Department of Health and Human Services

Public Health Service

National Cancer Institute

National Cancer Advisory Board

Summary of Meeting
October 7-9, 1985
Building 31, Conference Room 6
National Institutes of Health
Bethesda, Maryland

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

Summary of Meeting*
October 7-9, 1985

The National Cancer Advisory Board (NCAB) convened for its 55th regular meeting at 8:30 a.m., October 7, 1985, in Building 31, National Institutes of Health (NIH), Bethesda, Maryland. Dr. David Korn, Chairman, presided.

Board Members Present

Mr. Richard A. Bloch
Dr. Roswell K. Boutwell
Dr. Victor Braren
Mrs. Helene G. Brown
Dr. Ed L. Calhoon
Dr. Tim Lee Carter
Dr. Gertrude B. Elion
Dr. Robert C. Hickey
Dr. Geza J. Jako
Dr. J. Gale Katterhagen
Dr. David Korn
Mrs. Rose Kushner
Dr. LaSalle D. Leffall
Dr. Enrico Mihich
Dr. William E. Powers
Dr. Louise C. Strong

President's Cancer Panel

Dr. William P. Longmire, Jr.
Dr. John A. Montgomery

Ex Officio Members

Dr. Hollis Boren, VA
Dr. Dorothy Canter, NIEHS
Dr. Mary Ann Danello, FDA
Dr. Jean French, NIOSH
Dr. Lakshmi Mishra, CPSC
Dr. Robert Rabin, OSTP
Vice Admiral Lewis H. Seaton, DOD

Absent

Ann Landers
Dr. Armand Hammer

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

Liaison Representatives

Dr. Hugh Barber, Director of the Department of Obstetrics and Gynecology, Lenox Hill Hospital, New York, New York, representing the Society of Gynecologic Oncologists.

Dr. William Hendy, Vice President for Science and Technology, representing the American Medical Association.

Dr. William S. Hotchkiss, Chairman of the Board of Trustees, representing the American Medical Association.

Dr. Judi Johnson, Cancer Services Coordinator, North Memorial Medical Center, Robbinsdale, Minnesota, representing the Oncology Nursing Society.

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

Dr. Raymond E. Lenhard, Jr., Professor of Oncology and Medicine at the Johns Hopkins Hospital, Baltimore, Maryland, representing the American Society of Clinical Oncology.

Ms. Elaine Locke, Associate Director of Practice Administration, representing the American College of Obstetrics and Gynecology.

Mr. John H. Madigan, Washington representative, the American Cancer Society.

Dr. Edwin A. Mirand, Associate Institute Director of Administration, Roswell Park Memorial Institute, 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 and the Society of Surgical Oncology.

Dr. James Robertson, Director, Human Health and Assessment Division, U.S. Department of Energy, Washington, D.C., representing the U.S. Department of Energy.

Dr. Stefano Vivona, Vice President for Research Grant Awards, New York, New York, representing the American Cancer Society.

Dr. Richard D. Williams, Professor and Chairman of the Urology Department, University of Iowa, representing the Society of Urologic Oncology.

Liaison Representatives (Continued)

Dr. Sidney J. Winawer, Director of the Division of Gastroenterology, Memorial Sloan-Kettering Cancer Center, New York, New York, representing the American Gastroenterological Association.

Members, Executive Committee, National Cancer Institute

Dr. Vincent J. DeVita, 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 J. Fischinger, Associate Director, National Cancer Institute
Dr. Peter Greenwald, Director, Division of Cancer Prevention and Control
Dr. Alan S. Rabson, Director, Division of Cancer Biology and Diagnosis
Executive Secretary, Ms. Iris Schneider, Director of Staff Operations

In addition to NCI staff members, meeting participants, and guests, a total of 10 registered members of the public attended the meeting.

I. Call to Order, Opening Remarks, and Consideration of May 1985 NCAB Meeting Minutes--Dr. David Korn

Dr. Korn, Chairman, called the meeting to order and welcomed members of the Board, the President's Cancer Panel, liaison representatives, guests, staff of the National Cancer Institute (NCI), and members of the public. Procedures for conducting Board meetings were reviewed. Members of the public who wished to express their views on matters discussed by the Board were invited to submit written comments to Mrs. Bynum, Executive Secretary of the National Cancer Advisory Board (NCAB), within 10 days after the meeting. Dr. Korn emphasized the importance of having a quorum of 12 Board members present for each vote.

The following changes were requested to be made in the minutes of the May 13-15, 1985, Board meeting:

- A proposed future agenda item should indicate that the Board recommended that Dr. John Cairns be invited to give a presentation to the Board (page 17).

- Discussion of the Report of the Subcommittee on Innovations in Surgical Oncology should include the information that a written report on new directions in surgery was attached to the Subcommittee's Report (pages 13-14).

- The correct title of the journal for which NCI will provide phase-out support is Cancer Research (page 5).

- The members of the Board made special note of the achievements of Jane Henney, M.D., during her tenure as Deputy Director of NCI. It was stated that Dr. Henney's contributions were too numerous to detail, however, they wanted it noted that she provided leadership in a rare and well informed manner; it was recognized that she, often at great personal sacrifice, offered her time, effort, and energy to the NCI and the NCAB. The Board congratulated her on her accomplishments and wished her well in her new position in Kansas.

These changes were accepted, and the minutes were unanimously approved as amended.

The Board and guests observed a moment of silence in memory of Mrs. Angel Bradley who died on June 6, 1985. The eulogy of Mrs. Bradley, which was printed in the Congressional Record, was distributed.

II. Future Board Meeting Dates

Dr. Korn called the Board's attention to the fact that the May meeting has been rescheduled. Future Board meeting dates were confirmed as follows: December 2-4, 1985; February 3-5, 1986; May 19-21, 1986; October 6-8, 1986; and December 1-3, 1986.

III. Report of the President's Cancer Panel--Dr. William P. Longmire, Jr.

Dr. Longmire expressed Dr. Hammer's regrets that he could not attend the Board meeting and read Dr. Hammer's prepared statement. The Panel met on June 3, 1985, at the Memorial Sloan-Kettering Cancer Center in New York. As in previous meetings at the Wistar Institute and the Johns Hopkins Oncology Center, the Panel focused on two major issues: 1) the most important research opportunities at the Center, and 2) the effect on research programs at the Center if the NCI were to operate at or under current budget levels. The Panel has found the opportunities and problems to be very similar at the three Centers visited and therefore, believes it safe to assume that the same situation exists at most of the Centers throughout the country.

Center Directors told the Panel that reduced budgets would be most harmful to the clinical studies, which are much more expensive than basic laboratory research. At Sloan-Kettering, Dr. Lloyd Old reported on clinical studies on the tumor necrosis factor. Encouraging results were also presented from studies of interleukin-II. The Panel is convinced that advances in basic research are producing many promising approaches to clinical studies that will be essential in improving cancer treatment and that there must be support for the transfer of knowledge from the laboratory to patient care.

The Panel expressed concern that the NCI's basic mission should not be threatened by the demands of the Acquired Immune Deficiency Syndrome (AIDS) problem. The Panel suggested that the proper and most effective role of the NCI in dealing with the AIDS problem should be identified through discussion with members of the NCAB.

On September 18 and 19, Dr. Hammer sponsored a workshop at the Salk Institute in La Jolla on biological approaches to cancer control, including biological enhancers such as interleukin-II, interferon, tumor necrosis factor, the various roles of monoclonal antibodies, and general basic research on the immune system. At this workshop, Dr. Steven Rosenberg presented studies of cancer patients being treated with lymphokine-activated killer cells and recombinant interleukin-II. Eleven of 25 patients have shown very good results.

Dr. Hammer met with President Reagan on June 23 and discussed Dr. Rosenberg's work as well as other cancer issues and the need for more resources at the NCI. President Reagan recalled that discussion when he later met Dr. Rosenberg as one of the physicians treating him for cancer.

IV. Director's Report--Dr. Vincent J. DeVita

Dr. DeVita thanked the Board members for their farewell gestures to Dr. Jane Henney at the meeting of the NCAB in May and conveyed Dr. Henney's appreciation of their kindness on that occasion. He then welcomed guests.

Dr. DeVita announced that Dr. John Montgomery had been elected to the Board of Directors of the American Association for Cancer Research and had received the Alfred Berger Award from the American Chemical Society for his distinguished work in organic chemistry. Dr. Robert Hickey received the Alumni Award of Distinction from Cornell University for his work in clinical research and administration. Dr. Tim Lee Carter received an honorary Doctor of Law degree at the commencement ceremonies at the University of Kentucky.

On the NCI staff, several changes have occurred in recent months. Dr. John Antoine, from the Radiation Oncology department at the University of New Mexico, will join the NCI as Associate Director for the Radiation Research Program in the Division of Cancer Treatment (DCT) on November 1. Dr. Charles Smart, from the University of Utah, became the new Chief of the Community Oncology and Rehabilitation Branch, Division of Cancer Prevention and Control (DCPC), a few months ago. Finally, Dr. Ronald Herberman, former Acting Associate Director of the Biological Response Modifiers Program, DCT, left the NCI to accept the position as Director of the newly formed Cancer Institute at the University of Pittsburgh.

A concept for recompetition of the Frederick Cancer Research Facility (FCRF) contracts was approved by the Frederick Advisory Committee in July. Concurring with a recommendation from the Executive Committee, the FCRF approved the concept as a system of contracts and for a period of seven years to ensure stability at this government-owned, contractor-operated facility. An RFP will be issued in June 1986.

Followup Items

1) Smokeless Tobacco Initiative

It was announced that an Advisory Committee had been formed by the Surgeon General for the purpose of examining data on smokeless tobacco. The committee will be chaired by Dr. Joseph Cullen, Deputy Director of the DCPC. In response to concerns expressed by representatives of the tobacco industry, a review of the Advisory Committee's findings will be conducted by the Institute of Medicine. A Consensus Development Conference on the smokeless tobacco issue, to be chaired by Dr. Brian McMahon, Harvard University, has been planned for January 13-15, 1986.

2) NCI Supercomputer

A Small Business contract in the amount of $1.104 million has been signed with Falcon Industries for the installation of a Cray supercomputer at the Frederick Cancer Research Facility. The first computer unit, scheduled for delivery on March 1, 1986, is expected to be fully operational in April 1986. Dr. DeVita invited Board members to visit the facility which he described as the first supercomputer dedicated entirely to biomedical research and representing the state of the art in supercomputer technology.

3) Outstanding Investigator Grant Awards

Dr. DeVita reported that a total of 23 Outstanding Investigator Grant awards had been made. The announcement for the next round has been slightly revised in a few technical aspects not affecting the review process. The receipt date for applications under the revised announcement will be May 1986. Forty-nine applications had already been received and will be presented for review in the next Board cycle. He noted that a number of outstanding scientists outside the cancer research field were attempting to compete for these awards despite the fact that the awards are for cancer research. The NCI cannot accept noncancer related applications.

4) Organ Systems Program

Dr. James P. Karr has replaced Dr. Gerald P. Murphy as Acting Director of the Organ Systems Coordinating Center following Dr. Murphy's resignation from Roswell Park Memorial Institute. During the summer, Dr. DeVita met with four of the Organ Systems Program Working Group chairs to discuss their concerns over whether the concepts developed out of workshops would reach fruition. The chairs sought assurances that the NCI actually intended to support the Organ Systems Program. The discussions resulted in the clarification of the process for concept development and review: these are written in developed form by NCI staff based on workshop ideas and assigned by the NCI Executive Committee to the Board of Scientific Counselors (BSC) in the appropriate NCI Division to compete for resources in the marketplace of ideas. The Working Group Chair or designee will present the concept to the BSC. Four concepts developed by the Working Groups have already been forwarded to four Boards. One was recently presented to the Board of Scientific Counselors, Division of Cancer Treatment (BSC, DCT) and passed with revision so it will encompass a wider variety of cancers than only colon cancer. The approved concepts will then be announced as Requests for Applications (RFAs), Requests for Proposals (RFPs), or Program Announcements (PAs).

Dr. DeVita stressed that the progress of the Organ Systems concepts through the NCI review process would be carefully watched. At the annual NCAB Program Review meeting, the Chairman of the Organ Systems Coordinating

Center will present an annual report on all the concepts developed during the year and on priorities and plans for the coming year.

Dr. DeVita suggested that the structure and operation of the Organ Systems Program could be reevaluated at the time the concept for the Coordinating Center grant comes up for extension or recompetition. For the present, however, he assured Board members that all concepts reaching the various divisional Boards would be evaluated fairly.

5) Community Programs

Three community programs--the Community Hospital Oncology Program (CHOP), the Cooperative Group Outreach Program (CGOP), and the Community Clinical Oncology Program (CCOP)--created by the NCI in recent years have been under evaluation since 1983. This review will be completed and presented to the NCAB in fall 1986. The evaluation of these community programs was required in view of the upcoming DCPC presentation of a concept for continuation of the programs.

6) Small Business Innovation Research (SBIR) Awards

The entire NCI allocation of $9 million in set-aside funds for the SBIR Program has been obligated. A total of $3.7 million was obligated for grants and $5.3 million will fund 112 contracts. It was noted that the DCT had been very active in encouraging participation by scientists with small business in the contracts program. The DCT will fund 89 of the 112 awarded contracts.

7) West Virginia Cancer Center

Dr. DeVita thanked Board members for attending to the West Virginia Cancer Center issue in his absence. He reported that the Congress is still interested in the Center for which $4.5 million were set aside in the appropriation language. Funding is expected to be primarily for construction of the Center and will not come out of the NCI budget.

8) Physicians Data Query System (PDQ)

The licensing agreement with Meade Data Central, approved by the Board in May 1985, was followed up with the signing of a license with that vendor in August. The NCI plans to grant licenses to two other firms, one Swiss and one Norwegian.

The Board members were assured that the problem with non-M.D. users was being studied. An evaluation of the PDQ system was initiated with the award of a contract in September 1985. The PDQ Evaluation Plan Steering Committee is scheduled to meet November 4-5; Dr. William Dolan will represent the AMA.

The American College of Chemosurgery has joined the PDQ directory. After discussions with the American Urologic Association, member urologists will be able to request listing on the PDQ directory by using a self-select system of the type used by the American College of Surgeons. This brings the total number of organizations on the directory to 16.

The DCPC is developing a plan for a prevention package to be added to PDQ--the PDQ-P, which is expected to be completed around 1987. Information on preventive measures, cancer risks and screening will be included in this new package.

Dr. DeVita expressed his gratitude for the PDQ Editorial Board's efforts. Members of that Board have modified about 15 state-of-the-art statements per month in the past year.

Eleven new members have been appointed to the PDQ Editorial Board, including 4 radiotherapists, 3 surgeons, 2 pediatricians, and 2 medical oncologists.

9) NCI Semi-Centennial

Plans are being made for activities to commemorate the NCI's semi-centennial. NCI has formed a committee, chaired by Dr. Bayard Morrison, to study possible publications, activities, and displays for a month-long series of events in 1987.

10) NCI Positions

The number of full-time equivalent (FTE) positions at the NCI has been reduced by approximately 300 since 1984 and will again be reduced in 1986 by another 100. One casualty has been the former NCI Summer Program for students. The NCI made an appeal to corporate donors to the Gift Fund. As a result, their contributions along with others helped support a group of 52 students in the intramural program for 2 months each at $1,000 for the summer. The program helps introduce minority students to the NCI intramural research program.

New Items

1) Prevention and Screening Programs

- The DCPC has established a subcommittee of its Board of Scientific Counselors to review the NCI's screening research programs. This subcommittee will make recommendations on the advisability of the Institute having its own screening policies rather than simply following those of the American Cancer Society. A related issue is to decide whether these policies should be part of the DCPC's prevention awareness program. The Subcommittee report will be presented to the NCAB in spring or fall 1986.

- The Board was advised that there was a supplemental budget appropriation of $3 million for a Cancer Screening and Research Clinic in Utah, with funds available through FY 1987.

- Dr. DeVita reported that he had recently helped launch a prevention awareness campaign for Black Americans in Detroit, originally conceived in 1984 by a committee chaired by Dr. Lee Monroe. The NCI has formed the Joint Health Venture, a program involving universities, business, sports figures, and entertainers. Aretha Franklin has already produced TV spots to broadcast messages on cancer prevention to Black Americans. Dr. DeVita thanked Dr. LaSalle Leffall for his assistance in the program, which is administered by the Office of Cancer Communications.

2) Training Programs

- Surgical Oncology Training
  A new grant award mechanism, designed by the Subcommittee on Surgical Oncology of the DCT Board of Scientific Counselors with assistance from the NCAB Subcommittee on Innovations in Surgical Oncology, will be announced in the NIH Guide to Grants and Contracts in November 1985, and the receipt date for the first applications will be in January 1986. Unlike the KO8 grants which are awarded to individual surgeons, the new grants will be awarded to institutions with departments of surgery. The award will support two to four years of basic research and one clinical year in which surgeons will learn about other subspecialties.

- Clinical Traineeship in Oncology Nursing
  This new program, designed for recent graduates of nursing programs, is sponsored by the NCI in conjunction with the Clinical Center, NIH. It will consist of 6 to 9 months of didactic training in oncology nursing. Approximately ten trainees are expected to be enrolled per year.

- Biotechnology Training Program
  This NCI intramural training program, approved on July 1, 1985, by the Assistant Secretary for Health, is designed for training in the fundamental sciences with clinical applications for a period of six months to two years with a possible extension to three years. Trainees can be M.Ds. or Ph.Ds. The program will be supervised by the NCI's Executive Committee.

Budget

At the close of the fiscal year, the estimated obligations for FY 1985 were $1.178.260 billion, slightly up from the $1.081 billion FY 1984 budget.

The President's budget for FY 1986 proposed initially was $1.126 billion. This was later amended to a level of $1.131 billion.

The Administration's proposal to fund 5,000 NIH grants in FY 1985 dominated budget discussions throughout the year. Congress appropriated funds to support 6,500 competing grants. In January 1985, the Administration again instructed NIH to fund 5,000 grants in FY 1985. The Office of Management and Budget (OMB) then mandated multiple-year funding of some FY 1985 grants to reduce obligations in FY 1986 and 1987. The debate in Congressional Committees and in the scientific community produced a compromise that may result in the funding of 6,200 grants in FY 1986, although the issue has not been entirely resolved. The prospective reduction from 6,500 grants to 6,200 in FY 1985 would still allow the NIH to carry over up to $20 million into FY 1986. The amount of carry-over funds in the NCI budget would be $3.7 million. Concerning FY 1986, discussions in Congress continue on the 1986 appropriation level. In the interim, NIH is currently operating under a Continuing Resolution until mid-November.

In presenting budget highlights, Dr. DeVita pointed out a comparability transfer of funds in the amount of $12.722 million to cover an increased NCI share of costs of central service activities, including the Clinical Center, which will increase the NCI FY 1985 budget to $1.190.982 billion.

A review of FY 1985 estimated obligations against the FY 1985 appropriation reveals a $7 million decrease in the research project grants line part of which provided for small increases in the Cancer Centers Program and the Cooperative Groups as well as the $3.7 million directed carryover. Another small increase occurred in the R & D contracts, due in part to the Small Business Innovation Research (SBIR) Program.

The NCI's share of the originally proposed 6,500 grants in the FY 1985 obligations was 1,030 competing ROIs and POIs, with an estimated 170 payline and 35 percent of approved grants funded. Latest estimates for FY 1985 show a total of 1,019 grants. An additional thirty-two of these grants were funded as single year awards as directed by the Administration. Thirty-five percent of approved applications were funded in FY 1985, and the payline was 175.

For the FY 1986 NCI budget, the House markup used the latest 1985 estimates as a base and increased the amended President's Budget by $123.9 million to $1.221 billion, but this does not include funds for construction or NRSA training (due to a lack of authorization). The largest increase is in the research projects grants line, with smaller increases for cancer centers and cancer prevention and control.

The Senate Appropriations Committee used the amended President's Budget as a base and included construction and training. This resulted in a $1.254 billion budget with a $122.9 million increase over the base. Again, research project grants would get the largest share of this increase.

At the three 1986 budget levels, the number of funded competing grants would be as follows: 807 in the President's Budget, 982 in the Senate, and 945 in the House.

NCI obligations for AIDS research are projected to grow to an estimated $28.4 million for FY 1986. This will represent about 41 percent of the total NIH obligations of $70.7 million for AIDS in FY 1986, and the total DHHS FY 1986 obligations are estimated to reach $126.4 million. Both the Senate and the House are expected to appropriate additional funds for AIDS according to the latest reports. The distribution of these funds is reported to be different in each chamber. Under the Senate plan, the funds would be appropriated to the individual Institutes, while the House plan would give the funds to the NIH Office of the Director for distribution.

The discussion following Dr. DeVita's report brought out the following points:

- Dr. DeVita clarified that in the absence of an authorization, the House will not appropriate construction or training funds. This does not reflect any particular bias in the House against either program. The Senate has continued to enact appropriations for these programs and the House has agreed in conference.

- The FY 1986 By-Pass budget was $1.460 billion, approximately $200 million higher than either the Senate or House budget.

- Funding for the intramural research program will be at a relatively stable level. Individual programs, however, may be growing at a much faster pace than others. Decreases and staff reductions in other programs have contributed to maintaining a level budget.

- Several members of the Board expressed concern that grants they had recommended for exception funding had not been paid. It was explained that NCAB approval is required before a grant can be paid. However, the NCI Executive Committee looks at the universe of grants when deciding on exception funding. Recommendations by Board members are given careful consideration but are not always followed. Dr. DeVita supported a suggestion to have a summary sheet prepared for presentation at the beginning of each Special Actions Committee session reporting action taken on exception funding recommendations.

Legislative Update--Dr. Mary Knipmeyer

A written legislative update was provided to the NCAB. Dr. Knipmeyer identified recent hearings that involved the NCI, including the first hearing on smokeless tobacco. She summarized the status of legislation involving the reauthorization of the National Institutes of Health and the NCI. Both the House and Senate have passed bills which will soon go to

conference. These bills do not call for any major modification in the operation of the NCI or the revision of its mission.

Other legislation discussed dealt with the tobacco subsidy, cigarette package labeling, smokeless tobacco, orphan drugs, saccharin, animal welfare, food safety, and nutrition. During the NCAB's discussion about the NCI's position on the tobacco subsidy, Dr. Knipmeyer noted that the NCI only is asked about the health consequences of smoking, not about tax issues.

In the discussion, Dr. Jako expressed concern about strictures on animal research and pointed out the need for human tissue. Dr. Rabson described a new Tissue Procurement initiative.

In light of Breast Cancer Awareness Week (October 21) and the hearings that will be held by the House Select Committee on Aging on October 23, Mrs. Kushner asked for the Board's support of a bill to have Medicare pay for screening mammography of women older than 65. Dr. Korn asked Drs. Katterhagen and Leffall, co-chairmen of the Cancer Control Subcommittee, to prepare an appropriate resolution; however, it was agreed that the resolution should not refer to specific legislation. The following resolution subsequently was prepared and submitted as a motion of the Subcommittee on Cancer Control:

> The National Cancer Advisory Board strongly recommends that there be third party reimbursement, to include Titles XVIII and XIX, for scientifically established/cost effective screening procedures such as PAP smears, hemoccult testing, and mammography.

The Board unanimously approved the resolution.

V. Acquired Immune Deficiency Syndrome: An Overview

Dr. DeVita explained why the NCI is involved in AIDS research: 1) a retrovirus has been identified as the cause of AIDS and the NCI is fortunate to have many retrovirologists on its staff; 2) by studying AIDS, the NCI acquires information on how other viruses such as HTLV-I cause cancer and on drugs that might inhibit cancer; 3) NCI has a strong epidemiology program which can contribute to understanding the natural history of AIDS; and 4) NCI expertise caused Dr. Brandt to make NCI the lead Institute for vaccine development. He emphasized that the responsibility for studying AIDS and bringing the epidemic under control is shared with the National Institute of Allergy and Infectious Diseases.

The NCI and NIAID have jointly developed a drug development program based on a new screening system to identify drugs that inhibit HTLV-III. Drs. Samuel Broder and Robert Gallo have been using the system to test Suramin and an azido-thymidine derivative. It is expected that clinical trials for four drugs per year will cost about $3,500 per patient or

$3 million per drug. The cost is high because of the need to isolate the virus to evaluate its inhibition and to monitor the immune system in patients with very complicated illnesses. However, there are many ramifications to a clinical trials program, including treating the AIDS-related complex to prevent progression to AIDS and the spread of disease.

Presentation--Dr. Samuel Broder

Dr. Broder described the three known pathogenic human retroviruses, discovered in large measure by Dr. Gallo and his colleagues in the Division of Cancer Treatment. HTLV-I is a leukemogenic virus and the cause of endemic cancers in several parts of the world. HTLV-II is thought to have transforming properties *in vitro*, but its exact role in the pathogenesis of human disease remains controversial. HTLV-III, which is only distantly related to I and II, has tropism for and the capacity to destroy a special subset of T-cells in humans both *in vivo* and *in vitro* and is the agent that is responsible for AIDS.

AIDS appears to be a new disease that was introduced into North America and probably also appeared, for reasons not clear, in multiple parts of the world simultaneously. Dr. Broder said there are data to suggest that the AIDS virus may have originated in Central Africa. The number of cases of AIDS increases in each Centers for Disease Control (CDC) quarterly reporting period, with no sign of plateau or stabilization. In one study, it is estimated that as many as 80 percent of patients who have hemophilia have already been infected by this virus.

The virus is thought to be transmissible by homosexual and heterosexual contacts and through blood products. Dr. Broder presented preliminary data on the significance of seropositivity. In a study of gay men in Manhattan, within approximately a 3-year period, about 40 percent of the individuals who were seropositive have gone on to develop AIDS. Dr. Broder suggested that this finding should be viewed in the context that about 1 million Americans may carry the AIDS virus.

AIDS has served to clarify the relationship between certain immunodeficiencies and the development of some forms of cancer. For example, Kaposi's sarcoma is an index lesion in certain patients. It may take the form of a cutaneous disease or, in nearly half of the patients, will develop visceral forms. In AIDS patients, the Kaposi's sarcoma may present in unusual sites such as the conjunctiva of the eye, and may be a direct proximal threat to their lives.

In 1981 investigators began to observe a new lymphadenopathic type of Kaposi's sarcoma in Africa, and more recently, aggressive and in many cases untreatable lymphomas have occurred in these patients. These lymphomas have unusual sites of presentation, many involving the central nervous system.

Dr. Broder emphasized that the potential of the AIDS disease has not yet been defined. Researchers are seeing dementias and other neurological manifestations, both at a central and peripheral level. Therefore, there is a need to develop drugs that will penetrate the blood-brain barrier.

The drug screening program is based on the assumption that the AIDS virus can be attacked by antiviral therapy. A rapid assay has been developed to screen large numbers of compounds for antiviral effect and to obtain information on structure-activity relationships. Confirmatory tests are done in all cases.

Dr. Broder said that Suramin, at a dose attainable in humans, protects cell cultures against the cytopathic destructive activity of the virus, and there are data showing that Suramin has a virostatic effect in vivo. Whether there is a clinical effect has yet to be proven. Suramin has certain limitations, including the requirement that it be intravenously administered and its poor capacity to enter the central nervous system.

Dr. Broder summarized new developments that have resulted from collaboration of the Government and private sector. A drug that seems to be very promising is 3'-azido-3'-deoxythymidine, also called azido-thymidine. Through the cooperation of Burroughs-Wellcome Company and the Government, this drug went from preliminary analysis in February of 1985 to clinical treatment of patients in July 1985.

Some of the promising properties of the drug are its extremely high bioavailability when given orally and its ability to penetrate the blood-brain barrier. No toxicity has been observed in initial clinical trials, and patients' immune systems appear to be improved.

The discussion that followed Dr. Broder's presentation included the following points:

- It appears that HPA-23 may have a virostatic effect in vivo and trials should be continued
- Using a chemical test to predict drug activity, NCI researchers have found that almost any purine or pyrimidine can be converted to a potent antiretroviral agent in tissue culture by altering the sugar part of the molecule to have a certain configuration
- The AIDS virus probably does not directly cause cancers, such as Burkitt's lymphomas or immunoblastic sarcomas, but perturbs the immune system, thereby facilitating or permitting the emergence of the tumors.

Presentation--Dr. Peter Fischinger

Dr. Fischinger summarized the efforts to develop a vaccine against AIDS. He mentioned the following possibilities for developing a vaccine: a nonpathogenic virus variant; a killed virus; purified external viral glycoprotein; genetically engineered viral subunit proteins; a synthetic peptide derived from virus sequences; infectious recombinant viruses; and anti-idiotypes.

It has been estimated that as many as one million people have been exposed to the AIDS virus. However, it is not clear who can be currently considered to have been infected. A basic goal is to model a vaccine on the basis of a protected individual's reactivity. A viral antigen has been identified--gp120--that induces the neutralizing, and therefore protective antibody.

The optimal technology for antigen presentation is another area of consideration. Efforts are underway to determine whether an immune stimulating complex (ISCOM) can be prepared to induce antibodies from a viral preparation. Current studies suggest that an HTLV-III ISCOM preparation can stimulate antibodies that neutralize virus in rhesus monkeys. Although a problem with this process has been obtaining large quantities of the viral glycoprotein, recent technical advances have made it possible to obtain high yields of purified glycoprotein.

Dr. Fischinger said the HTLV-III ISCOMS have been put in a number of species and generated major antibody response to the DR chain that is found on the H9 cell, which produces HTLV-III. Viral proteins that have been found to be reactive include the viral internal major antigen, glycoprotein 41, and gp120. The next step is to see whether genetic engineering is going to be helpful in expressing a large amount of the envelope gene that produces gp120.

So far two series of successes have been recorded, one with the peptide 121, and the other with the envelope gene products. Researchers will have to look at how the body responds to the natural pure antigen under normal conditions and determine how to structure synthesized materials to produce an analogous response.

Dr. Fischinger noted that the virus isolation process is quite laborious and expensive. An important question is whether an antibody that protects against homologous virus will protect against heterologous virus. With some retroviruses, it is possible to hyperimmunize to get a response that will cross neutralize a broad range of types. Researchers need to study the protection in the rhesus monkey (that has neutralizing HTLV-III antibody) when challenged with a different virus. It also must be determined how long after virus exposure antibody is formed. Dr. Fischinger stated that scientists should be able to elicit a protective antibody reaction in the near future.

The following comments were made after Dr. Fischinger's presentation:

- Much of the progress in this area has been made intramurally, although there are very active outside groups and Government-private sector collaboration

- No seroconversions have occurred in people working with the AIDS virus in laboratories, except in two cases where individuals accidentally innoculated themselves with blood from AIDS patients

- Behavior modification and public education are appropriate methods for preventing the spread of AIDS

- The AIDS statement on PDQ is being modified so it can be a major information source

- The NCI has received 7 additional positions for AIDS research in 1985 and 20 for 1986

- The CDC has a major effort in public education on AIDS, and a DHHS leaflet on AIDS was distributed to the Board.

VI. Smokeless Tobacco

Presentation--Dr. Dietrich Hoffmann

Dr. Hoffmann discussed the public health implications of snuff dipping. Between 1978 and 1984, the sale of loose leaf tobacco in the United States has increased by 40.6 percent and of snuff by 32.5 percent. An estimated 7 million Americans use snuff, and a sizable proportion of those users are high school and college students. Four case control studies have implicated snuff as an etiologic factor in cancer of the oral cavity. In 1984, the International Agency for Research on Cancer concluded that there is "sufficient evidence" that snuff is carcinogenic and "limited evidence" that chewing tobacco is carcinogenic to humans.

Dr. Hoffmann described the animal studies that have been in progress in his laboratory for the past 24 months. A pinch of snuff is inserted daily into a surgically constructed canal in the rat's lower lip. Histologic data are now being evaluated.

The animal carcinogens that have been identified in snuff to date are nitrosamines, polynuclear aromatic hydrocarbons (primarily benzo(a)pyrene), and polonium-210. Carcinogens are formed during the processing of tobacco and are present in high concentrations in U.S. products. In comparing data from four countries, the highest concentrations of all three of the animal carcinogens are found in U.S. products. Tobacco-specific nitrosamines, which are derived primarily from nicotine, are present in snuff in concentrations

that exceed FDA acceptable limits for carcinogenic nitrosamines by three orders of magnitude. Nitrosamines and alkaloids have been found in the saliva of snuff dippers.

Dr. Hoffmann stated that nitrosamines are procarcinogenic and require in vivo metabolic activation to the active species which leads to the methylation of DNA. Polonium-210 is an alpha emitter, which some scientists think may contribute to lung cancer in cigarette smokers. Dr. Hoffmann suggested that reduction of the levels of tobacco-specific nitrosamines and polonium-210 in snuff is technically feasible and should be mandatory.

Presentation--Dr. Deborah Winn

Dr. Winn described the research on smokeless tobacco and cancer being conducted by the NCI. Oral cancers account for 2 percent of all cancers in the United States and in most parts of the country are caused primarily by smoking and heavy alcohol consumption. However, in areas where smokeless tobacco is commonly used, some of these cancers will have been caused by smokeless tobacco. More than a quarter of all white patients with oral cancer and more than a third of all black patients die within the first year after diagnosis.

The NCI studies of oral cancer were inspired by the U.S. Cancer Atlas for 1950-1969 that showed white women in the southeast to have death rates for mouth and throat cancer that in urban areas were 30 percent higher than national rates and in rural areas, 90 percent higher. A case-control study was done among female residents of North Carolina, and it was found that women with oral and pharyngeal cancer were more likely to have used snuff than controls. The most striking results were the 13-fold increased risk of cancers in the cheeks and gums for women who used snuff for 1 to 24 years and 50-fold increased risk for those who used snuff for more than 50 years. It was concluded that the practice of snuff-dipping among these women was responsible for their elevated death rates from oral cancer.

Dr. Winn said these findings were consistent with numerous other studies performed in the U.S. and Scandinavia on use of smokeless tobacco and oral cancer. Where it has been possible to distinguish tobacco chewers from snuff dippers, evidence of an association between oral cancer and tobacco chewing has been less definitive. Cancer risks have been found to be exceptionally high at anatomic sites in direct contact with the tobacco, although elevated risks occur in other parts of the oral cavity and pharynx. There is also suggestive evidence that smokeless tobacco use is linked to cancer of the esophagus, nasal passages, sinuses, and pancreas.

Dr. Winn said that the NCI has the lead role in several studies of smokeless tobacco and cancer. The Division of Cancer Etiology is conducting a case-control study of cancer of the oral cavity and pharynx in four areas of the United States. The Division of Cancer Prevention and Control has solicited proposals for innovative research on the prevention of smokeless

tobacco use and methods to get users to quit. With the National Institute for Dental Research and the National Center for Health Statistics, the NCI is assessing patterns of smokeless tobacco use in association with dental problems and other health consequences. In response to a question from the Board, Dr. Winn said that while the association between smokeless tobacco use and oral cancer is well established, current population-based studies are necessary to understand racial differences in the incidence of oral cancer and to evaluate the influence of and interactions among other factors, such as diet, denture wearing and other oral problems, occupational factors, smoking, and alcohol consumption.

In other discussion, the following points were raised:

- The Cancer Control Subcommittee has developed position papers that have been unanimously endorsed by the Board.
- Letters have been sent by Dr. DeVita and others to high school principals to alert them to the dangers of smokeless tobacco.
- Educational efforts and research are needed to counter advertising contentions that use of smokeless tobacco is safe because it does not involve smoking.

Presentation--Dr. Gregory Connolly

Dr. Connolly summarized changes in patterns of tobacco use and some of the regulatory efforts at both the state and Federal levels. The upswing in the use of smokeless tobacco began in the early 1970s, and in the 1980s the market began to gravitate towards the white collar 18- to 35-year-old group, of whom college students are an important segment. Recent surveys indicate that smokeless tobacco use is becoming popular among adolescents. Sales are growing at about 10 percent per year. Dr. Connolly said advertisements present snuff as an alternative to smoking and its use as macho, fun, safe, clean, convenient, and economical. A Washington state survey of smokeless tobacco use by grammar and junior high school students found that over a 2-year period, two-thirds of the smokeless tobacco users switched to cigarette smoking.

Dr. Connolly said that most of the regulatory efforts to discourage smoking were enacted when smokeless tobacco use was in a decline and thus do not apply to smokeless tobacco use. At the Federal level, there is no health warning label and no excise tax on smokeless tobacco. Only 21 states levy an excise tax on smokeless tobacco, and only 26 states ban its sale to minors. In response to recent requests to the FTC for a health warning label, the Surgeon General has requested an indepth report on the health effects of smokeless tobacco use.

In Congress, Representative Waxman has reported out of Committee the Comprehensive Smokeless Tobacco Health Risk Education Act (HR-3150) that

calls for rotating health warning labels on packages, a ban of all electronic advertising, national educational programs, a ban on sale to minors, and a listing of nicotine content. This act contains no state preemption provision so the states would be able to exceed a minimum Federal label.

Dr. Connolly said that in his state, Massachusetts, public hearings had found smokeless tobacco was a hazardous substance under the state Food and Drug Act, and a warning label will be required on packages effective December 1, 1985. Similar legislation is pending in other states, and enactment of different labeling requirements would place a burden on the industry. Dr. Connolly recommended that the regulatory efforts applied to smoking also be applied to smokeless tobacco and suggested that educational programs be encouraged to prevent smokeless tobacco use. He concluded that a coordinated Federal effort is needed to support research, especially on prevention and cessation intervention, collect and disseminate information, and organize a surveillance program.

The following additional points of information were provided:

- An NIH Consensus Development Conference on Smokeless Tobacco will be held on January 13-15, 1986.
- NCI has a state-by-state summary of cancer control legislation that is available to Board members.
- The Surgeon General provided lapel buttons that call for a smoke-free society by the year 2000 (SFS-2000).

VII. Breast Cancer Consensus Conference Update--Dr. John H. Glick

Dr. Glick reported the results of the Consensus Development Conference on Adjuvant Chemotherapy for Breast Cancer held at NIH on September 9-11, 1985. In 1985, 120,000 new cases of breast cancer will be diagnosed, and 38,000 women will die of breast cancer. In about 90 percent of the new cases of breast cancer, the disease is limited to the breast and axillary lymph nodes, and Dr. Glick suggested all these patients are potential candidates for some form of systemic adjuvant therapy.

The goal of adjuvant therapy is to prolong survival while maintaining an acceptable quality of life for the patient. Dr. Glick said the Consensus Panel used three measures to evaluate whether specific treatments met this goal: 1) overall survival; 2) disease-free interval; and 3) quality of life. Since the previous Consensus Development Conference in 1980, a number of trials have been undertaken and produced new information on the role of adjuvant therapy in the treatment of breast cancer. NIH convened the recent Consensus Conference to evaluate the new data and resolve some controversial issues. (The five consensus questions with the answers derived through the process were provided to Board members in the Consensus Development Conference Statement.)

lack of funding identified specifically for the Organ Systems Program. The Subcommittee requested a review of the funding history of the Organ Systems Program. Dr. Hickey said the Neuro-oncology Program and the Upper Aerodigestive Program will be presented at the December Subcommittee meeting. The Subcommittee suggested that the Working Group Chairs be invited to the December 1 meeting with a report presented to the Board on the following day. Dr. Hickey moved acceptance of the report.

The ensuing discussion dealt mainly with suggestions for accelerating funding in the context of established procedures and approved mechanisms. The possibility of setting up the Organ Systems Program as a Cooperative Agreement or RFA was raised. It was suggested that this discussion be continued in December. The Board received assurance that they would receive the review of funding for the Organ Systems Program by mail.

The Board voted to approve the report of the Subcommittee.

Subcommittee on Innovations in Surgical Oncology--Dr. Ed L. Calhoon

Dr. Calhoon presented the report of this Subcommittee's October 6 meeting. The Subcommittee endorsed continuing NCI research on lymphokine activated killer cells. Other subjects discussed were board certification for surgical oncologists; laser beam surgery for breast cancer; funding of surgical oncology grants; and the difficulty of finding surgeons to apply for K08 grants. The Subcommittee expressed the concern that surgical oncology grants might receive less than optimum review by nonsurgeons. The Subcommittee passed a motion that the new Deputy Director of NCI, to replace Dr. Jane Henney, should be a surgeon. Dr. Calhoon moved acceptance of the report.

The following amendments to the Subcommittee's report were approved:

- Deletion of the recommendation that a surgeon be appointed Deputy Director (item 4 of report)

- Rewording of sentence 2 of item 3 to indicate that optimal review of surgical oncology grants could be achieved by inclusion of surgeons.

The Board voted acceptance of the Subcommittee's report with these two amendments.

Subcommittee on Planning and Budget--Dr. Gertrude B. Elion

Dr. Elion reported on the October 8 Subcommittee meeting. Dr. DeVita reviewed the 1987 By-Pass budget that was submitted to the Office of Management and Budget and the subsequent amendment of the President's budget by Congress. He explained that the 1987 level was based on the same assumptions used for 1986: a 40 percent funding level for competing research

grants; a 50 percent increase in the number of Centers by the year 1991; a tripling of cancer prevention and control efforts by 1991; a doubling of patients entering into clinical trials between 1987 and 1991; stabilized training for the National Research Service Awards; and a $28 million construction request for 1987. The 5-year projection will culminate in 1991 with a request for $2.4 billion. The Subcommittee discussed the draft Annual Plan that had been provided to Board members for comment. Because several members felt there had not been sufficient time for review, it was agreed that those Board members who wished to recommend specific topics for inclusion in the plan should submit their narratives to Dr. DeVita, who would consult with Dr. Korn with respect to their inclusion.

The Subcommittee voted unanimously to accept the budget levels contained within the Plan and to endorse the Plan as modified by the changes recommended for inclusion by Dr. Korn.

The Board voted to accept the Subcommittee's report.

Subcommittee on Contracts and Budget--Dr. Roswell K. Boutwell

Dr. Boutwell summarized minutes of the Subcommittee meeting held on October 8, 1985. He noted that a reduction in the FY 1986 budget of the Office of the Director is largely attributable to a staff reduction of 71 persons. To partly compensate for the staff reduction, funds have been reprogrammed to five contracts that were approved by the Subcommittee.

There was discussion of whether any of the community health education activities might be duplicated by other agencies and other organizations. Coordination and cooperation with other organizations, such as the American Cancer Society, were emphasized as important attributes of NCI's health education efforts.

The Board voted to accept the Subcommittee's report.

IX. New Business

Dr. Korn called attention to a handout provided by Mr. Bloch listing institutions where multidisciplinary second opinions are available to patients. It was suggested that this practice be considered by the Cancer Control Subcommittee in reference to the Cancer Centers.

Format of Board Materials--Mrs. Barbara Bynum

Mrs. Bynum discussed the large volume of materials that are prepared and mailed to Board members for each meeting. She asked the Board to consider how much of this material they need, when they need it, and the desired form of the material.

The following modifications of the current procedures were presented for the Board's consideration:

- Printout of disapproved applications with the substance of the review that led to those decisions, rather than full summary statements

- Truncated summary statements that include a resume, the fiscal data in terms of the priority score, the dollars recommended, other actions that were part of the Study Section's review, a one-paragraph description of the work proposed, and a summary of the recommended action

- Hard copies of abbreviated summary statements and Division of Research Grants (DRG) recommendations plus indexed microfiche of full summary statements for all applications.

If the last option were to be implemented, each Board member would be provided with a portable microfiche reader. Board members would be provided hard copies of any materials upon request. Mrs. Bynum estimated the current cost of mailing Board materials was about $30,000 and a switch to microfiche would represent a considerable savings. Now that the DRG and the NCI Grants Review Branch data are on-line, there is the capability of tailoring Board materials to the needs and requests of the individual Board members. Mrs. Bynum asked that the Board make a decision about the format of materials at the December meeting, which would be implemented on a trial basis for the February meeting.

Mrs. Bynum provided Board members with five designs for new NCAB stationery. She asked members to indicate by writing their names on the sheet which design they preferred.

Future Agenda Items--Dr. David Korn

For the December meeting, Dr. Korn suggested that brief reports be presented by each Division and divisional Board of Scientific Counselor's Chairmen, leaving the remaining time for thematic presentations. In addition to the distributed list of proposed NCAB agenda items, the following items were suggested:

- Presentation on the limitations of the DRGs as prospective payment mechanisms with respect to severity of illness and what that means for cancer patients in clinical trials (suggested speaker: Dr. Susan Horn, Johns Hopkins)

- Mini-symposium on statistics to be organized by Dr. Edward Sondik and to include a presentation on cancer statistics, including SEER data, and a presentation by Dr. John Cairns;

it was agreed that the mini-symposium would be postponed if Dr. Cairns is not available in December

- Update on advances in basic cancer research in relation to the Organ Systems Program
- Combined overview of NCI international activities and presentation by a State Department representative on international science and foreign policy
- Presentation on childhood cancer studies
- Update on biological response modifiers
- Presentation on the Cancer Information Service and Office of Cancer Communications with respect to contracts, outside support services, and implementation in the community
- Presentation on research methodology in clinical investigations
- Discussion of NCI's role and responsibility in monitoring/regulating cancer therapy
- Presentation on the scientific uses of lasers in cancer research.

Dr. DeVita said the agenda for the December meeting will depend on the availability of appropriate speakers.

It was suggested and agreed that an evening reception be held for Board members on Monday, December 2, 1985.

X. Adjournment--Dr. David Korn

The 55th meeting of the NCAB was adjourned at 10:45 a.m., Wednesday, October 9, 1985.

NOV 2 5 1985

Date

David Korn, M.D.