dr. Pitot urged the Board to formulate an interim solution, while persuading the DRG to initiate a new study section.

Dr. Greenwald explained that a statistical review of applications for the behavioral medicine and cancer control areas was conducted. When an in-depth audit was attempted, he explained, two problems were encountered. One, the summary statements, or "pink sheets," reflected the opinions of the study section. Second, investigators of cancer control were not reapplying and resubmitting their applications because they believed the pink sheets were not asking for revised grants, but for new applications that addressed different areas. Dr. Greenwald pondered the issue of whether the pink sheets were suggesting that a clinical grant be converted to a basic science grant rather than be revised to a workable format.

Dr. Chabner commented that the real reason why clinical investigations are often not funded is because of the uncertainty of the success of the experiments. He stated that most clinical trials do not work, but many failed experiments lead to a few great successes.

Dr. Salmon suggested that the lower priority scores received by clinical grants may not actually represent a problem. He explained that, while serving on an outside foundation, he has reviewed and funded applications that were previously rejected by the NCI. The problem, he proposed, depends largely on the comparison of the grants.

Environmental Carcinogenesis

Dr. Becker reported that this subcommittee discussed research on radon as a carcinogen. He explained that radon is a proven human carcinogen, based on studies of uranium miners with high-level exposures over long periods of time. A current public concern involves accumulation of lifetime exposure to radon in the home. Dr. Becker explained that concern over potential hazards of radon exposure has stemmed mainly from studies on low-dose exposures that resulted in cancers in animal data, and predictions based on domicile levels measured across the country, particularly in certain geographic areas. He reported that the Environmental Protection Agency (EPA) will release a map specifying counties with high levels of radon exposure.

Dr. Becker noted that the EPA has made several costly recommendations for remediation of radon in the home. However, he stated, one subcommittee attendee asked whether factual information exists indicating that home exposure increases the risk of cancer.

Dr. Becker announced that there was agreement that large-scale or additive case studies are needed to more accurately assess domicile-related cancers. One of the meeting's speakers on epidemiological studies of home exposures and lung cancer concluded that there is no epidemiological evidence that domicile exposure relates to lung cancer. Large-scale studies, Dr. Becker stated, are planned or underway.

Dr. Becker described an exciting result of this meeting related to the presentation by Dr. Jonathon Samet of New Mexico. Dr. Samet is following the largest cohort of Native American (Navajo and Hopi Indians) uranium miners, who, Dr. Becker related, have an enormously high level of radon exposure and lung cancer incidence (based on sputum analysis). The subcommittee suggested that Dr. Samet's group might be an excellent population for chemointervention and prevention, rather than simple analysis toward cancer. The committee also informed Dr. Samet of a large group of clinical studies of retinoids in epithelial tumors at the M.D. Anderson Cancer Center. Dr. Becker concluded by noting that Dr. Greenwald had expressed his interest in helping, rather than merely studying, Dr. Samet's population.

Information and Cancer Control

Ms. Malek reported that the subcommittee discussed the concept review process, noting that five concepts were presented for review: 1) Editorial Services for the Scientific Publications Branch; 2) Budget Execution and Formulation Support System for the Financial Management Branch; 3) Program Support Services for the Office of Cancer Communications; 4) Evaluation Support Services for OCC; and 5) Media Support Services for OCC. Members unanimously approved these concepts. This summer, the members unanimously approved, by mail ballot, two Small Business Innovation Research concepts—"3D Interactive Graphic User Interface Prototype for PDQ and Cancerlit" and "Multimedia PDQ Prototype."

Ms. Malek stated that 26 NCI grants for the 1993-1994 Regional Breast Cancer Education Summits will be announced at a press conference in Dallas, Texas, on September 24, 1993. She related that the NCI has doubled its original contribution to the summits to $387,000 so that 16 large-scale summits and 10 mini-summits will be funded. The Komen Foundation will distribute $200,000 among the grant recipients. The American Cancer Society will also provide financial support to individual summits. Ms. Malek explained that the purpose of the summits is to educate leaders of community, business, voluntary, and health organizations about breast cancer and encourage them to sponsor breast cancer education and screening programs and activities in their communities. An emphasis is placed on reaching women at high risk for breast cancer and medically underserved or hard-to-reach women. Ms. Malek added that the summits will take place in 22 States and the District of Columbia.

She commented that the geographic distribution of the summits is well balanced—one in Appalachia, five in the Midwest, and three in California.

Ms. Malek announced that Dr. Ed Sondik will address progress toward the Healthy People 2000 objectives at a future meeting. Topics suggested by subcommittee members for future meetings include research on nutrition and cancer, information dissemination of the research findings, a review of the peer review process for nutrition grants, a review of International Cancer Information Center products and their distribution, a discussion of the ramifications of the recent needs assessment survey of voluntary organizations, and a review of outreach objectives in light of the new Cancer Information Service (CIS) configuration.

Interactions With Voluntary Organizations

Dr. Lawrence discussed the events leading to the survey of voluntary, advocacy, and health professional organizations to assess their communication needs and their interactions with the NCI. He reported that this subcommittee held a "mini-conference" of sample organizations since the last NCAB meeting to decide on the interests and needs of outside groups. Dr. Lawrence stated that it became apparent that the organizations' needs and interests are so vastly different that a national conference is not feasible.

Dr. Lawrence explained that Ellen Eisner of the OCC conducted a national needs assessment of 147 (mostly voluntary) organizations, to which there was a 47 percent response rate. He noted that the survey did not question the organizations' interest in a national meeting. Overall, the majority of outside organizations are pleased with their relations with the NCI. Survey results suggest that the NCI: create a point of entry for these groups to access information from the NCI; facilitate a one-on-one relationship between the NCI and the organization; and provide expanded mechanisms for continuing interaction and information exchange. Dr. Lawrence commented that the survey itself was a step toward improving communications between outside organizations and the NCI. He noted that copies of the survey had been distributed to Board members for review, and complimented the work of the OCC staff.

Dr. Lawrence reported that a summary of the report on survey results will be sent to all organizations. Organizations that did not respond will be encouraged to participate in the survey. Dr. Lawrence added that a follow-up evaluation of these efforts will be conducted at some point in the future.

Dr. Lawrence explained that subcommittee members agreed that the Committee on Interactions With Voluntary Organizations should be available to help convene meetings on specific topics that concern the NCI and outside organizations, and that there is no urgent need for a meeting at present. He noted that the staff members and agenda items of this subcommittee and the Subcommittee on Information and Cancer Control are similar and, thus, for efficiency, suggested that the two committees be combined.

Planning and Budget Task Force

Dr. Bettinghaus reported that this committee reviewed some aspects of the fiscal year 1994 budget in detail. During the remainder of the meeting, members discussed the recently released 1995 Bypass Budget and upcoming 1996 Bypass Budget. Most members felt that the 1995 Bypass Budget represented a significant improvement over previous documents. Dr. Bettinghaus suggested that the entire NCAB communicate with Dr. Judith Karp regarding improvements or special topics for the 1996 Bypass Budget.

Finally, Dr. Bettinghaus related that members of this subcommittee have been asked to list some potential policy-oriented issues and scientific advances that should be highlighted in the 1992-1993 Biennial Report of the NIH Director.

Program Project Task Force

Dr. Wells reported that this meeting was a continuation of a meeting of subcommittee members held by conference call on May 24, 1993. He explained that this subcommittee was initiated because of concern about the relationship between the NCAB site visit group and program staff intervention.

Dr. Wells noted that there has been a slight increase in the scores of P01 grants and a lower average score for R01s. There was a discussion at the meeting about creating a tripartite committee comprised of approximately 55 members. The committee would be divided into three subcommittees according to disciplines that are relevant to the subcommittee's purpose. The process of the site review teams would not change. Grants would be reviewed, using the general percentile rank format, and the subcommittee would review recommendations regarding funding. The committees and program staff would make final decisions together. Dr. Wells commented that the relationships between the subcommittees could be complicated.

Dr. Wells outlined recommendations resulting from this meeting. First, the NCI should continue its efforts to establish the single tripartite program project review committee described in the proposed charter, and obtain the Office of Management and Budget action regarding charter issues by the committee. If possible, this committee will be in place to review applications received by February 1, 1994. Second, two-level peer review should be the operating modality, with site visits by experts scoring individual subprojects, standing subcommittees of the parent joint committee awarding overall program project scores, and NCI program directors and the Executive Committee developing funding plans and making funding decisions, as appropriate. Third, the NCI should retain the site visit policy for P01s that is currently operative in the NCI Grants Review Branch.

Dr. Wells explained that the committee feels that these recommendations will facilitate a more equitable review of P01s. He stated that this was the last meeting of this subcommittee.

Dr. Bragg asked whether there has been any increase in the number of P01s. He noted that he read that P01s declined in 1992, and asked whether the decline has carried through to the present time. He asked if this is true; if yes, what are the reasons. Dr. Kalt answered that there has been a slight decline in 1993 because the NCI is receiving fewer Type I applications and the apparent raw score required to fall within the P01 pay line may have been a deterrent to the submission of new applications (Type I's) and resubmissions as amended applications. He surmised that because of a continued stricture in pay lines, the interactive R01 program will probably generate more program project applications in the future, reversing the current trend.

Women's Health and Cancer

Mrs. Johnson, Chair of the Women's Health and Cancer Subcommittee, stated that the subcommittee's meeting began with a legislative report by Ms. Tisevich, focusing on the provisions of Public Law 103-43 regarding women's health. Dr. Judith Karp, of the NCI Director's Office, presented a description of the Institute's Plan for Research on Cancers of the Breast and Female Reproductive Tract, developed in response to a mandate included as part of P.L. 103-43. The subcommittee, Mrs. Johnson added, unanimously approved the plan.

Dr. Greenwald then opened a discussion of breast cancer screening guidelines by providing an overview of breast cancer incidence and mortality trends and describing an NCI-sponsored workshop held in February 1993 at which experts reviewed findings from eight randomized controlled trials from around the world. Workshop participants concluded that these findings confirm the fact that screening reduces breast cancer mortality among women aged 50 to 69 by 30 to 35 percent and probably is useful for women over 69. However, findings showed no reduction in mortality rates during the first 5 to 7 years for women between the ages of 40 and 49. Dr. Barbara Rimer of Duke University and Dr. Russ Harris of the University of North Carolina spoke to the subcommittee about issues concerning mammography screening in women aged 40 to 49, including the high rates of diagnostic procedures generated by false-positive mammograms. Dr. Rimer stressed the need for public and professional education about current knowledge of mammography in this age group.

Following the workshop, NCI drafted a proposed revision of current breast cancer screening guidelines. Mrs. Johnson stated that these revised guidelines are included in the subcommittee's report. She emphasized that the American Cancer Society would like to work toward a consensus and is reviewing these proposed guidelines. The subject will also be discussed at the October 21st meeting of the Division of Cancer Prevention and Control's Board of Scientific Counselors, which NCAB members are invited to attend.

Mrs. Johnson formally submitted the subcommittee's report; Dr. Calabresi accepted the report and asked for a motion to approve all of the subcommittee reports. Dr. Salmon so moved, and the reports were approved unanimously.

Discussion—Breast Cancer Screening Guidelines

Dr. Calabresi then opened the floor to further discussion of the issue of breast cancer screening guidelines. Dr. Greenwald began by highlighting recent developments. The international workshop held in February, he said, synthesized data from the eight major trials mentioned earlier. A number of meetings and discussions have taken place since then. Dr. Greenwald reported that he met with an ACS committee on detection and treatment of cancer at which the committee voted to try to develop a consensus on guidelines with NCI. This process, he added, will take at least until mid-November. DCPC staff also met with a group representing relevant DHHS agencies; this group approved the process of revising the guidelines and suggested that other groups with an interest in cancer be included, in addition to NCI and ACS. Dr. Greenwald explained that the Institute plans to touch base with the leadership of such groups and to have a full discussion at the October 21st meeting of the Board of Scientific Counselors. He invited Board members to attend and participate in the discussion, which he predicted will focus primarily on the wording concerning the 40-to-49 age group.

Dr. Bragg expressed concern over the possible negative impact of changes in the guidelines, suggesting that mixed signals concerning screening might be perceived and that this could reduce the impact of the message that screening has value for women over 50, many of whom are not now complying with recommendations.

Dr. Lawrence stated that the dialog during recent meetings has been healthy, and expressed concern about the risk of creating a false perception among the public and media that the new guidelines have already been decided. He stressed that he does not believe that NCI staff have made any statements to suggest that the issue is settled; they have, he added, indicated that a revision of the guidelines is needed and that the NCAB should lead the effort to develop a consensus.

Dr. Lawrence pointed out that it has only been a few years since 12 national organizations put together a compromise consensus to clarify the issue for the public. Other

organizations have since come along, he acknowledged, that have ideas to contribute. Dr. Lawrence urged everyone involved to emphasize the need for further discussion and consensus building. He stated that he drafted a motion on this subject, but said that such a motion would not be needed if everyone agreed by the end of the meeting that the decision-making procedures described by Dr. Greenwald would be followed. His concern, he concluded, is avoiding mixed messages from various national organizations or a false impression that NCI has already changed the guidelines.

Mrs. Johnson suggested that this discussion could be resumed at the November NCAB meeting; Dr. Greenwald added that various interested parties should be invited to the October 21st meeting of the BSC.

Dr. Bettinghaus urged Board members to also put their comments into writing and make them available to Dr. Greenwald prior to the BSC meeting. These statements might be more clearly developed and expressed, and therefore more useful, he suggested, than comments during a meeting. Dr. Bettinghaus also suggested that discussions on this issue should take into account the nature of current experiences with mammography as a screening technique. He cited data from State programs that use Federal funds to provide screening to women of low socioeconomic status indicating that these patients are, for the most part, self-selected—that is, they come in voluntarily rather than being referred by a physician. This information, he said, raises questions about the recommendations concerning clinical breast examination and self-examination; some might suggest that if it is prudent to do a clinical breast examination, it is equally prudent to self-select for the mammogram.

Dr. Day asked for more information on the sequence of procedures that will follow the October 21st meeting. Dr. Greenwald replied that if a conclusion is reached at that meeting, NCI will then wait for input from the ACS, which could take another month. If the BSC and Executive Committee agree with the wording of the ACS recommendations, he said, NCI will incorporate this information with advice from the NCAB and proceed with the revisions.

Dr. Lawrence stated that he would object to proceeding without input from other organizations. Dr. Greenwald replied that NCI will have touched base with other organizations before October 21st. Dr. Calabresi observed that the issue can be brought back to the NCAB for further consideration in November, since it is too late to produce the new guidelines in time for Breast Cancer Awareness Month.

Dr. Broder stated that he cannot promise that the issue will be brought back for further discussion in November. He urged Board members to attend the October meeting and share their ideas at that time. He emphasized that NCI appreciates the advice of the Board, and stressed the fact that as a scholarly organization, the Institute cannot ignore the facts. It can continue confidently to recommend screening for women over 50, he said, based on studies that show a dramatic effect. However, he stated that any recommendation of screening for women between 40 and 49 should carry a note explaining that analysis of the studies has not shown the same effect. Dr. Broder noted that a risk algorithm could be developed by which individual physicians could determine the appropriateness of mammography for individual patients; the possible development of a screening assay for the BRCA-1 breast cancer gene might also play a part in this decision-making process. He added that current research efforts may produce new procedures that could make it possible to eliminate mammography altogether.

Dr. Broder stressed that the discussion should be brought to closure at some point to ensure that guidelines tied to a scientific database are available to the public. This will require taking the position that experts do not agree on certain points, he suggested, noting that the public is mature enough to understand this. Dr. Broder pointed out that the issue is not a matter of consensus if the consensus opposes the facts. There must be disclosure, he stated, as

to the reasons for making recommendations. Dr. Broder argued that in the treatment arena, NCI would never recommend an intervention on a public health basis without data to support it.

Dr. Salmon supported the idea of releasing the new guidelines during 1993, the year in which the relevant data appeared. The data will not change, he observed, and a consensus either will or will not be reached. NCI, he argued, has an obligation not to let the process continue into the next year.

Dr. Day agreed that no one has argued with the study results cited by Dr. Broder. He expressed concern that release of the study results could result in an overall drop in utilization of mammography. He argued that the issue of how information is communicated is important to NCI as well as to other organizations, so that the recommendations have the maximum benefit and do not turn off the interest of those who need screening. Dr. Broder replied that this is why consumer input is needed and expressed confidence that this will be incorporated into the process.

Dr. Bettinghaus noted that the same lack of evidence exists for the effectiveness of clinical breast examination or self-examination, but the draft guidelines conclude that these are prudent. He argued that the recommendations should be consistent in this area, suggesting that it should be possible to produce a statement that would inform the public about risk factors that would justify screening and discuss other kinds of screening techniques that have not proven useful.

Dr. Broder expressed the view that a case has been made for the merit of clinical examination. He observed that mammography, a technology-driven procedure, is not comparable to clinical examination by a qualified health professional.

Ms. Mayer asked whether the vote previously taken to approve the subcommittee reports applied only to the actual report of the Subcommittee on Women's Health and Cancer or whether it also implied approval of the draft breast cancer screening guidelines that were attached. Dr. Calabresi replied that the approval only applied to the subcommittee report.

XIV. NEW BUSINESS/ADJOURNMENT

There being no additional business, Dr. Calabresi thanked the group for their participation and adjourned the 87th National Cancer Advisory Board meeting at 12:40 p.m.

_____ _____

Date Dr. Paul Calabresi, Chairman

to the reasons for making recommendations. Dr. Broder argued that in the treatment arena, NCI would never recommend an intervention on a public health basis without data to support it.

Dr. Salmon supported the idea of releasing the new guidelines during 1993, the year in which the relevant data appeared. The data will not change, he observed, and a consensus either will or will not be reached. NCI, he argued, has an obligation not to let the process continue into the next year.

Dr. Day agreed that no one has argued with the study results cited by Dr. Broder. He expressed concern that release of the study results could result in an overall drop in utilization of mammography. He argued that the issue of how information is communicated is important to NCI as well as to other organizations, so that the recommendations have the maximum benefit and do not turn off the interest of those who need screening. Dr. Broder replied that this is why consumer input is needed and expressed confidence that this will be incorporated into the process.

Dr. Bettinghaus noted that the same lack of evidence exists for the effectiveness of clinical breast examination or self-examination, but the draft guidelines conclude that these are prudent. He argued that the recommendations should be consistent in this area, suggesting that it should be possible to produce a statement that would inform the public about risk factors that would justify screening and discuss other kinds of screening techniques that have not proven useful.

Dr. Broder expressed the view that a case has been made for the merit of clinical examination. He observed that mammography, a technology-driven procedure, is not comparable to clinical examination by a qualified health professional.

Ms. Mayer asked whether the vote previously taken to approve the subcommittee reports applied only to the actual report of the Subcommittee on Women's Health and Cancer or whether it also implied approval of the draft breast cancer screening guidelines that were attached. Dr. Calabresi replied that the approval only applied to the subcommittee report.

XIV. NEW BUSINESS/ADJOURNMENT

There being no additional business, Dr. Calabresi thanked the group for their participation and adjourned the 87th National Cancer Advisory Board meeting at 12:40 p.m.

November 18, 1993

Date

Paul Calabresi

Dr. Paul Calabresi, Chairman