DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

NATIONAL INSTITUTES OF HEALTH

NATIONAL CANCER INSTITUTE

NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
December 4-5, 1989

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

NATIONAL CANCER ADVISORY BOARD

December 4-5, 1989

Motions

- The Board unanimously approved, with changes noted, the guidelines for *The National Cancer Institute-Designated Comprehensive Cancer Center* (motion, Brown).

- The Board voted unanimously not to concur with the initial review group's recommendation to proceed with the Diet FIT project on grounds other than scientific or technical merit, exercising its responsibilities under its authority to ensure appropriate use of grant, cooperative agreement, and contract funds in the NCI's support and conduct of research and related activities and to assist the NCI in establishing objectives and priorities, in identifying resource allocation factors, and in enhancing program management and effectiveness.

- The Board unanimously accepted the report of the Subcommittee on Information and Cancer Control in the Year 2000 (motion, Brown).

- The minutes of the September 18-19, 1989, NCAB meeting were unanimously approved with the changes suggested by Dr. Bragg (motion, Bragg).

Action Items

Mrs. Bynum • At the January 1990 meeting, the Board will hear additional discussion on whether upper monetary limits should be specified for investigator-initiated research grants.

Mr. Roper • An agenda item for a future meeting will be focused on reordering priorities in the face of budget realities and meeting the year 2000 goals.

Dr. Gray • The Agenda Subcommittee will continue to evaluate Board meeting procedures and will review the revised program review format in January 1990.

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

Summary of Meeting*
December 4-5, 1989

The National Cancer Advisory Board (NCAB) reconvened for its 72nd regular meeting at 8:30 a.m., December 4, 1989, in Building 31, 6th Floor, Conference Room 10, National Institutes of Health (NIH). Dr. David Korn, Chairman, presided.

NCAB Members

Dr. Erwin P. Bettinghaus
Dr. Roswell K. Boutwell
Dr. David G. Bragg
Mrs. Nancy G. Brinker (Absent)
Mrs. Helene G. Brown
Dr. John R. Durant
Dr. Gertrude B. Elion
Dr. Bernard Fisher
Dr. Phillip Frost
Dr. David Korn
Dr. Walter Lawrence, Jr.
Dr. Enrico Mihich
Mrs. Irene S. Pollin
Dr. Louise C. Strong
Dr. Howard M. Temin
Dr. Samuel A. Wells

President's Cancer Panel

Dr. Armand Hammer (Absent)
Dr. William P. Longmire
Dr. John A. Montgomery

***Ex Officio* Members**

Dr. Allan Bromley (OSTP) (Absent)
Dr. Dorothy Canter, NIEHS
Dr. William Farland, EPA (Absent)
Captain Bimal Ghosh, DOD
Dr. Richard Greene, VA
Dr. John R. Johnson, FDA
Dr. Lakshmi Mishra, CPSC
Dr. William F. Raub, NIH (Absent)
Mr. James S. Robertson, DOE
Dr. Louis W. Sullivan, DHHS (Absent)
Mr. John J. Whalen, NIOSH
Dr. Ralph Yodaiken, DOL (Absent)

Members, Executive Committee, National Cancer Institute, NIH

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

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

Liaison Representatives

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

Dr. Walter Faggett, Executive Secretary of the House of Delegates, National Medical Association, representing the National Medical Association for Dr. Vivian Penn Williams.

Dr. Robert N. Frelick, Past President, Association of Community Cancer Centers, Wilmington, Delaware, representing the Association of Community Cancer Centers.

Dr. Ed Gelmann, Professor of Medicine and Pharmacology, Georgetown University, Washington, D.C., representing the American Society of Clinical Oncology for Dr. Randall Leonard, Jr.

Dr. Maryanna Henkart, Program Director for Cell Biology, National Science Foundation, Washington, D.C., representing the National Science Foundation.

Dr. Thomas J. King, Lombardi Cancer Research Center, Georgetown University Medical Center, Washington, D.C., representing the American Association for Cancer Research, Inc.

Ms. Elaine Locke, Associate Director for Practice Administration, American College of Obstetricians and Gynecologists, Washington, D.C., representing the American College of Obstetricians and Gynecologists and also the Society of Gynecologic Oncologists for Dr. Clarence Ehrlich, President.

Dr. James Lowman, Scientific Program Director, American Cancer Society, representing the American Cancer Society for Dr. John Laszlo.

Dr. Edwin A. Mirand, Associate Institute Director and Dean of the Roswell Park Memorial Institute Graduate Division, Buffalo, New York, representing the Association of American Cancer Institutes.

Dr. John F. Potter, Director, Lombardi Cancer Center, Georgetown University, Washington, D.C., representing the American College of Surgeons.

Ms. Yvonne Soghomonian, Associate Director, the Candlelighter's Childhood Cancer Foundation, Washington, D.C., representing the Candlelighter's Childhood Cancer Foundation.

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

I. CALL TO ORDER, OPENING REMARKS, AND CONSIDERATION OF SEPTEMBER 18-19, 1989, NCAB MEETING MINUTES--DR. DAVID KORN

Dr. Korn, Chairman, called the 72nd meeting of the National Cancer Advisory Board (NCAB) to order and welcomed Board members, the President's Cancer Panel, liaison representatives, guests, staff of the National Cancer Institute (NCI), and members of the public. He invited members of the public who wished to express their views on any part of the meeting to do so by writing to Mrs. Barbara Bynum, Director, Division of Extramural Activities (DEA), within 10 days of the meeting.

Approval of the September minutes was postponed until the following day's session.

Dr. Korn noted that, in accordance with the Board's request, only two divisions would present detailed reports at the annual program review, with the reviews alternating in subsequent years. The 1989 program review agenda therefore includes only the reports of activities in the Division of Cancer Biology and Diagnosis (DCBD) and the Division of Cancer Treatment (DCT), each Board member having already received written reports of FY 1989 program activities of the Division of Cancer Prevention and Control (DCPC) and Division Cancer Etiology (DCE). Dr. Korn then welcomed Drs. Vittorio Defendi of the DCBD Board of Scientific Counselors (BSC), Dr. John Niederhuber, chairperson of the DCT BSC, and Dr. Frank Meyskens, chairperson of the Advisory Committee for the Frederick Cancer Research Facility (FCRF).

II. FUTURE MEETING DATES

Dr. Korn called Board members' attention to the following confirmed meeting dates: January 29-31, 1990; May 14-16, 1990; October 1-3, 1990; and December 3-5, 1990; February 4-6, 1991; May 13-15, 1991; September 23-25, 1991; and November 25-27, 1991.

III. REPORT OF THE PRESIDENT'S CANCER PANEL--DR. WILLIAM LONGMIRE FOR DR. ARMAND HAMMER

Dr. Hammer commended members of the NCAB, on behalf of the Panel, for the resolution sent to Congress and the President recommending a raise in the Federal excise tax on cigarettes, with such revenue to be used for antitobacco education, health care services, and biomedical research. He noted that although progress has been made in recent years to educate the public to the dangers of smoking, much remains to be done. Citing the recent ban on smoking on all commercial flights in the United States that was enacted by Congress, in spite of heavy lobbying by industry, he suggested that the climate for passage of such a tax increase is more favorable than ever before. He noted that the Board's action would be helpful when the two bills on this subject are debated in Congress and said the Panel would do all that it can to be of assistance in this regard.

In delivering the Panel's annual report to the President, Dr. Hammer said he conveyed the Panel's great concern that recent budget increases for cancer research and training have not been sufficient even to sustain existing activities. He pointed out that the Stop Cancer campaign represents an effort to alleviate that situation, and he expressed pleasure at recent Senate Appropriations Subcommittee's actions with regard to authorizing the NCI to accept the funds raised by Stop Cancer and adding $12.5 million in matching Federal funds to the NCI budget to be allocated through the normal peer-review process.

Dr. Hammer reported that the third Panel meeting of the year was hosted by Dr. Korn at the Stanford University School of Medicine and focused on technology transfer, both in terms of new technology and state-of-the-art clinical practice. He said the Panel agrees with Dr. Samuel Broder, Director of NCI, that NCI should have vehicles for interacting with the private sector and that these should be the means for a flow of knowledge and ideas in both directions. He said the Panel would be exploring this issue in the year ahead.

Dr. Hammer commended the program at Stanford in the field of technology transfer and noted that various other universities have studied the methods and gained from the experience of Stanford's Office of Technology Licensing. He said the Panel believes that these efforts should be aided and encouraged by the NIH through the NCI, and he noted Dr. Broder's indication that NCI will study the suggestions and recommendations received at the meeting.

Dr. Hammer reported that the issue of training biomedical scientists was also addressed by the Panel at the Stanford meeting. He noted that most M.D. and Ph.D. students training for biomedical research are supported by about 25 programs nationwide, and he emphasized the need to encourage and support these programs whenever possible to ensure a future supply of highly qualified biomedical scientists. He pointed out that strategies are needed for bringing minority physicians and scientists into the system and he commended the efforts of Stanford University in this regard. He said the Panel would give serious attention to the continuing problem of adequate funding. He assured the Board that the many ideas and recommendations received at the Stanford meeting by the Panel and by Dr. Broder on behalf of the NCI would receive considerable attention in the coming year as the common goal is pursued of providing the most effective, efficient, and viable National Cancer Program that is possible with present resources.

Dr. Hammer announced that the final Panel meeting of the year, to be held at NCI, would include presentations by Dr. James O. Mason, Assistant Secretary for Health of the Department of Health and Human Services (DHHS), and Commissioner Frank Young of the Food and Drug Administration (FDA). He said the NCAB would also receive a status report on Tuesday from Dr. Louis Lasagna, Chairperson, on the work of the Committee to Review Current Procedures for Approval of New Drugs for Cancer and AIDS.

Finally, Dr. Hammer announced that the 1989 Hammer Cancer Prize would be awarded jointly to Dr. Vincent DeVita, Jr., of Memorial Sloan-Kettering Cancer Center and Dr. Emil Frei III of the Dana Farber Cancer Institute. He said Dr. DeVita was selected for pioneering the development of combination chemotherapy for the curative treatment of Hodgkin's disease and for his leadership of the National Cancer Program and Dr. Frei was chosen for the development of combination chemotherapy for the curative treatment of leukemia and for his many contributions to the field of combination chemotherapy. The award ceremony will be held in Los Angeles on January 5, 1990.

IV. NCI DIRECTOR'S REMARKS--DR. SAMUEL BRODER

Dr. Broder began by announcing several major awards to NCI staff members and investigators associated with the Institute. Dr. Bernard Fisher, NCAB member and professor of surgery at the University of Pittsburgh, received one of the Milken Family Medical Foundation 1989 cancer research awards for his lifetime of excellence in clinical research with particular emphasis on his contributions to adjuvant chemotherapy. Dr. Thomas A. Waldmann, Chief of NCI's Metabolism Branch, received the other major Milken Family Foundation award for his basic research on the physiology of the immune system. Recipients of the Milken Family

Foundation awards in clinical research included Dr. John Minna, Chief of the NCI-Navy Medical Oncology Branch.

Among other important awards, Dr. Broder noted the American Cancer Society Distinguished Service Award to NCAB member Mrs. Helene Brown. He also pointed out that the 1989 winners of the Nobel Prize for Medicine, Dr. Michael Bishop and Dr. Harold Varmus, had worked at NIH as young investigators and hold Outstanding Investigator Grants. Dr. Thomas Cech, who shared the Nobel Prize in chemistry, had held an NCI career development award.

Dr. Broder listed NCI staff changes as follows: Ms. Sharyn Sutton appointed Chief of the Information Projects Branch in the Office of Cancer Communication (OCC); Dr. Gordon Cragg appointed Chief of the Natural Products Branch in the Developmental Therapeutics Program (DTP); Mr. Larry Willhite appointed Chief of the newly created Administrative Management Branch in DCBD; and Dr. Wilna Woods appointed Chief of the Contracts Review Branch in the DEA.

Dr. Broder reported that Dr. Alan Rabson, Director of DCBD, and other NCI staff members had met with the Electronics Industry Foundation to discuss possible collaborations, particularly with respect to the development of new and more cost-effective mammography equipment and long-term instrumentation needs. He indicated that continued dialogue with the electronics industry is anticipated.

Dr. Broder next discussed some drug approval issues, noting first the recent FDA approval of a treatment IND for the use of AZT in children with AIDS. He pointed out that just 4 years ago the Board first heard reports of early Phase I results with AZT. Dr. Broder also noted DHHS Secretary Louis Sullivan's announcement of a treatment IND for dideoxyinosine (ddI) and a plan to make ddI available to patients who cannot take AZT and, in particular, to those who cannot participate in clinical trials. While recognizing the compassionate need to make drugs widely available, Dr. Broder called for reaffirmation of a commitment to the clinical trials process.

Dr. Broder also reported that FDA had granted Group C status to fludarabine for the treatment of patients with refractory chronic lymphocytic leukemia, the most common type of leukemia in adults. As most patients become refractory to the standard treatment, Dr. Broder described the development of fludarabine as an important milestone.

Turning to cancer prevention, Dr. Broder commented on reports that lung cancer deaths are declining significantly in some age groups, particulary in white men under age 45, the group with the most impressive decline in smoking. The major reason is thought to be antismoking campaigns that have reduced the prevalence of smoking. An article by Dr. Kenneth Warner in the *American Journal of Public Health* estimated that nearly 800,000 deaths have been averted or postponed from 1964 through 1985 due to the reduction in cigarette smoking prevalence. Dr. Broder called for redoubling of the effort to reach children and adolescents with information about the risks of smoking.

With respect to breast cancer, Dr. Broder noted a report from the San Francisco-Oakland SEER group highlighting what the authors describe as "striking changes in diagnosis and treatment of breast cancer" and a decrease in mortality among women in the San Francisco Bay area from 1970 to 1986. The report noted that finding is almost certainly related to early screening and treatment. The California report also noted a dramatic shift towards less radical surgical treatment.

Dr. Broder also reported the success of the Women's Leadership Summit on Mammography and congratulated Mrs. Nancy Brinker and others involved in the effort. The meeting featured speeches by Mrs. Barbara Bush and Mrs. Ginger Sullivan and received enthusiastic support from Secretary Sullivan and many members of Congress. The summit marked the beginning of the NCI Breast Cancer Screening Education Initiative, aimed at increasing the percentage of women who have mammograms. Dr. Broder estimated that breast cancer deaths would be cut by at least 30 percent if NCI's current mammography guidelines were observed.

Dr. Broder next recalled the transfer of the Organ Systems Program, Construction, Training, and the Cancer Centers Program to DCBD. To complete the transfer, three members with cancer center expertise will be added to the DCBD BSC. Dr. Broder stated that Mrs. Bynum would discuss the new guidelines for comprehensiveness for the Cancer Centers Program, and with the Board's approval, the intention is to implement the guidelines on January 1, 1990.

Upon the recommendation of the Office of International Affairs, Dr. Broder reported that he had signed documents to fund, with non-NCI resources, two U.S.-India collaborative projects (one on molecular epidemiology and one on the carcinogenicity of Indian tobacco products) and one U.S.-Yugoslavia project on bone marrow transplantation. The funds were placed in these countries for other purposes (formerly under P.L. 480) and cannot be moved.

Referring to the issue of construction, Dr. Broder noted that while the current budget does not provide funds for construction, NCI is committed to the concept of peer-reviewed construction grants and will continue to accept such applications in the event funds become available. The FY 1990 budget authorizes NIH to utilize $15 million for facilities for a number of possible uses, including a transgenic mouse breeding facility, and NCI will appeal to the Acting Director of NIH for consideration of its construction needs in the allocation of these funds.

Turning to discussion of the budget, Dr. Broder stated that NCI had spent all but $7,000 of its FY 1989 budget, and he congratulated Mr. John Hartinger and his staff for their skilled administration of the budget. The recently signed budget for FY 1990 provides $1.664 billion for NCI but with a Gramm-Hollings-Rudman sequestration estimate of about $23 million. Other reductions are slated as a result of procurement reform, an extramural salary cap, construction redirection, and a DHHS salary increase so that the projected operating level for FY 1990 will be about $1.630 billion. Of this amount, $1.480 billion is for cancer and $150 million for AIDS. Overall, NCI will receive about a 4 percent increase with cancer increasing 2.3 percent and AIDS 24 percent.

In response to concerns raised about funding instruments as they relate to investigator-initiated research, Dr. Broder presented information on the funding trends for the various mechanisms. He acknowledged that NCI is able to fund a comparatively small percentage of approved grants and the percentage is decreasing, but this situation is not unique to NCI. Actions that NCI has taken to increase the continuity and security of funding, e.g., Outstanding Investigator Grants (OIG) and MERIT awards, have had the effect of moving money from the competing to the noncompeting pool. In addition, increases in the cost of laboratory and investigator-initiated research have outstripped inflation. Dr. Broder also pointed out that there has been an increase in the number of applications received, and the amount of money available has not kept pace with this combination of factors. Nonetheless, the total money available for the research project grant (RPG) pool has kept pace with the overall NCI budget, and, in fact, has fared the best of any mechanism in the period between 1985 and 1989.

In comparing the research project grants by mechanism using 1985 constant dollars, the amount available for ROIs has fallen, the amount for POIs has remained comparatively constant, but the other mechanisms, e.g., OIGs, MERIT awards, FIRST awards, which are all also for investigator-initiated research, have increased by about $92 million from 1985 to 1989. These newer mechanisms accounted for 45 percent of the growth in the RPG pool. In conclusion, Dr. Broder reported that the 1991 bypass budget had been submitted to the Administration.

The following points were raised or clarified in discussion:

- The extramural salary cap, which affects primarily M.D. clinical investigators, establishes a maximum salary of $120,000, against which the percentage of time the investigator works on the grant must be applied.

- The mechanisms that have increased the length of certain grants were implemented on the basis of advice from the research community.

- Continued effort should be devoted to supporting the bypass budget.

- The RPG pool increased from 44 to 46 percent of the overall NCI budget between 1985 and 1989.

- NIH funds the vast majority of biomedical research in the United States.

- The centers budget has remained relatively stable. The current cohort of cancer centers probably cannot be sustained even with the budget increase for centers in the 1990 budget.

- The Centers for Disease Control (CDC), which might appropriately be responsible for the large-scale public applications campaigns that constitute phase V cancer prevention and control research, have received budget increases but largely for AIDS.

V. DEA: IMPLEMENTING THE NEW CANCER CENTERS GUIDELINES; REVIEW OF "COMPREHENSIVENESS"--MRS. BARBARA BYNUM

Mrs. Bynum directed attention to the latest draft of the Guidelines for National Cancer Institute-Designated Comprehensive Cancer Centers, which incorporated the comments, suggestions, and revisions received from NCAB members, DCBD BSC members, chairpersons of the DCT, DCE, and DCPC BSCs, and directors of clinical and comprehensive cancer centers. She noted that the draft had been reviewed by the NCI Executive Committee and represented DEA's effort to implement the criteria for comprehensiveness approved by the Board at previous meetings. She stated that she had asked to present the draft guidelines for Board consideration during the present meeting in order to implement the procedure by January, explaining that it was essential to announce the availability of the guidelines very soon if the schedule was to be maintained.

In reviewing the guidelines, Mrs. Bynum noted that the NCI has proposed two schema--one an administrative process, the other an adjunct to the peer-review process involving the Cancer Center Support Grant (CCSG) Review Committee. The administrative process will last only for a 2-year period beginning January 1, 1990, during which any institution that currently holds a cancer center support grant also called CCSG, P30, or core grant, may submit a formal request for designation as a comprehensive cancer center. As specified in the guidelines, the request is to

be an abbreviated statement of the capabilities of the center and a description of ongoing activities that address the eight criteria for comprehensiveness that have already been approved by the NCAB. Requests for administrative designation during that 2-year window will be reviewed and acted on by the Director of NCI in consultation with the Chairman of the CCSG Review Committee, and the Chairman of the NCAB Subcommittee on Cancer Centers, and others as deemed appropriate by the Director, NCI.

Mrs. Bynum called attention to three important points about the process: (1) a center may request administrative consideration only once during the 2-year period; (2) should a center fail to achieve this designation administratively, its director may ask that the request be considered by the full CCSG study section at its next regularly scheduled meeting; and (3) currently designated comprehensive cancer centers whose next scheduled competitive reviews will not take place within the 2-year period must request administrative consideration of their request for designation as comprehensive. As specified in the guidelines, any designation of comprehensiveness that is granted administratively during this initial 2-year period will be in effect only until the next regularly scheduled peer review of the center grant application, at which time comprehensiveness will again be evaluated at the center's request.

Mrs. Bynum said the second procedure involves the entire study section, and it will be the standard method of achieving the comprehensiveness designation after the initial 2-year period. She pointed out that centers desiring to submit a request for comprehensiveness at the time of their scheduled peer review may do so beginning in January. One important difference between the administrative and the study section review is that the center director will be invited to present the center's request for comprehensiveness to the study section after the P30 application review is completed. The study section recommendation regarding comprehensiveness will be presented to the NCAB along with the recommendation for the grant, and the concurrence of the NCAB with those recommendations will be requested. Mrs. Bynum said this process was initiated so that the dual review of the P30 application will not in any way be perturbed by the introduction of this procedure.

In response to Dr. Boutwell's question about the need for the 2-year administrative review option, Dr. Broder explained that the aim is to have all NCI-designated comprehensive centers meet the newly approved criteria for comprehensiveness as quickly as possible. In response to a question about procedures for accommodating those centers that have separate core grants but joint comprehensive designations, Dr. Broder gave assurances that unusual circumstances will be addressed as needed.

Dr. Broder, Mrs. Bynum, and Mr. J. Paul Van Nevel provided the following additional clarifications in response to other questions and comments:

- NCI policy specifies a funded core grant as a prerequisite for comprehensive designation.

- The proposed guidelines document is intended to be administered in conjunction with the CCSG guidelines, and dollar-based requirements for a core grant are included in the latter document.

- A significant amount of peer-reviewed control and prevention research will be necessary to qualify for comprehensiveness designation under the approved criteria.

- The NCI logo for designated comprehensive cancer centers has been designed and will be duly registered for their exclusive use.

Mrs. Brown proposed that the guidelines be modified to specify that NCI-designated comprehensive cancer centers must use the official logo to carry out the NCAB plan to make such institutions well known entities in the community. The Board concurred with this proposal, and a **motion** was made that the guidelines be approved as modified for implementation by the DEA. The motion was **seconded** and **approved** unanimously.

VI. DCBD PROGRAM REVIEW--DR. ALAN RABSON

In reviewing the organization of the DCBD, Dr. Rabson pointed out that the division had increased in size over the past year with the creation of the Centers, Training, and Resources Program (CTRP) and the establishment of the Administrative Management Branch to accommodate the increased size and responsibilities of the division. Other components of the division are the Planning and Analysis Branch, Extramural Research Program, and Intramural Research Program. He briefly reviewed the work and identified the chief of each branch and laboratory in the three programs and noted that the Extramural Research Program has one of the largest extramural grant programs in the NCI and supports much of the fundamental science in cancer research.

To show the distribution of funds among the programs, Dr. Rabson quoted FY 1990 budget estimates as follows: $52 million for the Intramural Research Program, $255 million for the Extramural Research Program, and $144 million for the CTRP. As an illustration of results achieved with funding from the DCBD budget, he pointed out that a K04 (training) grant provided support to Dr. Cech that enabled him to concentrate solely on the research into the enzymatic activity of RNA, which led to his receiving the Nobel Prize.

Turning next to a review of scientific highlights, Dr. Rabson listed the following three from among many intramural and extramural research activities sponsored by the DCBD: (1) demonstration that genetic alterations accumulate in human tumors and analysis of these alterations provides important clues for identifying genes critical to tumor progression; (2) identification and characterization of laminin receptor, autocrine motility factor, NM23 metastasis suppressor protein, Type IV collagenase, and TIMP-2 metalloproteinase inhibitor, novel proteins that may be involved in the positive and negative regulation of tumor invasion and metastasis, with diagnostic and therapeutic potential in human cancer; (3) demonstration that epithelial gamma delta T cells have great receptor diversity and can, in some cases, recognize nonclassical MHC cell surface molecules, possibly playing a role in the defense against newly emerging tumor cells.

Next, Dr. Rabson described a transgenic mouse model for multidrug resistance developed by Drs. Ira Pastan and Michael Gottesman and staff in the Laboratory of Molecular Biology. The mouse carries the human gene for P-glycoprotein, the multidrug resistance (MDR) protein, in every cell but has a particularly high expression of the gene in the bone marrow, making it a good model for the study of MDR. Dr. Rabson noted that the new model confirms the biological significance of the MDR gene and will be an important tool for the development of new strategies for overcoming drug resistance. He pointed out that Drs. Pastan and Gottesman and staff are also doing molecular studies to determine how the transporter works and how the energy of the nucleotide binding sites is translated into the pumping action. He said Dr. Gottesman will also be investigating other methods by which cells develop drug resistance.

Relating the transgenic mouse and other research of Drs. Pastan and Gottesman to the issue of training for clinical investigators, Dr. Rabson pointed out that Dr. Gottesman is one of the current pool of biomedical researchers who were trained at NIH. He emphasized the importance of the NIH training programs, where young physicians study in intramural laboratories in the various Institutes and have an opportunity to work in rigorous science. He expressed the opinion that the biomedical researchers of the future will come, in large part, from the extramural training program in DCBD's new CTRP.

VII. REPORT OF THE DCBD BOARD OF SCIENTIFIC COUNSELORS-- DR. VITTORIO DEFENDI FOR DR. ARNOLD J. LEVINE

In reviewing the work of the DCBD BSC, Dr. Defendi listed new members added to the Board during the past year and their fields of expertise as follows: Dr. Howard K. Schachman, molecular biology; Dr. Eugene A. Bauer, dermatology; Dr. Margaret L. Kripke, tumor immunology; Dr. R. Babu Venkataraghavan, application of computers to biomedical problems; and Dr. Noel L. Warner, immunology and government-industry liaison. He emphasized the diversity of disciplines represented on the Board in keeping with the present makeup of the division and the advisory responsibilities of the Board. Site visits were conducted in 1989 to the Metabolism Branch, Laboratory of Biochemistry, and Laboratory of Tumor Immunology and Biology. Dr. Defendi noted that the Laboratory of Pathology would be site visited the following week.

Next, Dr. Defendi listed presentations to the Board at the three regular meetings during 1989. The Board heard presentations on the supercomputer utilization by NCI and the NIH and the function of these computer programs as explained by representatives from universities. The Board passed a resolution to support the upgrade of the supercomputer facility. The Board also heard reports on the Human Tissue Procurement Network and, in recognition of the value of the program to studies of human tumors, proposed that the network be increased by two or three centers. A report was presented on a meeting on cancer and aging based on the assumption that tumors in the elderly may have different biological characteristics than in younger people. Finally, Dr. Defendi noted that the Board heard presentations on the new responsibilities of the DCBD, namely, cancer centers and training. He expressed the concern of the Board at the declining number of trainees supported since 1976, except for the current year. He noted that many laboratories are under construction where approaches to medicine developed over the past 10 years (e.g., molecular biology) will be applied, and he emphasized the need for many new investigators to staff the new facilities.

In conclusion, Dr. Defendi commended the organization and work of the DCBD on behalf of its BSC.

VIII. GENETIC BASIS OF COLORECTAL CANCER--DR. BERT VOGELSTEIN

Dr. Vogelstein stated that he would describe recent studies on colorectal cancer in progress at the Johns Hopkins University Oncology Center as an example of the progress that is being made in understanding human cancers in general. He noted that colon cancers are particularly worthwhile for study because they occur in stages that have been recognized clinically for many years. He pointed out that the various stages of colorectal neoplasia include adenomatous polyps of various size, carcinomas, and metastatic carcinomas. The only difference between adenomas and carcinomas is the ability to invade the bowel and metastasize. For conceptual purposes, he divided the process of colorectal neoplasia into discrete stages: normal epithelial cells can hyperproliferate, and one of the hyperproliferating cells can acquire a mutation and become a

small benign tumor that enlarges, becomes more dysplastic, and acquires a villous finger-like morphology; the villous tumor can eventually become a carcinoma; and the carcinoma can metastasize.

Dr. Vogelstein stated that the underlying hypothesis for the Johns Hopkins studies is that each of these steps is generated by an individual mutation. It has become possible to test this hypothesis at the molecular level only within the last 10 years. Because these studies are focused on human tumors removed at surgery rather than *in vitro* systems, a multidisciplinary bowel tumor working group was assembled at Johns Hopkins, composed of molecular biologists, pathologists, oncologists, gastroenterologists, surgeons, and epidemiologists. Dr. Vogelstein credited the successful efforts to determine the pathogenesis of colorectal cancers to this collaboration in a setting that focuses on human neoplastic disease.

Dr. Vogelstein said these studies on colorectal cancer, as well as studies on other tumors, suggested that oncogenes and tumor suppressor genes are the two kinds of genes apparently responsible for progression and initiation--oncogenes promote neoplastic growth when they are mutated; suppressor genes lose their normal growth-inhibitory powers through mutation. Dr. Vogelstein noted that most genes in colorectal tumor formation appear to be suppressor genes, although oncogenes also play an important role. The K-*ras* oncogene, in particular, is often mutated in colon tumors, and a single base pair change in this gene appears to be responsible for converting a normal gene into an activated oncogene with the ability to promote colon tumor progression. Dr. Vogelstein said that this mutation is found in over 50 percent of carcinomas as well as in a high percentage of advanced and intermediate stage benign tumors but rarely in early stage tumors. From these studies, it was concluded that *ras* oncogene mutations usually occur in one cell in an already extant benign tumor and cause that cell to further proliferate.

In searching for other genetic changes involved in tumor progression, Dr. Vogelstein said that Southern blot analysis using probes from chromosome 17 revealed that one copy of part of the short arm of chromosome 17 was deleted in most colorectal cancers. The deletion of a 17p allele has been found to be a late event in tumorigenesis, occurring somewhere near the transition from benign to malignant tumor and perhaps driving that process. Allelic deletions of specific chromosomal lesions, including 17p, were found to be quite common in colorectal cancers and in most common solid tumors of adults. In a panel of 60 colorectal tumors, the most commonly deleted regions were those on the long arm of chromosome 18 and the short arm of chromosome 17. The short arm of chromosome 8 and the long arm of chromosome 5 are also lost in many colorectal carcinomas.

Dr. Vogelstein said that after looking at a large series, it was possible to construct a working model of the way in which tumor progression occurs in the colon. The first gene that plays a role may be the gene on chromosome 5q, presumed to be responsible for the development of polyps in patients with an inherited syndrome called familial adenomatous polyposis. The same gene may mutate somatically in patients who have not inherited a defective gene. In addition to mutations in chromosome 5 (and other genes), adenomas have undergone a biochemical change in their DNA--a decrease in DNA methylation. Studies suggest that this decrease in methylation could predispose the cell to lose other genes, particularly those on chromosomes 18 and 17, which could result in further tumor progression. The processes of a transition to carcinoma and metastatic carcinoma probably arise through additional chromosomal events. The total accumulation of mutations usually requires several decades.

Dr. Vogelstein and his colleagues over the past few years have devoted much of their effort to identifying the putative target genes of chromosome losses in colon cancer. Beginning with

chromosome 17, the most common site of loss, a series of mapping experiments was begun using tumors that had lost parts of chromosome 17p. A small region of chromosome 17 was consistently lost in all colorectal cancers that lost any parts of that chromosome. It was also noted that a gene called p53 was located in this region. This gene, discovered in 1979, was thought to be involved in transformation by tumor viruses. Initial tests to detect abnormalities of this gene in colon cancer were negative. Dr. Vogelstein said Knudson's model predicted that the residual p53 gene would have to contain a mutation, however, if p53 was the target of allelic deletion. Additional cloning of a p53 gene in a tumor that had only one copy of chromosome 17 and comparison with the sequence of the gene in the patient's normal DNA demonstrated that there was indeed a mutation, changing the encoded amino acid (codon 143) from valine to alanine. Subsequent investigations similarly showed that mutations of the p53 gene were found in the residual p53 genes of 12 additional colorectal carcinomas studied.

Dr. Vogelstein pointed out that losses of chromosome 17 have been reported in many kinds of human cancers, including brain, breast, lung, and bladder, and mutations have been detected, in most cases, in the p53 gene that remains. He observed that finding that a single gene is mutated in a high proportion of human cancers of diverse type has important implications.

Turning next to chromosome 18, the second most frequently lost chromosomal locus in colorectal cancer, Dr. Vogelstein noted that markers on the long arm of chromosome 18 were used to determine the minimum region of loss. A chromosomal walk in this region allowed the isolation of a gene (called DCC for deleted in colorectal cancer) that is a candidate for the tumor suppressor function. Dr. Vogelstein said the gene is not expressed in most colorectal cancers, but it is expressed in normal colon epithelial cells. This gene will be subjected to biologic testing to determine whether it is a suppressor gene.

Dr. Vogelstein suggested that applications of these findings to the clinic may include assessing prognosis and detecting early stage neoplasia. He described a study of 29 patients with less advanced stages of colorectal cancer in which classification of genetic alterations was used to predict which tumors were curable by surgery and which would recur after surgery: 80 percent of the tumors in the high genetic alteration group recurred in a lethal fashion, compared with 7 percent of tumors with fewer genetic alterations. Dr. Vogelstein pointed out that death from colorectal cancer is entirely preventable in theory; therefore, if tumors could be identified at any stage prior to the last (metastatic) stage, surgery or colonoscopy with removal of the polyps could cure the patient. He said that knowledge of the mutations promoting tumor progression may make it possible to identify early stage tumors in two ways: first, mutant genes or their products could be identified in the blood or stool; second, blood cell DNA could be examined to determine the presence of genes that are inherited in mutant form and predispose the patient to neoplasia. Patients who have inherited the defective genes would be candidates for intensive screening throughout their lives.

In summary, Dr. Vogelstein stated that for colon cancers and many other common human malignancies, some of the genes that are altered have been identified and the precise locations of these mutations mapped at the nucleotide level. This represents an emerging understanding of the molecular pathogenesis of common neoplastic diseases.

In response to questions, Dr. Vogelstein provided the following additional information:

- Mutations in the p53 gene appear to occur before the loss of the well type copy. Exactly when the mutation occurs during colorectal tumor growth will be determined by studying different stage adenomas.

- Epidemiological studies show that colorectal cancers in certain patients are more likely to occur on the right versus the left side of the colon; while the implications for diagnosis are uncertain, such studies may be providing information on pathogenesis. More research is needed to link environmental influences with molecular alterations.

- One study suggests that *ras* gene mutations apparently increase the proclivity of cells containing them to be susceptible to mutations after exposure to radiation or carcinogens. This may address the question of whether mutations somehow destabilize the chromosomal mechanisms that limit genetic instability.

Dr. Greenwald commented that the identification of genes involved in the process of tumor progression also has an important application in tumor prevention in that it implies that chemoprevention is possible at multiple points in progression and that prevention of late stage cancer is possible.

IX. GENETIC BASIS OF CANCER INVASION AND METASTASIS--DR. LANCE LIOTTA

Dr. Liotta stated that he would discuss three projects related to the negative regulation of metastasis in keeping with the concept of suppressor genes outlined by Dr. Vogelstein. He pointed out that the ability of a tumor cell to invade and metastasize is the culmination of a series of genetic changes, which may be over and above the genetic changes that cause unrestrained growth. There is known to be a balance between positive and negative regulation of cancer invasion and metastasis: certain proteins made by the invading tumor cell, such as motility-stimulating cytokines, adhesive receptors, and destructive proteases, may be balanced by protease inhibitors or metastasis suppressor genes.

Dr. Liotta first described Type IV collagenase, an enzyme that has a built-in suppressor or inhibitor whose function may be lost during cancer progression, causing the tumor cells to have an increased ability to invade. The identification of this enzyme derived from the hypothesis that destructive enzymes may help a tumor cell invade by degrading components of the extracellular matrix, such as the basement membrane, that normally provide a barrier to tumor cells. Studying this process *in vitro* led to the identification of Type IV collagenase, so named because it binds to and cleaves basement membrane Type IV collagen. Dr. Liotta characterized this proteinase as a prototype member of the metalloproteinase gene family. Using models, such as *ras* oncogene transfection in the bronchial epithelial cells or rat embryo fibroblasts, Type IV collagenase was found to be markedly augmented during the development of metastatic tumors. However, Dr. Liotta noted, this enzyme and all other members of the metalloproteinase family are secreted in a latent form unable to degrade their substrate.

Referring to the work of Dr. William Stevenson in his laboratory, Dr. Liotta said that it was found that the trigger for activation of the enzyme was removal of an 80-amino acid piece from the end of the enzyme. The relevant regions of the enzyme are the cystine-rich region, which is responsible for the binding of the enzyme to its substrate; the meta-binding domain, which cuts the substrate; and the amino acid terminal portion, which folds over and blocks the active site of the enzyme. To establish that the amino terminal propeptide region really was an intrinsic inhibitor, protein peptides were synthesized that contained the sequence corresponding to this region, and these were found to be very potent inhibitors of Type IV collagenase. In addition, Dr. Liotta said that a new natural inhibitor was identified that is made by many types of cells and binds specifically to Type IV collagenase. This new inhibitor, named TIMP-2, is tightly regulated by both control of activation and inhibition of metalloproteinases.

Dr. Liotta said that to determine whether the conformational change that caused the enzyme to become activated was augmented in more aggressive human cancers, antipeptide antibodies were made that recognize the active form of the enzyme. The activated form of Type IV collagenase was found in *in situ* carcinoma of the breast but not in normal epithelial cells. Positive intracytoplasmic staining for the enzyme was also observed in invasive breast cancer cells and in metastatic lesions. In studying the percent of positive cells, the invasive carcinoma lesions had the highest percent, *in situ* lesions a lower percent, and the epithelial cells were always negative. Increased expression of the activated form of Type IV collagenase was also found in the progression of human colorectal cancer. Dr. Liotta suggested that these findings indicate that the intrinsic suppressor or inhibitor region of the enzyme may be defective in these tumor cells, or they may have lost natural inhibitor proteins such as TIMP-2. Understanding the mechanism of activation and the identification of these new inhibitor propeptides may lead to new therapeutic strategies for blocking the activity of the enzyme.

Dr. Liotta next described the work of Dr. Pat Steeg in his laboratory, who is attempting to identify suppressor genes that may naturally block the metastatic process but are lost in aggressive or metastatic tumors. She cloned and sequenced the entire mouse and human NM23 gene, which is present in high amounts in nonmetastatic tumors but is lost in metastatic tumors, and found a consistent loss of expression in the more metastatic breast carcinomas. In patients with node-negative tumors, there is a spectrum of NM23 expression, but in those patients with four or more positive nodes, there is a loss of NM23 expression. Those tumors with low NM23 expression may be undifferentiated and have a greater tendency to progress.

In searching for a known gene with the NM23 protein sequence, Dr. Liotta found a gene (AWD) involved in normal drosophila development to be almost identical. Mutations in different regions of the AWD gene cause abnormalities in different epithelial structures in the adult drosophila. Dr. Liotta suggested that this gene is a universal organizer of epithelial structure and differentiation. In transfection experiments, Dr. Steeg has been able to transfect the NM23 gene into metastatic murine tumor cells and block their ability to metastasize. She also located the gene on p23 and identified allelic loss in a number of human carcinomas, including renal, colon, lung, and breast, which have been shown to have allelic loss at the 17p region. Dr. Liotta suggested a new therapeutic strategy of replacing the missing NM23 protein product in metastatic cancers.

The final project described by Dr. Liotta involved a pharmacologic approach to treating cancer metastases based on his study of tumor motility. Dr. Elliott Schiffman has identified AMF, a cytokine produced by tumor cells, which profoundly stimulates their ability to migrate and is required for invasion. AMF works through a specific transducer system in the cell membrane, and in screening compounds that block this pathway, it was found that carboxyaminoimidazole, an antiparasitic agent, blocked motility and signal transduction from the AMF. In a dose-dependent manner, this compound inhibited tumor cell motility in a variety of tumor cell lines when the motility factor was used as a stimulant. Additionally, this compound blocked tumor cell proliferation, inhibited metastases formation and growth, and prolonged survival *in vivo*. The compound was unanimously approved for sponsorship by the Decision Network Committee, and Dr. Liotta stated, it is hoped that Phase I studies can soon begin.

The following points were raised in discussion:

- Using PCR, a study is underway to determine the exact nature of the mutation of the NM23 gene and whether there is actually a mutation in the allele that is retained in the tumor.

- Carboxyaminoimidazole was tested in the *in vitro* screen and inhibited all tumor cell lines, as well as drug-resistant P glycoprotein amplified cell lines.

- Type IV collagenase can be blocked outside of the cell where it acts.

X. CANCER DIAGNOSIS PROGRAM--DR. SHEILA TAUBE

Dr. Taube stated that the Cancer Diagnosis Program has changed very rapidly over the past several years to try to capitalize on the exciting developments in tumor biology and immunology. RFAs were developed to encourage collaborations between molecular biologists and clinicians and the development of better technology in cytogenetics and culturing of solid tumors. Dr. Taube said that currently about one-third of the branch's grants portfolio is devoted to applications of genetics to diagnosis. The branch also developed the Cooperative Human Tissue Network to respond to the needs of the research community for resources to facilitate diagnosis as well as basic research.

Dr. Taube noted another major change as a focus on identifying promising diagnostic approaches and moving them rapidly to the clinic. To use available NCI resources efficiently, a system is being developed to include ancillary studies of diagnostic or prognostic tests in ongoing clinical trials. A cross-divisional committee, the Diagnosis Decision and Implementation Committee (DDIC), was established to identify promising new diagnostic tests that are ready to be evaluated in large clinical studies and set priorities for introduction of the most promising tests into clinical trials. Criteria for setting priorities relate to the preliminary evaluation of the test, its anticipated impact, and whether a trial can be effectively implemented. When the DDIC agrees on the need for a trial, appropriate clinical populations are identified and protocols solicited and reviewed. To be able to move quickly, it has been proposed to use administrative supplements to ongoing trials and to research grants in laboratories where the techniques can be performed.

Dr. Taube identified collaboration with industry as another priority activity. Ongoing efforts, including the establishment of an information clearinghouse, are aimed at better understanding the interactions between industry and academia and encouraging technology transfer.

XI. CENTERS, TRAINING, AND RESOURCES PROGRAM--DR. BRIAN KIMES

Dr. Kimes stated that the reorganization of the CTRP in the DCBD represented the first time that the resources programs of the NCI have been integrated under one administrative authority, allowing them to have a more unified visibility and advocacy within the Institute. He suggested two major philosophical emphases for these resource programs: they will serve all of NCI, and wherever possible, they will be integrated with each division's research programs.

Beginning with the Organ Systems Coordinating Branch, Dr. Kimes recalled that the restructuring of the program had involved the dismantling of working groups and a focus on responding to current needs and interests of the Director. He noted Dr. Broder's support of an emphasis on solid tumors, which is reflected in initiatives in prostate cancer and breast cancer. The planning of workshops has involved NCI staff from all divisions, as well as members of the scientific community, thereby enhancing horizontal communication within the Institute. Topics for small workshops include the discrepancy between blacks and whites in the incidence and mortality from myeloma and the mechanisms of 5-FU and levamisole adjuvant therapy. R13 applications are expected on bladder cancer, ovarian cancer, and upper digestive tract cancers.

Moving on to discussion of the Research Facilities Branch or construction program, Dr. Kimes pointed out that there has not been any significant budget for construction since FY 1980. Although there is now no budget and no staff for the construction program, in the past, the program has provided construction funds to major cancer centers. Dr. Kimes suggested the need for long-term advocacy of such support. In addition, he stated that there is an inherent value in maintaining an active construction application process, because if applications receive good priority scores from NCI, this might help institutions get private funding. Further, NCI may receive some of the $15 million for construction authorized to be allocated by the NIH Director and because NCI has construction authority, it represents an information resource for NIH. Dr. Kimes noted that he and Mr. Philip Amoruso would be meeting with NIH representatives about an RFA for construction of animal production facilities.

With respect to the Cancer Training Branch, Dr. Kimes pointed out that while the branch is fully staffed, it has existed in isolation from the rest of the Institute for about 10 years. He stated that the goal for the next year will be to fully integrate the training program with the rest of the Institute and analyze the current overall training situation. A particular focus will be involving physicians in translating basic research into more applied areas.

In discussing the Cancer Centers Branch, Dr. Kimes first expressed appreciation to Mrs. Bynum for the preparation of the guidelines on cancer center comprehensiveness. He described the Cancer Centers Branch as the most important element of the CTRP and said that considerable effort will be devoted to strengthening the cancer centers. Because of the dilemma of increasing opportunities and a level budget, Dr. Kimes stated that it will be necessary to set priorities more efficiently and use resources more effectively.

Recalling the budget-related recommendations for strengthening the cancer centers from the Institute of Medicine (IOM) report, Dr. Kimes emphasized that the centers are intertwined with all the other NCI programs and a budget increase for centers would detract from some other programs. He said that progress is being made on the other IOM recommendations: Dr. Roper is chairing the Cancer Centers Program Planning Committee that is developing a 5-year plan with the help of an elected ad hoc consultant group of cancer center directors. The plan will address the issue of cancer centers' participation in the planning and decision-making process of the NCI, and efforts have been initiated to involve some of the cancer center directors in the decision-making process of the Cancer Therapy Evaluation Program, DCT. The management capacity of the centers NCI staff is being strengthened by the appointment of Dr. Margaret Holmes as acting branch chief and recruitment of program directors. Dr. Kimes invited suggestions of candidates for the position of branch chief. The goal of the program will be a more proactive and interactive approach.

In concluding his remarks, Dr. Kimes stated his intention to emphasize the use of the resource programs as catalysts and facilitators for horizontal communication, coordination, and implementation across the research programs of NCI. A strong interactive partnership with the cancer centers will be established and will build on the effective relationship with the American Association of Cancer Institutes.

The following information was provided in response to questions:

- Publications will emanate from all the organ systems program workshops. The larger workshops will also define potential areas for research initiatives and develop priorities.

- The restructured ad hoc nature of the organ systems working groups is expected to sustain the generation of new ideas.

XII. THE ADVANCED SCIENTIFIC COMPUTING LABORATORY AT FCRF--DR. JACOB MAIZEL

Dr. Maizel recalled that the supercomputer originated with the recognition of a need to exploit new knowledge of molecular biology through the maximum possible computing ability. The machine is located at the FCRF where it is operated by a contractor. The computer is tied by a high-speed phone line to the Laboratory of Mathematical Biology at NIH, and from there, it is connected to the Public Health Service Computer Network, other NIH local area networks, and through the National Library of Medicine and University of Maryland to the extramural community. NCI and the extramural community are the heaviest users of the computer.

From among the many uses of the supercomputer, Dr. Maizel discussed sequence analysis and structure prediction. The supercomputer allows correlation of local secondary structure features of RNA with biological properties. Using the example of HIV's genome, Dr. Maizel described how segments of a sequence are put through a program called FOLD that predicts the structure and the stability of that piece of RNA. When that same piece is shuffled and the folding process is repeated, the same base composition is found but in a totally random sequence. A Z score, a measure of the difference from randomness, is used to determine how unique or unusual a structure is. Certain regulatory features have been confirmed on the basis of the sequence analysis; knowledge of their structure may be very useful in understanding how to interact with them and control them.

Dr. Maizel also described the work of Wlodawer and colleagues on HIV protease, which is apparently essential for the infectivity of the virus and is involved in maturation of the proteins of the virus, as Dr. Maizel had found for the polio virus in the 1960s. The current studies involve determination of the structure of a related protease from a sarcoma virus, building an HIV model by analogy, performing a direct structure determination on a synthetic HIV protease, and producing a compound that serves as a prototype of inhibitors of this protease. The supercomputer's speed and size enabled the computations required for these studies to be performed in days rather than months. In conclusion, Dr. Maizel stated that the supercomputer should facilitate exciting new discoveries that will benefit diagnosis, treatment, etiology, and prevention of cancer and other diseases.

In discussion, it was pointed out that the existing supercomputer cannot be upgraded, but that funds have been included in the budget of the NIH Director for a more advanced supercomputer. A goal is to become part of the National Science Foundation's network and enhance file transfers with other supercomputers.

XIII. RECENT ADVANCES IN CYTOPATHOLOGY--DR. DIANE SOLOMON

Dr. Solomon began by defining cytopathology as a subspecialty of pathology that examines cells in order to reach a diagnostic decision about ongoing biologic/pathologic processes. Cytology specimens can be obtained from virtually any body site by scraping, brushing, tapping, and fine needle aspiration.

Dr. Solomon reviewed the development of one of the earliest cytopathological techniques, the Papanicolaou smear for detection of cervical cancer. Concomitant with the development and use of the Pap smear since the 1940s, there has been a 70 percent decrease in cancer deaths due

to cervical cancer. Dr. Solomon noted recent concern about the accuracy of cervical cytopathology, and in response, she and representatives of the Centers for Disease Control organized two national conferences to address quality assurance issues in cervical cytology. These meetings resulted in the first-ever consensus statements from various professional societies involved in cytology laboratory performance, and the conclusions are being used by the Health Care Financing Administration (HCFA) in revising and implementing national laboratory quality assurance regulations.

Dr. Solomon described as shocking the finding that more than 70 percent of cytology laboratories across the country are continuing to use the obsolete Papanicolaou classification system. Therefore, she and Dr. Charles Smart from DCPC organized a workshop to develp a rational, uniform diagnostic terminology for cervical cytology. The resulting product was recently published in the *Journal of the American Medical Association* and has come to be known as the Bethesda System for reporting cervical-vaginal cytologic diagnoses. The workshop participants recommended that: (1) the Pap classification no longer be used because it is obsolete, (2) an assessment of the adequacy of the smear should be included as part of any evaluation of a cervical smear, and (3) a descriptive diagnosis should be used for all cytopathology reports of anything other than a negative result. Dr. Solomon stated that the Bethesda System has received widespread national and international support, and she emphasized the importance of more effective communication between the cytopathology laboratory and the clinician. She suggested that the use of the system would lead to the development of a meaningful data base of diagnostic information that will facilitate research on the epidemiology and biology of cervical neoplasia. Also, improvements in Pap smear screening potentially affect 80 million women in the United States alone and could have a significant impact on health care.

Next, Dr. Solomon discussed fine needle aspiration, a technique developed in the 1930s but then largely abandoned in the United States until recently. She said the use of the technique is now growing exponentially, due in part to the development and use of highly sophisticated radiologic imaging techniques and in response to the current emphasis on cost-effective medical care. The advantages of fine needle aspiration include speed, the ability to sample multiple areas at one time and over time, simplicity, cost effectiveness, and high patient compliance. Dr. Solomon emphasized that the very fine needles now being used have virtually eliminated the risk of tumor implantation with this procedure. The cytopathology section is working on several collaborative projects to investigate extending the application of fine needle aspiration for pathologic diagnosis. These include a project with the Surgery Branch to use the technique as an initial diagnostic procedure for soft-tissue lesions in carcinomas and a project with the Medicine Branch to evaluate the use of fine needle aspiration in the diagnosis of lymphomas. Dr. Solomon concluded that cytopathology is no longer a screening procedure, but a cost-effective diagnostic modality for the present as well as future health care needs.

XIV. DCT PROGRAM REVIEW--DR. BRUCE CHABNER

Dr. Chabner began the DCT program review by explaining the DCT administrative structure and noting personnel changes. He provided the budget figures for FY 1989 and stated that DCT's budget represents about 30 percent of the Institute's budget. He also illustrated a budget summary by Program. He emphasized the importance of the DCT's interaction with the National Committee to Review Current Procedures for Approval of New Drugs for Cancer and AIDS, which is addressing issues such as endpoints for drug approval, and payment by third parties or Medicare for patients participating in clinical trials and for off-label use of drugs. The Committee has encouraged increased cooperation between the NCI and the FDA, and working committees from both the NCI and the FDA have been formed and will draft a document

outlining proposals for resolving the two agencies' differences of opinion on the drug-approval process.

XV. CLINICAL ONCOLOGY PROGRAM--DR. GREGORY CURT

Dr. Curt reviewed the organization of the Clinical Oncology Program (COP) and listed the Chiefs of the five Branches. He reminded the Board of previous presentations on accomplishments of the COP, including reports by Dr. Charles Myers, Chief of the Medicine Branch, on the use of suramin in prostate cancer, and by Dr. Steven Rosenberg, Chief of the Surgery Branch, on tumor infiltrating lymphocytes (TILs) as adoptive immunotherapy. He highlighted other accomplishments of the COP, as follows, beginning with studies within the Medicine Branch on:

- Markers for drug resistance, including the p170 glycoprotein, the glutathione transferase gene, and the ERCCI gene product.

- Antisense compounds as therapeutic agents in cancer and AIDS, for example, the c-*myc* antisense gene product in Burkitt's lymphoma.

- Dose intensity using GM-CSF in combination with FLAC (5-fluorouracil, leucovorin, Adriamycin, Cytoxan) in breast cancer and with high-dose CBDCA, a platinum analog, in cis-platinum-refractory ovarian cancer.

- Suramin in prostate cancer, as discussed at previous Board meetings.

He explained that Dr. Myers has reorganized the Medicine Branch into disease-specific clinics, including special Phase I studies (headed by Dr. Myers); breast cancer (Dr. Kenneth Cowan); GI cancer (Dr. Carmen Allegra); ovarian cancer (Dr. Eddie Reed); AIDS (Dr. Robert Yarchoan); and lymphoma (Drs. Ivan Horak and Wyndham Wilson). He also listed several collaborative clinical trials with investigators outside the Medicine Branch.

Turning to the Pediatric Branch, Dr. Curt first noted that the Branch has used its unique animal model for candidiasis to identify a new agent, itraconazole, which is an effective antifungal agent used in candidiasis, and a 48 kd cytoplasmic antigen, which may be useful as a diagnostic reagent. He then described research on differentiation and autocrine growth factors, particularly insulin-like growth factor (IGF)-II, in rhabdomyosarcoma by Dr. Lee Hellman. To determine whether IGF-II can function as an autocrine growth factor in rhabdomyosarcoma, Dr. Hellman established the cell line RD in serum-free media and then incubated the cells in the presence of a monoclonal antibody (MoAb) to the IGF-II receptor; a single application of 1 μg/ml of the MoAb significantly inhibited the growth of the rhabdomyosarcoma cell line. Further research indicated that transretinoic acid can also significantly inhibit the growth of rhabdomyosarcoma, but studies are ongoing to determine whether this occurs as a result of modulation of IGF-II expression. Clinical studies within the Pediatric Branch have focused on optimal management of febrile neutropenia, and results of a randomized study have shown that monotherapy is an effective, cost-effective, and convenient alternative to polymicrobial chemotherapy for neutropenic fever. The Branch has also continued to play a leading role in Phase I studies in children and has recently focused on studies of piritrexim, IL-2, and various intrathecal agents in cancer, and AZT and ddI in AIDS.

Next, Dr. Curt outlined research within the NCI-Navy Medical Oncology Branch (NCI-NMOB), including the demonstration of opioid/nicotine receptors in both non-small cell

(NSCLC) and small cell lung cancer (SCLC) cell lines and studies of p53 as a tumor suppressor gene (anti-oncogene) in lung cancer. Clinical studies within the NCI-NMOB focusing on chemotherapy and hyperfractionated radiotherapy in limited SCLC have shown a survival rate about twice that reported in previous studies. In the area of NSCLC, studies within this Branch have correlated *in vitro* sensitivity to clinical response and have documented that neural endocrine markers in NSCLC are prognostic for better response.

Within the Surgery Branch, Dr. Curt noted Dr. Rosenberg's recent results in TILs showing MHC-restricted lysis in melanoma, the finding that TILs with specific lytic capacity can be obtained from patients with lung and breast cancer, and an ongoing trial using lymphocytes as vehicles for human gene transfer. He also summarized research by Drs. Marston Linehan and Berton Zbar suggesting that recessive oncogenes or anti-oncogenes may be important in the pathogenesis of renal cell cancer. Clinical studies within the Surgery Branch include:

- TILs in melanoma, which has shown a 50 percent objective response rate
- Combination therapy with IL-2 and alpha-interferon in melanoma
- Phase I trial of M-CSF
- Modulation of IL-2 toxicity.

Dr. Curt concluded by describing the Radiation Oncology Branch studies. In the laboratory, studies are ongoing of nitroxides as radiation protectors, and work has begun on water-soluble chemoluminescence substances. Nitroxides can protect against radiation damage, radiometric drugs, and oxygen toxicity; studies are ongoing to determine their usefulness against postischemic reperfusion injury. In clinical studies, the Radiation Oncology Branch is continuing Phase I trials of photodynamic therapy (PDT) and is studying IUdR as a radiation sensitizer in sarcoma and dose fractionation in limited stage SCLC. The PDT trials, which have all used hematoporphyrin, have shown that PDT is very effective as a local therapy for surface malignancies; trials are now focusing on systemic treatment including hematoporphyrin derivatives and laser light for intraperitoneal malignancies using lipid vesicles to diffuse light uniformly.

XVI. BIOLOGICAL RESPONSE MODIFIERS PROGRAM--DR. DAN LONGO

Dr. Longo stated that the Biological Response Modifiers Program (BRMP) represents a unique program of both intra- and extramural basic and clinical research components charged with the responsibility of developing biological therapeutic agents. He listed the two branches and three laboratories that constitute the BRMP and emphasized the extensive network of meetings and conferences to ensure close collaboration between laboratory and clinical research. Rather than list a series of findings and accomplishments within the BRMP, Dr. Longo selected one example of a research project to illustrate how the BRMP follows a single observation made in an intramural laboratory through its preclinical development to clinical trial. He explained each step in the development of anti-CD3-activated T cells from the application of basic research on T-cell response to antigens. He summarized the key steps as follows:

- The identification of a different type of T-cell receptor, which includes a zeta-eta heterodimer instead of a zeta-zeta homodimer.

- The determination that two distinct pathways are initiated in the T cell in response to a single stimulus and identification of possible mechanisms of tolerance induction in the T cell through the thymus.

- The demonstration of polyclonal T cell activation as a viable therapeutic approach against cancer.

- The development of a new cell--anti-CD3-activated T cells--for adoptive cellular therapy.

Dr. Longo noted that clinical studies are underway to evaluate the use of anti-CD3 as a polyclonal T-cell activator and as an antitumor biological response modifier.

XVII. DCT BOARD OF SCIENTIFIC COUNSELORS--DR. JOHN NIEDERHUBER

Dr. Niederhuber outlined the major responsibilities of the Board of Scientific Counselors indicating its role in budget review of contracts, RFAs, and cooperative agreements. He noted that a primary concern of the Board was the inadequate funds available to NIH and NCI, particularly the funds available for investigator-initiated research through R01s and P01s, as well as training grants.

An additional BSC activity is conducting intramural site visits to ensure quality research activities in the DCT intramural program. During 1989, the Laboratory of Experimental Immunology and the Pediatric Branch received site visits. For the upcoming year, three have been scheduled including the Radiation Oncology Branch, the Laboratory of Biochemical Physiology, and the Clinical Research Branch.

Dr. Niederhuber briefly reviewed the concepts for new procurements, recompetitions, RFAs, and cooperative agreements, together with proposed dollar amounts, that were presented to the Board during 1989 and noted actions the Board had taken in approving the concepts and funding amounts. The Board heard scientific presentations on suramin and antigrowth factor compounds, oncogenes and transcription factors in human SCLC, computer radiology imaging, updates of progress on extramural trials with biologicals, accrual efforts for cooperative groups, high priority clinical trials, progress of IL-2/LAK clinical trials and plans for future trials, proton beam therapy, and PDT. The Board also participated in discussions with FDA on issues of concern regarding the drug approval process.

XVIII. DEVELOPMENTAL THERAPEUTICS PROGRAM--DRS. MICHAEL BOYD, JOHN NIEDERHUBER, AND WILLIAM MITCHELL

DEVELOPMENTAL THERAPEUTICS PROGRAM--DR. BOYD

Dr. Boyd explained that during the decade from 1975 through 1985 new compounds were tested initially *in vivo* in a disease-specific, mouse leukemia screen. Active compounds underwent more vigorous testing, and those agents exhibiting a broad spectrum of activity were prioritized and a few selected for full preclinical development and entry into clinical trials. These agents were tested in patients representing a multiplicity of tumor types. Although clinical trials are still ongoing with several of these agents, results are not particularly encouraging. He added that prior to 1975, this screening strategy was useful in identifying clinically active agents, but most of them were active against leukemias and lymphomas.

Dr. Boyd continued with a description of the new disease-oriented antitumor drug screening methodologies, in which new compounds are screened *in vitro* against a battery of tumors representing a diversity of cancer types with follow-up testing of active agents *in vivo* against the same tumor lines. This approach permits identification of disease-specific or tumor type-specific agents which then become candidates for disease-specific clinical trials. The endpoint of the antitumor screen is cell viability or cytotoxicity. The development and implementation of this screening program have required extensive effort in acquisition and characterization of cell lines, development of automated growth inhibition assays, utilization of data support systems, as well as construction of additional facilities to accommodate large-scale screening.

Dr. Boyd provided several examples illustrating how the *in vitro* screen permits profiling or characterizing drugs by patterns, cell lines, or tumor panel sensitivity, thus permitting identification of novel leads, as well as identifying and evaluating compounds with similar mechanisms of action and structures and new analogs. Pilot studies using well characterized compounds have been performed to evaluate the screen and its reproducibility.

Dr. Boyd then described the HIV screen, noting that as in the antitumor screen, a colorimetric *in vitro* assay is utilized; multiple concentrations of an agent are tested to determine the most effective concentration that prevents HIV from killing the host cells but is not toxic to the cells themselves. This screening procedure is used for empirical testing of large numbers of new agents as well as identifying new actives from previously identified active anti-HIV classes of compounds.

Both the anticancer and anti-HIV screening programs receive materials from a variety of sources worldwide, and most of these materials are maintained in NCI's chemical repository. Dr. Boyd pointed out the importance of the natural products drug discovery effort, which involves the collection of tropical plants and a wide taxonomic variety of marine organisms and extraction of pure fractions for testing in the antitumor and the anti-HIV screens. Pure extracts are needed so that the structure of any biologically active component can be determined. Data were presented on the anti-HIV activity of two natural product extracts with unique structures.

In response to questions, Dr. Boyd provided the following information:

- Very few breast cancer lines are represented in the *in vitro* tumor panel; lines that are satisfactory and that meet minimal criteria are not available. A contract-supported effort is ongoing to develop breast cancer and prostate cancer lines specifically suitable for incorporation into the panel.

- Studies are currently in progress to determine whether active constituents of crude extracts can be detected by testing the crude extracts in the antitumor screen for a unique profile of sensitivity. The most uniquely sensitive lines can then be used to track the active constituents. Preliminary results with fungal extracts indicate that this may be feasible.

- As new information (e.g., molecular findings on drug resistance) becomes available on cell lines currently in the panel, it is included in their characterization summary.

AD HOC EXPERT ADVISORY COMMITTEE FOR DTP ANTITUMOR AND ANTI-AIDS SCREENS--DRS. NIEDERHUBER AND MITCHELL

The DTP antitumor and anti-HIV drug discovery screens were reviewed by the Ad Hoc Expert Advisory Committee on November 13-15, 1989. Dr. Niederhuber summarized the conclusions from the Committee's report on the antitumor screen, which had been distributed to Board Members. The Committee unanimously felt that Dr. Boyd and his staff had made remarkable achievements in the development and implementation of the overall program. The collection and processing of natural products have become a unique national resource. Data confirm that the screen can be successfully utilized to identify molecules exhibiting tissue-selective cytotoxicities, and it is likely that new candidates for clinical evaluation will be discovered in the coming years. There was unanimous and enthusiastic recommendation by the Committee that the project be fully implemented without delay and be given the highest priority.

Among the Committee's recommendations were the following:

- Breast, prostate, and squamous cell lung cancer remain to be included in the panel, although a 60-cell-line panel was considered sufficient size for initial screening.
- A substantial increase in the number of chemists is needed for fractionation of natural products extracts and structure determinations, and allocation of additional space for the chemistry section was designated as an urgent priority.
- DTP should continue to explore alternative ways to analyze and present the *in vitro* data.
- The criteria for designation of active agents need to be established and clearly defined.
- Strategy for pharmacologic and toxicologic evaluation in the xenograft model should be defined and developed. Addition of staff with expertise in tumor biology and pharmacology was strongly endorsed.

During discussion, Dr. Mihich remarked that despite limitations of the number and types of lines in the cell panel, the antitumor drug discovery effort was progressing well, and he commended Dr. Boyd for his efforts. He expressed the concern that while the screen as designed can select specific compounds that are active against specific types of tumor cells, it is not capable of picking up elements of selectivity of the agents. An additional concern was that compounds requiring *in vivo* activation may be missed by the *in vitro* screen. He recommended that the xenograft model would be more appropriately utilized as a stage II system to validate the *in vitro* approach to selection of antitumor agents. Dr. Elion concurred and added the suggestion that stage II testing be an *in vivo* model, rather than more *in vitro* testing. Dr. Boyd stated that compounds of interest currently go on to further testing in xenograft models without delay. The expanded battery of cell lines representing a particular panel for stage II evaluation would be utilized to confirm specificity in the initial *in vitro* panel. He said many cell lines are currently available to pursue this stage II strategy.

Dr. Mitchell summarized recommendations from the Committee's report on the anti-HIV screen. Among these were recommendations that the resource of cell lines from the tumor panel be used to determine if they can predict chronic human toxicity and that acute toxicity studies be conducted in mice to reduce effort in pursuing anti-HIV testing of compounds with unacceptable acute toxicities. It was suggested that priority be given to development of a nonhazardous, HIV double-mutant assay and that expertise gained from development of anti-HIV screen be used to

develop anticytomegalovirus screens in order to focus on another major viral disease associated with AIDS.

Dr. Mitchell commended DTP on behalf of the Review Committee for progress made in the development and implementation of the anti-HIV screen.

XIX. RADIATION RESEARCH PROGRAM--DRS. JOHN ANTOINE, BARBARA McNEIL, AND HERMAN SUIT

RADIATION RESEARCH PROGRAM -- DR. ANTOINE

Dr. Antoine began with a description of the organization of the Radiation Research Program (RRP) and an overview of its activities. The RRP is an extramural research program with the primary mission of developing research activities using radiation and related forms of energy for the diagnosis and treatment of patients with cancer. It consists of two branches, the Radiotherapy Development Branch (RDB) and the Diagnostic Imaging Research Branch (DIRB).

In describing RDB's activities, Dr. Antoine noted that fast neutron beams generated by cyclotrons are being studied for their potential as treatment for localized tumors. Phase III trials in head and neck, prostate, and lung cancer are currently underway and will be completed in early 1992 or 1993. Participating institutions are the University of Washington, M.D. Anderson, and the University of California in Los Angeles.

Proton beam therapy, which was discussed by Dr. Suit in greater detail (see below), is under investigation for treatment of critically located tumors. Dr. Antoine stated that the advantage of proton therapy is that a high energy beam can be focused so that radiation is concentrated in the tumor while sparing normal tissue from damage. Hyperthermia, known to have an anticancer effect, is under study for use in combination with radiation and/or chemotherapy.

Another high priority of the RRP are radiosensitizers, chemicals that enhance the ability of radiation beams to kill cells. Sensitizers are selectively retained by tumor tissues rendering them easier to destroy by radiation. Dr. Antoine remarked that the sensitizer designated SR-2508 is presently being evaluated in RTOG clinical trials and has shown encouraging results.

The RRP also supports the testing of compounds for use in light delivery systems (photodynamic therapy) for cancer therapy. When certain compounds selectively taken up by tumor cells are activated by light, cell killing occurs. At present, limited trials are being conducted with the compound photofrin II.

Next, Dr. Antoine described systemic radiation therapy (SRT), the delivery of cell-killing radiation to primary and distant tumor sites. An isotope coupled with a carrier is injected and targets tumor cell antigens. Dosimetry is critical for this type of system, and the RRP has been instrumental in development of a dosimetry center which supports clinical SRT trials throughout the United States.

Dr. Antoine next turned to the highlights of the DIRB. One of the new programs developed by this branch is the Radiologic Diagnostic Oncology Group (RDOG), which meets the need for diagnostic imaging studies in the diagnosis and staging of cancer. The Group's current clinical trials, which were discussed by Dr. McNeil (see below), are the first prospective cooperative studies to be performed in the field of diagnostic imaging.

To illustrate research in the area of nuclear medicine, Dr. Antoine described the applications of positron emission tomography (PET) and radioimmunodiagnosis (RID). He pointed out that PET provides not only three-dimensional imaging but also quantitative information on the degree of tumor malignancy and viability of tumor tissue following treatment. Dr. Antoine also remarked that by utilizing an appropriate combination of radiolabeled antibodies in RID, it is theoretically possible to diagnose tumor presence anywhere in the body. Should this prove to be the case, he noted that many expensive complementary diagnostic imaging procedures could be eliminated.

One of the goals of the RRP is the development of imaging techniques that permit noninvasive diagnosis, are cell- and tissue-specific, and provide accurate diagnosis and staging of cancer. Dr. Antoine commented that the field of magnetic resonance imaging (MRI) has been very dynamic over the past several years and has made detailed anatomic imaging possible. Improvements in MRI and other modalities may yield tissue-specific diagnosis without the need for surgical biopsy.

DIAGNOSTIC RADIOLOGY COORDINATING COMMITTEE: BACKGROUND--DR. ANTOINE

Dr. Antoine reported that Congress, in recognition of the many contributions of diagnostic imaging to patient care, directed the NIH to establish a Diagnostic Radiology Coordinating Committee. This Committee, which is sponsored by several of the Institutes, is charged with developing a 5-year research plan for diagnostic radiology/imaging. The Committee meets monthly and is responsible for information dissemination and improvement of the NIH diagnostic imaging computerized data base.

RADIOLOGIC DIAGNOSTIC ONCOLOGY GROUP--DR. McNEIL

Dr. McNeil stated that the major long-term activity of this group is to design protocols for the optimal care of cancer patients. To achieve this overall objective, she cited the importance of obtaining absolute and relative information from diagnostic imaging modalities by optimizing patient reimbursement, conducting comparative imaging studies with state-of-the-art equipment and staff trained in the most current techniques from participating institutions, and identifying specific areas for improving image interpretation.

For purposes of clarification, Dr. McNeil pointed out several basic differences between the organization and implementation of diagnostic trials and therapeutic trials. Patient randomization is seldom if ever performed in diagnostic trials because the basic objective is comparison of imaging modalities. In diagnostic trials, the endpoint is diagnostic information compared with pathological diagnosis, whereas in therapeutic trials the endpoint is a survival or remission parameter. The statistical approaches and analytical approaches for evaluating data generated are completely different and are essentially separate disciplines. Diagnostic trials also have the unique problem of institutional and image reader variability.

Core activities of the RDOG include collection, validation, and monitoring of data as well as maintenance of an imaging bank. The American College of Radiology is responsible for these aspects. The Harvard Medical School oversees the second group of core activities, which involves quality control of data and conducting data analyses.

Diagnostic imaging studies are currently underway on lung, prostate, colorectal, and pancreatic cancers. Two study areas projected to begin next year will include head and neck

tumors, and musculoskeletal tumors. RDOG includes nine participating institutions, and for each institution, key individuals responsible for each protocol (e.g., surgeons, pathologists, and radiologists) are identified. Considerable management time is required to ensure appropriate and timely data analysis and quality control, adequacy of patient accrual rates, and adherence to imaging protocols developed by the RDOG.

Dr. McNeil described the prostate cancer protocol to illustrate the nature of the diagnostic imaging studies currently in progress. The primary objective is to compare transrectal ultrasound with MRI for staging patients with early operable disease (stages A and B). A secondary objective is to determine the ability of ultrasound and MRI to detect small cancerous nodules and hence their utility for screening patients.

Dr. McNeil reported that the results, based on approximately 200 patients over 16 months of study, were disappointing. Of patients who were diagnosed by pathology as stage A or B, ultrasound correctly classified only 46 percent and MRI approximately 57 percent. Based on the sample size, there does not appear to be a significant difference between the diagnostic accuracy of the two modalities. Previously published results suggested considerably higher accuracies for both of these imaging modalities, particularly for MRI, with figures ranging from 80 to 90 percent. Dr. McNeil asserted that the data from the RDOG study are reliable because the patient sample was five to six times larger than in any previously published study, and there were no significant differences among the participating institutions in accuracy of the two imaging modalities.

In terms of ability of these imaging modalities to detect lesions according to size, ultrasound detected only 58 percent of lesions that were diagnosed pathologically as cancerous, and only about 37 percent of those under 1 cubic centimeter, the target size that corresponds to a radius between 5 and 10 millimeters. These findings suggest that detectability by ultrasound is low, and its usefulness as a screening modality with current instrumentation may not be ideal.

In response to a question from Dr. Greenwald regarding omission of controls from diagnostic imaging trials, Dr. McNeil pointed out that these studies could be designed with or without randomization, but unlike therapeutic trials, which are intended to affect patient mortality, clinicians generally prefer to obtain comparative diagnostic information from the diagnostic imaging trials. She acknowledged that the number of false positives from diagnostic imaging is probably high.

PROTON BEAM THERAPY--DR. SUIT

Dr. Suit began his presentation with an overview of the goal of cancer treatment, emphasizing that the patient be free of tumor and treatment-related morbidity. Tumor cells must be inactivated at primary, regional, and distant disease sites. He pointed out that with available treatment modalities, considerable morbidity is associated with treatment of primary tumor, and the treatment is often unsuccessful.

Improvement in local control, by improving radiation dose distribution, not only produces better control of tumor but also less morbidity from radiation damage outside the target. Dr. Suit added that historically it has been demonstrated that each major technical advance in dose distribution has yielded gains in local tumor control, gains in survival, and reduction in morbidity. Dr. Suit expressed the opinion that prospects for future gains for improved dose distribution are excellent and that with the technical means available, for example, proton therapy, these gains are attainable.

Dr. Suit cited examples of malignancies (malignant melanoma of the eye, sarcoma of the skull base) in which proton therapy resulted in significantly greater local tumor control and increased survival or local tumor control equivalent to that achieved with standard treatment. He also suggested that proton therapy might be useful for several sites of malignancies (brain, head and neck, larynx) as well as advanced disease states for which most deaths occur from local progression of the disease or complications of treatment. For some anatomic sites, protons enable a much higher concentration of dose to target than x-rays.

Dr. Suit identified the cyclotron facilities located in the United States and foreign countries and reviewed their status of operation. The two operational facilities in the United States are currently equipped with older cyclotrons and have a very limited patient treatment capacity. He proposed that there be at least four regional proton therapy centers in the United States. In addition to serving as clinical research facilities, these centers would serve as referral centers for patients with tumors for which proton therapy has established effectiveness and patients with special problems.

In discussion, Dr. Bragg inquired whether a worldwide network protocol approach was being utilized. Dr. Suit stated that the Proton Therapy Cooperative Oncology Group, a U.S. organization with participants from Europe, Japan, and the Soviet Union, is currently planning protocols that will be utilized in the various centers. The proposed four regional centers in the United States would cost about $160 million. The current cost for proton therapy is about 2.5 times higher than regular radiation therapy.

XX. REPORT FROM THE COMMITTEE TO REVIEW PROCEDURES FOR APPROVAL OF NEW DRUGS FOR CANCER AND AIDS--DR. LOUIS LASAGNA

As introduction, Dr. Roper recalled then-Vice President Bush's request to the President's Cancer Panel to establish a committee to review procedures and issues associated with approval of new drugs. Since the initiation of the committee about a year ago, many speakers have had the opportunity to present their views on a variety of questions, including speed of drug approval, early release of drugs, payment for drugs, and insurance coverage. Dr. Roper congratulated Dr. Lasagna, chairman of the committee, for the work accomplished to date.

Dr. Lasagna described the committee as well constituted for its task because of the range of relevant expertise represented and the fact that members come from academia, industry, and government. He acknowledged the assistance of Dr. Elliott Stonehill and his staff.

Dr. Lasagna stated that the interest of committee members in their tasks is reflected in their support of new and better remedies for diseases that are currently not well treated, adequate payment for clinical research dealing with these life-threatening diseases, payment for the cost of treatment, and all deliberate speed in drug approval. The committee opposes regulatory lethargy or unreasonableness.

Dr. Lasagna listed accomplishments of the committee as follows: NCI and FDA have instituted monthly meetings to discuss areas of mutual interest on which there is disagreement; the recurrent problem of an inadequate appeals mechanism when there is a conflict between the sponsor and FDA has been addressed; the public has been reminded of unmet patient needs and the impatience of those who are dying for the remedies they need; HCFA and third party payers have been confronted with the inconsistencies in their reimbursement practices for investigational drugs and off-label uses of drugs; and the inadequacies of FDA staffing and facilities have been recognized. Among the problems that the committee has encountered, Dr. Lasagna noted the

early perception among the FDA leadership that the committee was overly critical of FDA; the vocal, and, on occasion, unruly participation of patient advocacy groups in committee meetings; and the potential loss of impact because of FDA's current problems. Dr. Lasagna expressed his admiration for the effectiveness of some of the patient advocacy groups from the AIDS community.

As to future plans of the committee, Dr. Lasagna stated that there is no simple solution to the basic problem of scarce resources in the face of the high costs of research. He indicated that the committee's report and recommendations should be completed within about 6 months.

Dr. Elion, a member of the committee, reiterated the idea that the committee's contribution has been to allow problems to be aired openly and to provide a forum for those who have a stake in the situation. She also emphasized that the committee had succeeded in bringing about discussion of the criteria for judging anticancer drugs. Dr. Broder expressed gratitude to Dr. Lasagna and committee members and pointed out that the organized clinical trials that are critical to drug development do not have to be slow. On behalf of the President's Cancer Panel, Dr. Longmire also expressed appreciation to Dr. Lasagna and the committee.

XXI. RESEARCH APPROACHES TO DIETARY INTERVENTIONS FOR CANCER PREVENTION IN WOMEN: REPORT OF A WORKSHOP-- DR. PETER GREENWALD

Dr. Greenwald reported that the DCPC Board of Scientific Counselors held a workshop in October 1989 to consider options for pursuing studies of the diet and breast cancer relationship. Among the participants were NCAB members Mrs. Helene Brown, Dr. Erwin Bettinghaus, and Dr. Roswell Boutwell.

Before discussing the studies presented at the workshop, Dr. Greenwald reviewed evidence behind the fat and cancer hypothesis, focusing in particular on dietary fat and breast cancer. Beginning with animal studies, he noted Tannenbaum's 1945 study in which rats on a high fat diet, at every level of caloric intake, got more tumors than rats on a low fat diet. The effect was greatest at the higher or *ad libitum* level of calorie intake. In international correlation studies, more women in countries where there is high fat intake get breast cancer, with a five- to sixfold differential in death rates across nations. A migration study by Armstrong, which separates data by age group, showed that even in older age groups the breast cancer rate continued to increase 6 to 16 years after migration from Italy to Australia. Responding to comments from Board members, Dr. Greenwald acknowledged that there is some instability in the small numbers reported in the Armstrong study, but he emphasized that these are the best available data on age at migration.

Dr. Greenwald cited data from other studies as follows:

- A study by Hirayama in Japan found that over 20 years there was a 2.5-fold increase in fat intake and approximately a 50 percent increase in breast cancer over the same period.

- A study by Kolonel in Hawaii, involving five different ethnic groups, found that regardless of the type of fat consumed, there was a strong correlation between fat intake and breast cancer.

- A study of Seventh Day Adventists by Phillips found approximately a 30 percent decrease in mortality, compared with the general population, for colorectal and breast cancer; this population gets about 32 to 34 percent of their calories from fat.

- A case control study by Toniolo in Northern Italy found a significant positive relationship between higher levels of fat intake and breast cancer in postmenopausal women.

- A study by Willett of 90,000 nurses found no association of fat intake, as reported by mail questionnaire, with breast cancer, although an association was found with bowel cancer. Among a subgroup of this population, the use of four different 7-day food records to identify fat intake revealed a large measurement error, especially in the lowest quintile of fat intake which served as the baseline in the analysis.

- A very recent study by Willett's group found that postmenopausal weight gain is associated with increased breast cancer risk.

Dr. Greenwald suggested that given the current state of the art of epidemiology, there will be both positive and negative studies even if there is, in fact, a direct association between fat intake and breast cancer. Therefore, what is needed is testing of a strong hypothesis through a clinical trial.

Dr. Greenwald reported that at the October workshop different investigators had proposed various trials. Among these was a prevention pilot trial involving tamoxifen proposed by Dr. Richard Love at the University of Wisconsin. The pilot would further test the favorable effects of tamoxifen with respect to heart disease risk factors and assess potential side effects, particularly in women with osteoporosis. If the pilot is successful, a full-scale trial would require about 16,000 postmenopausal women, with the endpoint being a 50 percent lower frequency of breast cancer. The total cost estimate for such a trial would be about $64 to $96 million over 7 years.

Dr. Norman Boyd at Princess Margaret Hospital in Toronto discussed his current pilot trial in which 600 mostly premenopausal women are randomized to a low fat diet or control group. The conclusions to date are that compliance to a low fat diet is feasible, extensive mammographic dysplasia appears to identify women at increased risk, and mammographic dysplasia is associated with dietary fat and fat metabolism.

Dr. Charles Smart considered whether a study could be done of women with lobular carcinoma *in situ* who are at high risk of developing breast cancer. He concluded that these tumors are too rare and the patients too scattered for such a study to be feasible.

Dr. Rowan Chlebowski has a pilot adjuvant trial (Women's Intervention Nutrition Study or WINS) in progress in which dietary fat is reduced in postmenopausal women with stage I or II breast cancer. All of the women get standard treatment, and the endpoint is prevention of recurrence. A full-scale trial would require 1,600 women at a cost of $6 million to $7 million.

Also at the workshop, Dr. Boutwell discussed the mechanisms of the fat effect, highlighting these hypotheses: (1) the overabundance of essential fatty acids such as linoleic acid results in higher prostaglandins and enhanced tumor promotion, and (2) the effect is related to the overabundance of calories. He emphasized the complexity of the experimental data.

Dr. Ross Prentice presented an update on the Diet-FIT trial proposal and stated his belief that an intervention trial like Diet-FIT should be a central element in NCI's evaluation of the role of a low fat diet in cancer prevention. He reported that the feasibility phase of the Women's Health Trial verified long-term compliance in 1,700 women. Another study showed that hormonal changes, especially in estradiol, result when postmenopausal women change their diets. Analytic epidemiologic work suggests the effects of fat are independent of calories although both are important. Dr. Prentice stated that a meta-analysis by Dr. Howe of case control studies provides evidence of a fat effect as well as a calorie effect. He suggested some design improvements over the Women's Health Trial, including limiting the sample to 59- to 69-year-old women and looking at several cancers, heart disease, and total mortality. He also suggested that the trial involve simply reduction in fat (rather than changes in certain type of fat intake) because it is easier for people to understand and comply with and is sensible in terms of the study's multiple endpoints.

Dr. Greenwald indicated that the BSC had not been asked to perform a technical review of the Diet-FIT trial, but to examine options for diet and breast cancer studies. Most DCPC Board members expressed support for a large-scale trial, were impressed with the improvements over the Women's Health Trial, and accepted the point that the different studies proposed were complementary and not duplicative. The discussion is expected to be continued at a later BSC meeting.

In summarizing his own view, Dr. Greenwald emphasized the need to maintain a strong research agenda related to prevention and clinical prevention trials as well as basic research. He recognized the problem of limited resources but suggested a need for more aggressive support of prevention and control activities. He noted that if the dietary fat hypothesis is borne out, it would present the opportunity for a very large reduction in cancer incidence. Responding to Dr. Korn's questions, Dr. Greenwald acknowledged that Dr. Virginia Ernster, a member of the DCPC Board, contends that the hypothesis is weak and cited epidemiologic studies in progress as supporting her view. He suggested that these studies are too preliminary to draw valid conclusions, and that others have the opposite view--that the evidence is so strong we should make public recommendations without clinical trial testing. It is just such a situation where trials may be most needed.

Dr. Temin questioned what the public health impact of a trial like Diet-FIT would be when the reduction of dietary fat is now so widely prescribed in Amercian society. Dr. Greenwald agreed that there are adequate data to support interim guidelines for decreasing fat and increasing fiber in the diet, but the evidence is not absolutely documented. Also, the trends are not as clear as DCPC would like. A randomized trial would provide the strongest evidence of an effect and would provide the only solid evidence on time relationships. In addition, because there would be major implications for the food industry if the fat and cancer hypothesis is supported, the best possible evidence is needed.

Mrs. Brown asked whether the results of studies on fat and colon cancer demonstrate an effect of dietary fat on the causation of cancer. Dr. Greenwald replied that these studies suggest that the more fat consumed, the higher the risk of colon cancer. Clinical trials are needed to provide the best evidence of an association, but none with a cancer endpoint are in progress, either for colon cancer or breast cancer and dietary fat.

Dr. Fisher asked for an estimate of the reduction in cancer incidence that could be anticipated from the Diet-FIT trial. Dr. Greenwald answered that a 50 percent reduction after 10 years (average 15 percent reduction for the entire 10 years) could be expected. Responding to

Dr. Durant's question about the public health impact from the reduction of dietary fat, Dr. Greenwald said that the most important public health endpoint might be reduced overall mortality, of which the major components would be heart disease, colon and breast cancer, and possibly ovarian and endometrial cancer. He stated that the reduction in cancer incidence, a Diet-FIT endpoint, would be reflected at some later time by a decrease in mortality.

Responding to Dr. Mihich's questions about possible biases in the data, Dr. Greenwald said that in epidemiology, the bias is chiefly toward the null hypothesis and derives from measurement errors, e.g., people do not know or cannot remember what they ate. Some epidemiologic studies do not have built-in validation factors. Another bias is the homogeneity bias--people are too similar to discern differences. These biases are in the direction of obscuring true differences; they do not allow the demonstration of a relationship based on artifact. Dr. Boutwell indicated there are not adequate animal data to determine how long it would take to observe an effect following a change in diet.

Among the other points raised in discussion were the following:

- Because cancer may be present before it is diagnosed, in some dietary studies, cancers diagnosed in later years are weighted more heavily.

- The National Heart, Lung, and Blood Institute has been contacted about co-funding a possible low fat dietary trial but would require more information on the specifics of any such trial and an indication of NCI support before indicating interest.

- A study with incidence as an endpoint is a prevention trial but overall mortality can also be monitored to consider factors such as competing risks.

- It is no longer ethically possible not to advise all groups in a dietary trial to decrease their fat intake and decrease total calories. However, controls are given the general DHHS recommendations. The intervention group that receives counselling and is monitored by various instruments may be more likely to comply with the lower recommendations so that there will be clear differences between the control and study groups with respect to dietary fat intake.

- Epidemiologic studies have provided important evidence about the relationship between disease and certain causative factors (e.g., cigarette smoking), but dietary studies are extremely complex because of the number of variables involved and the uncertainty about what people are eating. This complexity also makes clinical trials difficult.

Following discussion in closed session, Dr. Korn made the following announcement: " The National Cancer Advisory Board has voted unanimously not to concur with the recommendation of the initial review group relating to the grant known as Diet-FIT on grounds other than scientific merit under its authority to (1) ensure appropriate use of grant, cooperative agreement, and contract funds in the NCI's support and conduct of research and related activities and (2) assist the NCI in establishing objectives and priorities, and identifying resource allocation factors and in enhancing program management and effectiveness." He added that the Board would provide a written statement documenting its decision to the Director of NCI as soon as possible.

XXII. CLOSED SESSION: SPECIAL ACTIONS SUBCOMMITTEE

A portion of the second day of the meeting was closed to the public because it was devoted to the Board's review of a specific grant application requesting support, which the Board recommended not to be funded.

XXIII. NEW BUSINESS

ACCEPTANCE OF LARGE INVESTIGATOR-INITIATED RESEARCH GRANTS

Dr. Broder introduced the first item of new business by asking the Board to consider whether the NCI should institute an upper funding limit for investigator-initiated research grants (R01s). He explained that the NCI does not currently have a limit, but as an operating practice brings any large R01 proposal of approximately $1 million per year or more to the Executive Committee for consideration before the application is sent out for review. He added that proposals of this level have been uncommon. He asked the Board members to discount Outstanding Investigator Grants in their consideration of this issue and referred the Board to a handout summarizing levels of past R01/P01 grant awards.

Dr. Mihich seconded a motion by Dr. Temin that a limit (e.g., $1.5 million per year) that is outside the historical distribution range of funding be set. Discussion ensued about factors, such as large equipment, that might justify a large budget, and Dr. Broder emphasized the need to establish a format in which R01s truly represent investigator-initiated research and are not used when other mechanisms (e.g., cooperative agreements) would be more appropriate. Mrs. Bynum suggested that the Board postpone consideration of setting an upper funding limit for acceptance of R01s, noting that the NIH is currently considering publishing a notice addressing this issue for the entire NIH extramural community. The Board concurred that at the January 1990 meeting there will be further consideration on whether upper monetary limits should be specified for investigator-initiated research grants. Dr. Temin withdrew his motion.

JANUARY 31, 1990, WORKSHOP ON NCI CLINICAL TRIALS

Dr. Korn referred to the distributed preliminary agenda and list of participants for the January 31, 1990, meeting, explaining that the workshop was primarily for airing issues related to the release of information derived from NCI-supported clinical trials. He noted that several Board members will be attending the workshop as participants and welcomed others to attend. He added that the workshop will be an open meeting and that a report will probably be issued. In response to a suggestion from Mrs. Brown, the title of the workshop will be changed to reflect more clearly the focus of the meeting on dissemination of information from clinical trials.

REPORT OF THE SUBCOMMITTEE ON INFORMATION AND CANCER CONTROL IN THE YEAR 2000

Mrs. Brown presented the minutes of the December 4, 1989, meeting of the Subcommittee on Information and Cancer Control in the Year 2000 to the Board and summarized the discussion therein on two agenda items: (1) interim measures of progress to reach the year 2000 goals and (2) the new Philip Morris advertising campaign. She enumerated the Subcommittee's decisions for upcoming steps to address progress towards the year 2000 goals.

The Board unanimously accepted the report of the Subcommittee on Information and Cancer Control in the Year 2000.

FUTURE AGENDA AND ACTION ITEMS

- An agenda item for a future meeting will be focused on reordering priorities in the face of budget realities and meeting the year 2000 goals.

- The minutes of the September 18-19, 1989, NCAB meeting were unanimously approved with the changes provided by Dr. Bragg to Mrs. Bynum.

- The Agenda Subcommittee will continue to evaluate Board meeting procedures and will review the revised program review format in January 1990.

XXIV. ADJOURNMENT--DR. DAVID KORN

There being no further business, the 72nd meeting of the National Cancer Advisory Board was adjourned at 3:09 p.m., December 5, 1989.

January 22, 1990
Date

Dr. David Korn, Chairman