Department of Health and Human Services

Public Health Service

National Institutes of Health

National Cancer Institute

National Cancer Advisory Board

Summary of Meeting
February 1-3, 1988
Building 31, Conference Room 6
National Institutes of Health
Bethesda, Maryland

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February 1-3, 1988

The National Cancer Advisory Board (NCAB) reconvened for its 65th regular meeting at 8:30 a.m., February 1, 1988, in Building 31, 6th floor, Conference Room 6, National Institutes of Health (NIH). Dr. David Korn, Chairman, presided.

NCAB Members

Mr. Richard A. Bloch
Dr. Roswell K. Boutwell
Dr. Victor Braren
Mrs. Nancy G. Brinker
Mrs. Helene G. Brown
Dr. Ed L. Calhoon
Dr. John R. Durant
Dr. Gertrude B. Elion
Dr. Bernard Fisher
Dr. Phillip Frost
Dr. Geza J. Jako
Dr. David Korn
Dr. Enrico Mihich
Mrs. Irene S. Pollin
Mrs. Barbara I. Shook (Absent)
Dr. Louise C. Strong
Dr. Louis W. Sullivan
Dr. Howard Temin

President's Cancer Panel

Dr. Armand Hammer
Dr. William P. Longmire
Dr. John A. Montgomery

Ex Officio Members

Dr. Dorothy A. Canter, NIEHS
Captain Stephen R. Veach, DOD
Dr. Stephen Litwin, VA
Dr. Lakshmi Mishra, CPSC
Mr. Richard A. Lemen, NIOSH

Members, Executive Committee, National Cancer Institute, NIH

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

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

Liaison Representatives

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

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

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

Ms. Deborah Mayer, President, Oncology Nursing Society, Cambridge, Massachusetts, representing the Oncology Nursing Society.

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. M. V. Parthasarathy, Program Director for Cell Biology, National Science Foundation, Washington, D.C., representing the National Science Foundation.

Dr. Warren H. Pearse, Executive Director, American College of Obstetricians and Gynecologists, Washington, D.C., representing the American College of Obstetricians and Gynecologists.

Dr. John F. Potter, Professor of Surgery, Vincent T. Lombardi Cancer Research Center, Georgetown University, Washington, D.C., representing the Society of Surgical Oncology and American College of Surgeons.

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

Ms. Kerrie Wilson, Legislative Representative, American Cancer Society, Washington, D.C., representing the American Cancer Society, New York, New York, for Alan C. Davis.

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

In addition to NCI staff members, meeting participants, and guests, a total of 30 registered members of the public attended the meeting.

I. Call to Order, Opening Remarks, and Consideration of November 16-17, 1987, NCAB Meeting Summary--Dr. David Korn

Dr. Korn, Chairman, called the 65th meeting of the National Cancer Advisory Board (NCAB) to order and welcomed members of the Board and the President's Cancer Panel (PCP), liaison representatives, guests, staff of the National Cancer Institute (NCI), and members of the public. Those who wished to express their views on topics discussed in the meeting were invited to submit written comments to Mrs. Barbara Bynum, Executive Secretary of the Board, within 10 days after the meeting.

Approval of the November 1987 NCAB meeting summary was postponed until the Wednesday's session (February 3).

Dr. Korn announced that an in-depth presentation on the Biological Carcinogenesis Program of the Division of Cancer Etiology would precede the en bloc vote during Tuesday's closed session. This was in response to a Board request for information on the Institute's extramural programs.

II. Future Board Meeting Dates

Dr. Korn called the Board members' attention to the following confirmed meeting dates: May 9-11, 1988; September 26-28, 1988; December 5-7, 1988; February 6-8, 1989; May 15-17, 1989; September 18-20, 1989; and December 4-6, 1989.

III. Report of the President's Cancer Panel--Dr. Armand Hammer

Dr. Hammer reported that the President's Cancer Panel held its final meeting for 1987 on November 20 at the National Cancer Institute, where members had an opportunity to meet NCI Division Directors and discuss the reauthorization of the National Cancer Act, which is due in 1988. Dr. Hammer asked Dr. DeVita to prepare a comprehensive report on the reauthorization issue as a preliminary step to the Panel's contacting appropriate members of the Administration and Congress.

Dr. Hammer noted that the Panel would probably recommend that the reauthorization period be extended from 3 to 5 years, thereby providing NCI the stability necessary for further development of important recent discoveries and advances. He speculated that a possible outcome could be the reauthorization of the National Cancer Act with a few minor changes, along with a provision for the extended period between reauthorizations. However, he noted the uncertainty of the reauthorization process and the need for Panel members to prepare to support renewal of the Cancer Act. He added that the PCP would strongly oppose elimination of the special authorities available to the NCI Director. Dr. Hammer noted that Dr. DeVita's report, due to be completed soon, will be a useful resource for all and will be made available to NCAB members.

Continuing his report of the November 20 meeting, Dr. Hammer said the Panel heard presentations on research in the Divisions of Cancer Treatment, Cancer Biology and Diagnosis, and Cancer Etiology by

Drs. Bruce Chabner, Alan Rabson, and Richard Adamson, respectively, and a report by Dr. Paul Rambaut on NCI/Soviet cancer research collaborations.

In discussing the Division of Cancer Treatment presentation, Dr. Hammer expressed satisfaction at hearing the results of Dr. Steven Rosenberg's latest research on TIL--tumor infiltrating lymphocytes--(of four patients treated with a combination of TIL, IL-2, and cytoxan, one had a complete response and three had 50 percent reduction in tumor size). He noted that more recent reports from Dr. Rosenberg indicate continued good results in the preliminary trials, and he predicted that TIL will emerge as a major cancer therapy if Dr. Rosenberg is able to expand the trials and make required adjustments in the protocol.

Dr. Hammer said that Dr. Chabner's report on the Drug Development Program and the biologicals included information on notable successes of the newer drugs deoxycoformicin (for treating hairy cell leukemia) and ifosphamide (for treating testicular cancer). He expressed the Panel's concern over the Food and Drug Administration's (FDA) restrictive criteria for approval of drugs for marketing and the consequent delay in their reaching cancer patients who might benefit from their availability. He expressed the hope that meetings presently scheduled between NCI and FDA would result in some improvement in the situation.

With regard to biologicals, Dr. Hammer expressed the Panel's satisfaction that extramural trials at six cancer centers have confirmed some of the responses in melanoma and renal cell cancer patients treated with IL-2/LAK that were achieved intramurally. He noted that NCI is expanding clinical trials of the IL-2/LAK protocol to treat patients with other types of advanced cancers.

Turning next to the report from Dr. Rabson, Dr. Hammer stressed the importance of basic research in cell biology (particularly of monoclonal antibodies and immunotoxins) and the molecular genetics of drug resistance to the understanding of cancer mechanisms and the eventual development of effective treatments.

Dr. Hammer said Dr. Adamson described work on RNA and DNA viruses, advances in the study of the hepatitis virus, studies with the human immunodeficiency virus (HIV), and problems encountered with animal models in which to test HIV. He said the session at the NCI proved useful to the Panel and might be repeated at the end of the year, although the majority of future Panel meetings would probably continue to be held at cancer centers throughout the country.

Next, Dr. Hammer reported that the first Panel meeting of 1988 will be held on March 1 at Columbia University in New York and will include a presentation on colony-stimulating factors (CSFs) by Dr. Malcolm Moore, a winner of the 5th Hammer Cancer Prize for his pioneering work in CSFs. He said that a previous report by Dr. Moore (on the use of GCSF after M-VAC chemotherapy in treatment of advanced bladder cancer) underscored the potential value of CSFs in the mediation of the toxic effects of chemotherapy on the immune system. He predicted that survival rates of cancer patients

will dramatically improve if it is possible to increase doses of chemotherapy without excessive toxicity and adverse effect on the immune systems of patients.

Dr. Hammer then announced that the annual PCP report would be submitted to the President later in the day and would include the Panel's conclusion that NCI's network of programs, mandated by the Cancer Act, has produced extensive benefits in basic research for cancer prevention, control, and treatment. In addition, Dr. Hammer said he suggested in the report that $500 million in Government funding be set aside for NCI to be matched by $500 million that the Panel hopes to raise from non-Government sources. He noted that the amount would double the funds available to NCI and enable funding of projects that cannot now be supported.

In support of that goal, Dr. Hammer said he has worked with well-known entertainer Bill Cosby to encourage the public to call their Congressmen and Senators in support of this project. He said he has received a very positive response. Dr. Hammer said he subsequently contacted House Speaker Jim Wright who expressed an interest in the proposal and suggested other sources of support, which he said he plans to pursue. Responding to a question as to use of the additional funding should the project be successful, Dr. Hammer stated that he favored immunological research.

IV. Director's Report--Dr. Vincent T. DeVita, Jr.

Dr. DeVita began his report by recognizing the contribution of Board members Mr. Richard Bloch, Dr. Victor Braren, Dr. Ed Calhoon, Dr. Geza Jako, and Mrs. Barbara Ingalls Shook, whose terms expire in March 1988. Each was presented a certificate of appreciation.

In noting organizational changes, Dr. DeVita said the Office of Technology Development has been established in the Office of the Director and will be headed by Dr. Barney Lepovetsky. This new Office will be responsible for implementing the Stevenson-Widler Technology Transfer Act, advising the NCI Director on matters related to patent policy, and assisting intramural scientists in formulating research and development agreements with industry and academia. Dr. DeVita said that more information about this office and its activities would be provided at the May NCAB Meeting.

Other organizational changes were discussed at the January retreat and will be presented to the Board as more details are developed. Dr. DeVita said the basic idea is to strengthen the prevention program and the programs used to apply the results of basic research. Combining cause and prevention into one division is one option being considered. A first step might be combining the Epidemiology Program of the Division of Cancer Etiology with the Prevention Program. Dr. DeVita said consideration is also being given to putting all application programs (i.e., the Cancer Centers Program, Organ Systems Program, CCOPs, training programs, construction, and clinical cooperative groups) together, perhaps in the Office of the Director under an associate director.

Dr. DeVita said that all NCI extramural staff are being moved into one building a few miles from the NIH campus. Approximately 900 staff will move by July 1988. Should there be reorganizations, they would be easier when staff is all in one building.

Turning to staff changes, Dr. DeVita announced that Dr. Maxine Singer had left as Chief of the Laboratory of Biochemistry in the Division of Cancer Biology and Diagnosis to become President of the Carnegie Institute of Washington. Dr. Singer, who recently received the Distinguished Executive Service Award, will remain as a scientist emeritus with NCI. Dr. DeVita's other staff announcement was that Dr. Werner Kirsten, Chairman, Department of Pathology at the University of Chicago, will assume AIDS-related responsibilities at NCI, while Dr. Peter Fischinger is detailed to the Department as the AIDS coordinator.

Follow-up Items

Dr. DeVita noted the following items that would be the subject of presentations to the Board: the annual cancer statistics to be presented in a slightly changed format; a report on the recommendations on the Women's Health Trial; proposals for changes in the Organ Systems Program; and further discussion of problems in patient accrual to clinical trials. Dr. DeVita said a Government Accounting Office (GAO) study on the dissemination of new technologies had been transmitted to Representative Henry Waxman, who had requested the report. The report will be made available to the Board. The report found a significant time lag between the development of a new therapeutic breakthrough and its incorporation into general medical practice. Among the findings were that 20 percent of patients with Hodgkin's disease, 25 percent with one type of lung cancer, 60 percent with rectal cancer, and 94 percent of those with colon cancer did not receive what NCI considers state-of-the-art treatments. Dr. DeVita suggested that this was a very useful report in that it reiterated many of the problems involved with patient accrual to clinical trials.

Dr. DeVita said another GAO report on IL-2/LAK therapy, requested by Representative Ted Weiss, had not yet been completed. Questions are being asked about the effect of putting IL-2/LAK into a modified Group C category, which requires less reporting to FDA, and the slow accrual of patients to the modified Group C protocol at cancer centers. Dr. DeVita stated that these were worthwhile questions, but suggested that the interest was related to the continuing discussions with FDA about making available a treatment for which testing is incomplete, when it is the only treatment for certain kinds of cancer. He said that IL-2/LAK treatment is the only therapy that has produced consistent, complete remissions for metastatic renal cell cancer and metastatic malignant melanoma. Approximately 10,000 of these patients per year could receive this treatment with perhaps 1,500 who might achieve complete remission.

Dr. DeVita said the Senate Appropriations Committee had also requested a committee to review the measures NCI uses to determine progress against cancer. The Committee is chaired by Dr. Edward Sondik and includes

Dr. John Bailar. The report will be finished in the spring and will be presented to the NCAB.

Next Dr. DeVita reported that although NIH had agreed to restore to NCI its full historical complement of 149 beds at the Clinical Center, the 12-East Ward that had been opened on January 25 has provided only one day bed for NCI. He said the problem continued to be a shortage of nurses. NCI has asked to be given responsibility for its own nursing service so that it will have control over all resources needed for clinical research.

Dr. DeVita said the revised procedure is in place for reviewing P01 grants using the site visit team as the review group, but NIH continues to have concern about eliminating parent committee review. He said that as the revised procedure had been approved by the NCAB, NCI would continue to use it while discussing the issue with NIH.

The first issue of the new NCI journal, combining the Journal of the National Cancer Institute and Cancer Treatment Reports, will be published on March 7, 1988. Dr. DeVita said this will be the only journal devoted exclusively to cancer, providing information on both clinical and basic sciences.

With respect to the Board's concerns about inconsistencies between the text of summary statements and their scores, Dr. DeVita said that the Chief of Program Directors has been asked to call such discrepancies to the attention of the Executive Secretary. There will be an attempt to rectify these discrepancies before they reach the Board.

In commenting on AIDS-related issues, Dr. DeVita said that the PHS AIDS Task Force's Subcommittee on Therapeutics is co-chaired by Dr. Bruce Chabner and Dr. Anthony Fauci; the Subcommittee on Vaccine Development has been co-chaired by Dr. Maryann Roper but will be one of Dr. Kirsten's responsibilities when he joins the Institute. Dr. DeVita said a license has been signed with Bristol Pharmaceutical Company for dideoxy-adenosine and dideoxyinosine. In response to concern among scientific staff about HIV infection of laboratory workers, NIH has registered all those who work with HIV. They are required to attend a seminar on techniques for handling the virus, and they will be encouraged to participate in a voluntary blood testing program. Those who participate will be tested every 4 months, and the reports will be mailed directly to the workers within 4 weeks of the test.

Dr. DeVita reported that there is some difficulty in getting voluntary protocols onto PDQ. All protocols that are part of Government supported work are automatically put onto PDQ. NCI has asked the cancer centers to also enter protocols that are supported by private sources. Dr. DeVita said part of the reasoning for that request is that the cancer centers are now able to show their privately supported research as part of the review for core grants. In addition, it is important to know about all active protocols. Dr. DeVita said seven cancer centers (Memorial Sloan-Kettering, University of Pennsylvania, Wayne State, Mayo Clinic, Johns Hopkins, the Illinois Cancer Council, and Columbia University) have not

participated, and the usual reason given is that they have sufficient patient accrual.

Budget Update

Dr. DeVita's budget presentation was based on levels contained in the December continuing resolution. He expressed the hope that OMB would return to the traditional system of apportionment of funds directly to the Institute rather than consolidated at the NIH level. He also pointed out that Congress had requested a review of the construction program and how to fund it; they did not provide any construction funds while that review is in progress.

The FY 1988 budget, without AIDS, is $1.379 billion, a 3 percent increase over FY 1987. With a 41 percent increase in the AIDS portion, the total FY 1988 NCI budget is $1.469 billion, a 4.7 percent increase over last year. As part of the Federal Deficit Reduction program, the NCI budget was reduced from the original House budget of $1.542 billion and the Senate level of $1.527 billion. AIDS monies are provided directly to the Institute, although the House had asked that all AIDS monies be moved into the Office of the Assistant Secretary.

Dr. DeVita noted that although research project grants were increased over the previous year, negotiations of about a 10 percent reduction in recommended levels for competing grants and about a 5 percent reduction from recommended levels for non-competing grants will be necessary. Including non-competing awards, there will be over 3,115 total research project grants funded in 1988, a 34 percent funding rate which is slightly less than 1987. Cancer centers received a 5 percent increase over 1987. With respect to the AIDS budget, Dr. DeVita noted that a significant amount of the Institutes's AIDS activities--drug and vaccine development--is supported through contracts, while existing grant referral guidelines send the majority of all AIDS grants to the National Institute of Allergy and Infectious Diseases (NIAID). In addition, Dr. DeVita said NIH will be changing some programs now run by contracts to grants. For example, the AIDS Treatment Evaluation Units (ATEUs) are being converted from contracts to grants.

In discussion, the following points were raised:

- NIH is continually faced with the dilemma of whether to fund fewer competing grants fully or fund more grants at reduced levels.

- The IL-2/LAK treatment is specifically for "kidney cancer."

- The CCOPs have been successful in bringing 4,000 to 5,000 additional patients into protocols at the grass roots level. The Cooperative Groups have not considered patient accrual to protocols as part of their mission. The climate in which private cancer medicine is practiced also is not conducive to enrolling patients in clinical trials.

- NCI has 108 open beds at the Clinical Center and another 25 could be opened if nurses were available.

- NCI willingly cooperates with the private sector in amplifying results of proven therapies.

New Items

Dr. DeVita pointed out that the Board will be receiving information about funding of grants on a percentile basis rather than the absolute priority scores. He said this is being done throughout NIH to get around the priority score compression problem. However, this will not change the process whereby a grant that is not in the payline can be selected for funding. Dr. DeVita also noted that a new GAO study will examine the qualifications of investigators who receive grants and contracts.

As mentioned by Dr. Hammer, Dr. DeVita reported that a study combining four drugs (M-VAC) with GCSF achieved elimination of the leukopenia associated with combination chemotherapy. The patients also did not suffer mouth ulcers that usually accompany the chemotherapy. This is the first time that an effective treatment for metastatic bladder cancer has been used as an adjuvant. Dr. DeVita said the Board would be kept informed of progress in the use of colony-stimulating factors together with chemotherapy.

In conclusion, Dr. DeVita directed attention to the upcoming hearings on appropriations and reauthorization. He also said that some aspects of the 1989 budget would be discussed in closed session.

Legislative Update--Dr. Mary Knipmeyer

Dr. Knipmeyer began her report by commenting on NCI's efforts in testifying or preparing testimony for Congress. Dr. Charles Smart testified on screening mammography before the Senate Committee on Labor and Human Resources. Dr. Knipmeyer pointed out that although the Department of Health and Human Services recognizes the value of screening mammography, the cost is not covered under Medicare. NCI, therefore, comments only on the scientific value of mammography and how it contributes to the year 2000 goals. Dr. Knipmeyer said that Dr. Greenwald has been invited to testify on diet, nutrition, and cancer before the Senate Governmental Affairs Committee in early March.

Dr. Knipmeyer also noted that NCI had received two congressional visits. Representative Robert Dornan visited NIH to discuss issues associated with workers' exposure to the AIDS virus. He also visited NCI's pediatric ward at the Clinical Center and discussed NCI's AIDS research in children. Representative Dornan inserted a complimentary report about his visit into the Congressional Record. Dr. Knipmeyer said that Mr. Tim Westmoreland, Counsel to Representative Henry Waxman's House Subcommittee on Health and the Environment, visited the Clinical Center to discuss resources needed to open AIDS beds and support AIDS research at NIH.

In discussing reauthorization, Dr. Knipmeyer said hearings may begin in late February and the process may proceed quickly because of election year pressures to end the session early. She also remarked that NCI had sent to Representative Waxman a response to Dr. Samuel Epstein's article in the Congressional Record on problems in the National Cancer Program. The response was provided to Board members.

Dr. Knipmeyer stated that legislation pending included 11 new bills relating to AIDS. She called attention to the Waxman Bill HR-3825, which would require no less than 50 beds each from NCI and NIAID for clinical research on AIDS. Such a requirement would necessitate a large amount of additional resources. Dr. Knipmeyer said Congress continued to discuss ways of expediting grants and contracts for AIDS research.

With respect to animal welfare, Dr. Knipmeyer noted that a number of bills are pending and some, in particular the Pet Protection Act, have quite a bit of support from Congress, as demonstrated by the large number of co-sponsors. She explained that the Pet Protection Act or Pound Act would ban the use of pound animals in Federally supported research and that the Senate version would prevent Federally supported researchers from purchasing research animals through an intermediary. In discussion, it was reiterated that this is a very serious, controversial, and emotion-laden issue, which in several States has resulted in restrictions on the use of animals in biomedical research. Some attempt at compromise may involve tattooing animals who are pets so that they could be identified as pets if they were to be taken into a pound. Dr. Knipmeyer added that NIH was moving toward a more proactive approach on the issue. It also was suggested that NIH and NCI notify researchers and ask them to testify before State legislatures. Dr. Knipmeyer recalled that the Animal Welfare Act that was revised in 1985 still does not have final published regulations and the regulations may be reevaluated this spring. Without final regulations, there is no guidance on what changes may need to be made in procedures. In response to the Board's concerns, Dr. Korn requested that Dr. Knipmeyer develop a packet of information detailing key issues and costs for the May NCAB meeting. Dr. DeVita added that cancer centers may be able to supply information to their States and local areas.

In concluding her report, Dr. Knipmeyer stated that starting April 23, 1988, smoking will be banned on airplane flights of 2 hours or less for a trial period of 2 years. She will verify whether this rule pertains to flights or flight numbers.

In response to a question from Dr. Roswell Boutwell, Dr. DeVita said that no special initiative has been undertaken for sequencing the human genome. The National Institute of General Medical Science (NIGMS) has issued an RFA to support areas that would enhance technology development, speed of sequencing, and other aspects. NCI's supercomputer is a resource for sequencing efforts.

V. Annual Cancer Surveillance Review--Dr. Edward Sondik

Dr. Sondik called Board members' attention to the report before them, Annual Cancer Statistics Review, including Cancer Trends: 1950-1985, and noted the many contributions from NCI staff. He identified the major measures as incidence, detection, treatment, survival and the quality of life, and mortality. The report includes a new section on cancer trends from 1950 through 1985. Dr. Sondik defined incidence as the rate of new cancers per year, mortality as the annual rate of cancer deaths, survival as the amount of time a person lives following the diagnosis of cancer, and 5-year relative survival rate as the percent of persons surviving at least 5 years past the diagnosis of cancer. The 5-year relative survival rate is normalized by dividing that percentage by the percentage of persons from the general population matched by age and sex. This gives an average percent of persons surviving at least 5 years if cancer were the only cause of death. The source of the incidence and survival data is the Surveillance, Epidemiology, and End Results (SEER) Program, and the source of mortality data is the National Center for Health Statistics (NCHS). The SEER data come from 11 population-based registries around the country and do not constitute a representative sample. NCHS collects data on every death occurring in the United States from state offices of vital statistics.

Dr. Sondik identified statistical biases that should be considered in interpreting the data. These included changes in the mix of cancer sites; for example, lung cancer mortality in 1950 was much lower relative to overall cancer mortality than it is today. There have also been changes in stage definition because of changes in practice or technology. With advances in screening, it has become possible to detect diseases earlier, and longer lead time may result in an artificial inflation of survival rates. Slow-growing tumors also add a length bias, and changes in diagnosis, particularly related to technology, constitute another statistical bias. The selection of the relative survival comparison group may also be a source of bias. For example, relative survival for lung cancer patients is calculated on the basis of a random sample from the general population as a comparison group normalized by age and sex. However, a more appropriate comparison group might be smokers in general. Dr. Sondik suggested that if smokers were used as a comparison group, survival rates from lung cancer would appear higher.

In discussing trends in data from 1950 to 1985, Dr. Sondik noted that without lung cancer, overall cancer mortality has declined by 13.3 percent since 1950. Breaking out the data by age, mortality has declined for all age groups up to age 54. Excluding lung cancer, the decline in mortality extends up through age 84. Thus, the only increase over the time period is among those 85 years old and above, when lung cancer is excluded. It was suggested that it is appropriate to examine lung cancer separately because it is largely preventable. Mortality and survival data show that treatment for lung cancer is not very successful, but incidence data reflect progress in preventing cigarette smoking.

In combining data on average years of life lost with incidence, lung cancer is dominant, followed by breast cancer. Dr. Sondik said that data from 1973 to 1985 show that lung cancer incidence has leveled off and begun

to decline in white males and that mortality also appears to be leveling off. Lung cancer mortality among females has been increasing since 1950, although the percent increase in mortality between 1983-84 and 1984-85 has been the lowest in many years. Dr. Sondik said these changes coincide with trends in smoking, although data from the first quarter of the 1987 National Health Interview Survey showed an increase in smoking.

The data for breast cancer indicate that mortality has remained essentially level from 1950 to 1985, although incidence has been increasing. Dr. Sondik noted that a spike in incidence in 1974 probably indicates early disease detection because of publicity about breast cancer among a number of prominent women. He said it is not known whether the continuing rise is due to screening or some changing risk factors in the population. Since 1979 there has been a steady increase in mortality in women over 50, which is in line with the increased incidence. In women under 50, mortality gradually declined up through 1983 probably because of aggressive treatment and early diagnosis. However, there was a 7 percent increase in mortality from 1983 to 1984 and another small increase to 1985. Dr. Sondik mentioned that although the National Health Interview Survey shows some increase in the number of women who receive screening mammography, 46 percent of women have never had mammography.

Dr. Sondik next reviewed sites that have shown major changes in incidence and emphasized the importance of incidence to the cancer problem. Over the period 1950 to 1985, incidence of cervical cancer decreased 77.5 percent and mortality fell 73 percent. There has also been more than a 70 percent decline in incidence and mortality from stomach cancer. The greatest increase in incidence has occurred for melanoma (more than 200 percent), with an increase in mortality of 150 percent, although survival has increased. Combining males and females, there has been a 238 percent increase in lung cancer incidence, but also an increase in survival, although survival remains relatively low. The incidence of non-Hodgkin's lymphoma increased 123 percent and mortality 100 percent, but there was also an increase in survival. The incidence of testicular cancer increased 85 percent but mortality declined 60 percent. For kidney cancer, mortality has not kept pace with the 82 percent increase in incidence; however, for cancer of the larynx, mortality has declined with the rise in incidence. In considering data back to 1935, for colon and rectal cancer, mortality increased through the 1940s and since then declined unabated, although there has been an increase in incidence. Dr. Sondik called attention to a section of the report that outlines advances in diagnosis and therapy and noted that the decline in colorectal cancer mortality corresponded to an increase in the number of patients who had surgery.

The report compiles data on therapeutic advances and their impact, and recent trends in treatment for some cancer sites. For bladder cancer, childhood cancers, and Hodgkin's disease, there were significant declines in mortality although incidence has increased. Dr. Sondik suggested the declines are due to improvements in the detection and treatment of the disease.

In summarizing the data, Dr. Sondik pointed out some findings that are clues for cancer control. There are differences in survival between blacks and whites, which are particularly significant for cancer of the oral cavity where survival for whites is 53 percent compared with 31 percent for blacks, and uterine cancer where survival for whites is 83 percent and 52 percent for blacks. He said there was a need to study these and other sites to determine the reasons for the differences. He also noted the differences in mortality for whites and blacks: for oral cancer, mortality among blacks is 75 percent higher than for whites, and for colorectal cancer, mortality has been declining among whites but rising among blacks.

In conclusion, Dr. Sondik reiterated the major points that can be derived from the surveillance data: 1) incidence is very important, especially in considering data over time; 2) the data should be considered on a site by site basis; 3) differences between blacks and whites and among geographic areas offer clues for cancer control; and 4) there are gaps in technology transfer where the best treatments are not being applied.

Points raised in discussion included the following:

- The decline in the incidence of stomach cancer may be related to refrigeration and improvements in diet.

- SEER data do not include socioeconomic data on individuals; analysis is based on census tracts.

- DCPC is currently conducting a black/white survival difference study and DCE is conducting a study on differences in incidence.

- The impact of competing causes of death on relative survival appears to be relatively small.

- DCE will present a concept to its Board for a case-control study to examine the possible role of numerous factors, such as occupational exposure to the father, exposure to radon, exposure to cigarette smoking by the mother, neonatal and childhood exposures, in the increased incidence of childhood cancers.

- Total, overall 5-year survival remains in the range of 50 percent although for individual sites it has changed considerably.

- The SEER program does not collect separate statistics for the Hispanic population, although some are available from the SEER registry in Puerto Rico. In general, the incidence of cancer for many sites is lower among Hispanics.

- Increases in bladder cancer may be associated with smoking, exposure to chlorine in drinking water, exposure to diesel exhaust, and occupational exposures.

- EPA estimates that 5,000 to 20,000 lung cancers per year may be due to radon. Four studies on radon are in progress. Radon appears to have a multiplicative effect with smoking.

VI. Human Papillomaviruses

Epidemiology of Cervical Cancer--Dr. Louise Brinton

Dr. Brinton stated that speculation about the role of a number of new risk factors has sparked renewed interest in cervical cancer. These risk factors include smoking, oral contraceptive usage, male characteristics, and specific infectious agents. Dr. Brinton indicated that although she would emphasize the putative role of papillomaviruses, the proper interpretation of their effect is dependent on understanding an entire spectrum of variables and their interrelationships.

In reviewing demographic patterns, Dr. Brinton pointed to the profound geographic variation as one of the most striking features of cervical cancer. The highest rates have been observed in certain Latin American countries, specifically Colombia and Brazil, while the lowest rates have been observed in Israel and in white women in the United States. The SEER program has documented decreases of about 50 percent in the United States over the past 30 years. Dr. Brinton said this decline was generally thought to reflect the influence of Pap smear screening programs, although the fact that rates were declining even before the advent of these mass screening programs raises the possibility that other factors may also have been involved. In spite of this decline, incidence of cervical cancer remains approximately two times higher for blacks and Hispanics than for whites. Dr. Brinton noted that there are also significant inverse correlations between both income and education and cervical cancer for both whites and blacks. In fact, when adjustment is made for differences in the distribution of these socioeconomic factors, the difference between whites and blacks is reduced from 70 percent to about 30 percent.

Dr. Brinton stated that the associations with socioeconomic variables reflect the influence of correlated factors, and the most likely explanatory factor is sexual behavior. Numerous case-control studies have found a strong inverse relationship between cervical cancer risk and age of first intercourse: those with first intercourse before age 20 are at about a 50 percent higher risk than those who initiate sexual activity at later ages. In addition, Dr. Brinton said, a number of studies have found a strong correlation between disease risk and number of sexual partners. Women who report two or more partners experience approximately a 2-fold lifetime excess risk compared to those with only one partner. Risk also appears to increase directly with the number of sexual partners. Additional evidence for the sexual transmission of cervical cancer has come from studies in which clusters of effects were found. For example, preliminary results from a study by Kessler et al. indicated both a higher rate of cervical cancer and abnormal cervical cytology in the wives of men who had previously been married to women who had cervical cancer, compared to control wives.

Dr. Brinton said that a similar excess risk of cervical cancer has been noted in at least three studies (Puerto Rico, New York, and England) in wives of patients with penile cancer. She suggested that these findings indicated that male characteristics as well as female characteristics should be considered in defining etiologic factors for cervical cancer. Direct evidence of the male contribution was provided in a study by Buckley of women with cervical cancer who said their husbands were their only sexual partners. When the husbands were interviewed in a setting apart from the wives, these men were found to be considerably more promiscuous than the husbands of controls. Dr. Brinton said the risk of wives developing cervical cancer increased with the number of sexual partners reported by their husbands, and there was also a correlation with the age at which the husbands initiated sexual activity. Further, the husbands of cases reported more extramarital affairs and sexually transmitted diseases than the husbands of controls.

Although it is generally accepted that an infectious agent or agents is involved in the etiology of cervical cancer, Dr. Brinton said the definite agent has not been identified. Herpes virus type 2 was a focus of interest during the 1970s, but more recent research has focused on the role of papillomaviruses. In addition, Dr. Brinton said there has been speculation about a possible etiologic role for chlamydia and cytomegalovirus. She said that interview studies have not been very helpful in trying to define the role of infectious agents. In a case-control study conducted in five areas of the United States, few of more than 500 women with invasive disease reported a history of specific infections, although a fairly large proportion reported a history of nonspecific genital infections, which was associated with a statistically significant 2.5-fold excess risk.

Dr. Brinton said these findings point to a need for laboratory techniques to define specific oncogenic agents. Within the past few years techniques have been developed for the detection of papillomaviruses that appear promising for clarifying mechanisms of carcinogenesis. These are primarily DNA hybridization techniques that identify specific types of papillomaviruses. To date, approximately 60 types have been identified and 6 have been linked with the occurrence of cervical abnormalities. Dr. Brinton emphasized that the strength of the association between papillomavirus infection and cervical neoplasia is based on both histologic evidence of infection and DNA hybridization studies, which seem to correlate well with each other.

Dr. Brinton next turned to discussion of the effects of other risk factors, namely smoking and oral contraceptives. In a U.S. study, smoking was associated with a significant increase in risk that persisted even after adjustment for a number of sexual and other risk factors. Risk increased both with number of cigarettes smoked and number of years of smoking. Those who smoked for 40 years or more had a 2-fold excess risk compared to nonsmokers. Dr. Brinton said further evidence of causality was derived from the histologic specificity of the association, with the association seemingly restricted to squamous cell tumors. In the same U.S. study, initially no association was observed between the use of oral contraceptives and the occurrence of disease. Dr. Brinton pointed out, however, that after accounting for various intervening or confounding variables--the most

important being interval since last Pap test--a strong relationship was observed between duration of use and increased risk. Those women who used oral contraceptives for 5 or more years had a 2-fold excess risk compared to non-users.

Dr. Brinton said that the U.S. study was not able to clarify the role of other postulated risk factors, such as diet, specific infectious agents, and the male factor. To address hypotheses related to these other factors, a case-control study was conducted in Colombia, Costa Rica, Mexico, and Panama. Cases were women with newly diagnosed invasive cervical cancer. Approximately 200 women in each of the four study areas were identified over an 18-month period. Controls for each case were matched on age and geographic factors and were either hospital controls or a mixture of hospital and community controls. Dr. Brinton said this population was ideally suited to study the role of the male factor as approximately 50 percent of the women reported having only one lifetime sexual partner. By recruiting the husbands of these women for study, it was possible to examine the effects of male behavior on risk, unencumbered by the recognized effects of female behavior.

Dr. Brinton said that female subjects were usually interviewed in the hospital, and blood samples and cervical smears were obtained for papillomavirus testing. Pap smears were also taken from controls to ensure that they were free of cervical disease. The men were interviewed at their homes or workplaces out of hearing distance of the wives. Following the interview, the men were examined and a blood sample and a coronal sulcus swab and a urethral swab were obtained. The state of their hygiene and whether the men were circumcised were also noted.

In spite of the problems encountered--an earthquake in Mexico City that destroyed one study hospital, a volcano eruption in Colombia, and floods in Panama --Dr. Brinton said the study was successful in terms of numbers of completed interviews and response rates. For the biochemical component of the study, blood specimens and either cervical or penile scrapes or swabs were obtained from more than 90 percent of the interviewed subjects. Dr. Brinton said laboratory tests are now being performed using these biologic specimens, and it is hoped that these will provide important additional information about the etiology of cervical cancer.

With respect to the interview data, Dr. Brinton said analyses were just beginning, but she related some preliminary findings. She said the behavior of the males appears to be an important predictor of risk for their wives. The risk of cervical cancer for the wives increases with the number of lifetime partners reported by the males, such that the wives of men reporting more than 25 partners have a 2-fold greater risk compared to the wives of men who reported 5 or fewer lifetime partners. Dr. Brinton also noted that for women, although the trend in risk with increasing numbers of sexual partners was significant, the main difference appeared to be between monogamous and non-monogamous women. She called this an unexpected finding that possibly indicates the importance of the intervening male behavior in predicting risk.

Dr. Brinton said another surprising finding was the very strong effect of number of pregnancies, even after adjustment for a variety of factors including sexual behavior. A substantial number of women had 10 or more pregnancies which were associated with a 4-fold excess risk compared to those who had none or 1 pregnancy. Dr. Brinton said that although number of pregnancies had not been thought to be a risk factor, recent clinical findings of a higher prevalence of papillomavirus infection among pregnant women, possibly due to immunosuppression, supported a possible association. The trauma associated with pregnancy and delivery may also increase the susceptibility to infection with papillomaviruses or other infectious agents.

Dr. Brinton said filter in situ DNA hybridization assays for type-specific papillomaviruses had been conducted for nearly all of the female subjects. Preliminary results indicate quite a strong association with types 16 and 18, which are putative risk factors for invasive cervical cancer. In addition, Dr. Brinton said there is evidence of enhancement of risk with co-infection with types 6/11 and 16/18, with 6/11 being viral subtypes that in the past have been linked with precursors for cervical cancer. Another analysis in progress is an examination of risk factors for human papillomavirus-positive versus negative cases in Panama where scrapes and tumor tissues were obtained. Dr. Brinton said this analysis will enable determination of the correlation of these assays and comparison of positivity using filter in situ hybridization versus the southern blot technique. In conclusion, Dr. Brinton said a further area to be pursued is the assessment of possible modifying effects of other cervical cancer risk factors, including herpes virus, smoking, and oral contraceptives.

The following points were raised in discussion:

- Analysis of the Latin American studies will try to identify risk factor differences between the human papillomavirus-positive and negative cases.

- Whether or not husbands are circumcised does not appear to be associated with risk of cervical cancer among their wives.

- The sexual behavior of husbands of cases who reported only one sexual partner was compared with the sexual behavior of the husbands of controls. A relative risk or an odds ratio was calculated as a cross-product ratio of case-control status and exposure status.

- Reducing cervical cancer in countries where the incidence is high requires developing effective screening and follow-up programs.

Biology of Papillomaviruses--Dr. Peter Howley

Dr. Howley stated that he would review the biology of the papillomaviruses and then discuss data that associated specific human papillomaviruses with specific human cancers. He noted that SEER data estimate about 4,500 deaths from cervical cancer per year in the United

States, but approximately 500,000 women worldwide die each year from cervical carcinoma.

Dr. Howley said that although the first papillomavirus was described by Dr. Richard Shope more than 50 years ago, this group of viruses remained refractory to study until the late 1970s because of the inability to grow any of these viruses in tissue culture. Advances have only come following the application of modern techniques of molecular biology. Dr. Howley pointed out that distinct papillomaviruses are widespread in nature and infect a variety of higher vertebrates. There are now recognized to be 53 distinct human papillomaviruses (HPVs) associated with a variety of clinical lesions in humans. In showing slides of papillomavirus-associated lesions, he noted that they induce benign proliferative lesions of the squamous epithelium. Dr. Howley described the life cycle of these viruses as epithelial-specific which is tied to the differentiation cycle of the squamous epithelial cell. The close linkage to cell differentiation is thought to be the reason why investigators have not been successful in growing these viruses in tissue culture. The papillomaviruses are highly restricted and do not cross infect different species. In terms of their tissue tropism, the viral replicative functions are limited to the squamous epithelial cells. Late functions, such as vegetative viral DNA replication and virion capsid protein synthesis occur only in the fully differentiated squamous epithelial cells.

Dr. Howley said it has been known since the early 1960s that a group of papillomaviruses induces fibroblastic tumors in hamsters. The list of tumorigenic papillomaviruses includes the bovine, deer, sheep, European elk, and reindeer papillomaviruses. The papillomaviruses contain doublestranded DNA genomes of approximately 8,000 base pairs. Dr. Howley said that to date about a dozen papillomavirus genomes have been sequenced in their entirety, including those associated with human cervical carcinoma (HPV-16 and HPV-18). They encode approximately ten genes including the L1 and L2 genes that encode the capsid proteins required for the assembly of virions. The L1 and L2 genes are expressed only in the terminally differentiated keratinocytes. In addition, the papillomaviruses contain transforming genes, genes that are involved in the maintenance of plasmid DNA replication, and genes that regulate transcription.

Dr. Howley explained that a human papillomavirus isolate is considered a new type if it shares less than 50 percent sequence homology with other defined papillomaviruses. As there are no serologic reagents to distinguish between these papillomaviruses, the types are distinguished by DNA hybridization. Dr. Howley said that each of the types tends to be associated with specific clinical lesions, e.g., HPV-1 is associated with plantar warts, HPV-2 with common warts, HPV-6 and HPV-11 with condyloma acuminata, HPV-16 and HPV-18 with lesions at risk for development of cervical carcinoma, and others (HPV-31, 33, 39, 42, etc.) with specific ano-genital lesions. In the early 1970s, herpes simplex virus-2 (HSV-2) was thought to be linked to cervical carcinoma, but molecular studies failed to find a convincing association of HSV nucleic acids in cervical carcinoma tissues. Furthermore, subsequent sero-epidemiologic studies have failed to substantiate an association of cervical carcinoma with either HSV-1 or 2

infections. Dr. Howley suggested that HSV could be dismissed as the cause of cervical carcinoma.

The first evidence linking a papillomavirus to cervical cancer came from the observations of cytologists in the mid-1970s who realized that the cellular atypia seen in cervical dysplasia was the cytopathic effect of a papillomavirus infection. They found both papillomavirus-specific antigens and papillomavirus particles within dysplastic lesions, thus linking a papillomavirus infection with a lesion generally accepted to be a precancerous condition. Using nonstringent DNA hybridization techniques, investigators in West Germany succeeded in cloning the HPV-16 and HPV-18 genomes from cervical carcinoma tissue and used them as specific probes to examine cervical carcinoma biopsies. In summarizing studies from three groups, Dr. Howley said that over 90 percent of condyloma acuminata examined contained HPV-6 or HPV-11 DNA. Only a very small percentage of these condyloma acuminata could be demonstrated to contain HPV-16 or HPV-18 DNA. Cervical intraepithelial neoplasia (CIN), stage I or II, a mild to moderate dysplasia, contains HPV-6 and HPV-11 in about 20 percent of cases, but approximately 30 percent of these cases contain HPV-16 or HPV-18. Dr. Howley said these studies demonstrated that dysplasia is associated with specific HPVs, and a different set of HPVs is associated with condyloma acuminata. HPV-16 or 18 is found in more than 70 percent of cases of carcinoma in situ or invasive cervical cancers. Dr. Howley stated that altogether about 90 percent of carcinomas can be demonstrated to contain an HPV DNA.

In summarizing the evidence supporting an etiologic role for HPV in human cervical carcinoma, Dr. Howley said that 1) a high percentage of tumor biopsy specimens and established cell lines from cervical carcinomas contain HPV DNA; 2) cervical dysplasias considered as precursor lesions to cervical carcinomas are induced by HPVs; 3) precursor lesions containing HPV-16 and 18 appear to be more highly associated with malignant progression; and 4) a specific portion of the genome of viral DNA is generally transcriptionally active within the tumor cells. He next discussed the genome of HPV-16 and noted that a number of laboratories are studying HPV-16 and 18 to try to define mechanistically what functions these viruses may encode that could play a role in malignant progression. The bovine papillomavirus (BPV) has served as a model for HPV because the genomes are similar. All papillomaviruses, including HPV-16 and HPV-18, contain the E2 gene, which like the tat gene of the HTLVs encodes transcriptional regulatory factors. Dr. Howley pointed out that within the cervical carcinomas associated with HPV-16 and 18, integration of the viral DNA occurs randomly with respect to the host chromosome but in a way that generally disrupts the expression of the E2 gene of the virus. The result is that expression of the viral promoters within the cervical carcinomas is thus deregulated, no longer under control of the factors encoded by the E2 gene. The major viral promoter active in cancer tissues is just upstream from the E6 and E7 open reading frames. The E6 and E7 genes are transforming genes. Dr. Howley showed slides demonstrating that the HPV-16 E7 gene is an immortalizing viral oncogene that could provide a pool of cells which could expand and become a target cell population for random chromosomal events that may then progress to full cancer.

Dr. Howley stated in conclusion that cervical carcinoma was not the first cancer associated with HPV. Skin cancers in patients with epidermodysplasia verruciformis generally contain HPV-5, 8, or 14. Other human tumors have also now been associated with specific HPVs. Busche-Lowenstein tumors (giant invasive condyloma acuminata) contain HPV-6 and 11; vulvar and penile carcinomas contain HPV 16 and 18; a variety of oral and tongue cancers contain HPV-11 and 16; and verrucous carcinomas of the larynx contain HPV-16 and 30. An article in the New England Journal of Medicine in the fall 1987 described a patient with squamous cell carcinoma of the lung which had developed from recurrent laryngeal papillomatosis. Transcriptionally active HPV-11 was found in the carcinoma and in the liver and lymph node metastases of this patient.

The following points were raised in discussion:

- There is some antigenic relatedness of all papillomaviruses, but it is not known whether this would provide the basis of an effective vaccine.
- There are various subtypes for different HPVs, but the sequence variability among isolates of a specific type seems to be small.
- Molecular Genetics, a biotechnology company in Minnesota, has developed a bacterially generated vaccine for BPV which is being tested.

VII. Women's Health Trial--Dr. Peter Greenwald

Dr. Greenwald presented the report and recommendations of the Ad Hoc Subcommittee for the Women's Health Trial (WHT), which had been approved by the Board of Scientific Counselors (BSC) of the Division of Cancer Prevention and Control (DCPC). The Committee was chaired by Dr. Philip Cole and included three epidemiologists (Dr. Cole, Dr. Jennifer Kelsey, and Dr. Malcolm Pike) who have done extensive research on breast cancer; two experts on carcinogenesis (Dr. Roswell Boutwell and Dr. Edward Bresnick); two nutritional scientists (Dr. Elaine Feldman and Dr. Wayne Calloway), who also have expertise in endocrinology; and an ex-officio member, Dr. Paul Engstrom, who chairs the DCPC BSC. The Committee's recommendations were as follows:

1) The WHT as currently proposed should not go forward.

2) At the discretion of NCI staff, the WHT centers now active should be considered for continuing financial support in order that the education and followup of enrolled women, or a sample thereof, may continue and in order that scientific proposals based on the study groups can be generated and possibly implemented.

Eleven members of DCPC BSC voted in support of the recommendations with 1 opposed and 2 abstentions.

In reviewing the background of the WHT, Dr. Greenwald said the study was begun after an NCI-sponsored study by the National Academy of Sciences (NAS). The NAS study concluded that the combined epidemiologic and experimental evidence was most suggestive for a causal relationship between fat and the occurrence of cancer, especially breast cancer. The specific hypothesis of the WHT was that if women, 45 to 69 years old, consume a diet in which 20 percent of calories are from fat, they will have about a 50 percent reduction in breast cancer incidence over a 10-year period. The basic design involved randomizing 32,000 women with 40 percent getting the low-fat diet and 60 percent the high-fat diet.

Dr. Greenwald said the WHT Committee had examined several issues associated with the hypothesis. The Committee found that evidence from animal studies raised questions about the validity of the hypothesis. It is clear from animal studies that one component of a diet cannot be changed without changing other components. Animal studies also show that even a moderate restriction of calories reduces the frequency of mammary neoplasms even with a high-fat diet. In ad libitum feeding studies, the frequency of cancer is increased with higher levels of fat in the diet, with type of fat also having an influence.

In considering the epidemiologic data, the Committee questioned whether the trial would be able to achieve a 50 percent reduction in the occurrence of breast cancer on the basis of available epidemiologic evidence. The Committee concluded that a reduction in risk of more than 25 percent was unlikely. Dr. Greenwald pointed out the probability of error measurement in determining the percent of an individual's diet that comes from fat, which affects interpretation of several epidemiologic studies. There is no available biochemical marker of an individual's fat intake over time.

Other issues considered by the Committee were logistics and cost, challenges to the hypothesis, absence of a low-fat marker, acceptability of a null outcome, and study design. Dr. Greenwald noted the DCPC BSC recommended that NCI keep its present dietary guidelines and plans for periodic review as new research results are assessed. The present recommendations are that individuals eat a variety of foods that are low in fat and calories, and that consumption of whole grains, vegetables, and fruits--the fiber-containing foods--be increased. NCI will await the results of the Surgeon General's Report on Nutrition and Health and an NAS study on Diet and Health before considering changes in the guidelines.

With respect to the Committee's second recommendation to consider continuing some financial support to the WHT, Dr. Greenwald said the annualized cost of maintaining the study is $3.2 million. That cost is to support 3 clinical centers, a statistical center, and a nutrition center. Although there is a population of 1,500 women on a low-fat diet, there are no peer-reviewed proposals to study that unique population. Dr. Greenwald raised the possibility of a no-cost extension of the WHT past the March 1988 expiration and continued study of a sample of the population for durability of the intervention. He suggested it might also be worthwhile to collect more blood samples to try to develop a biochemical marker and to continue statistical analyses of the population.

Board members expressed the following views in discussion:

- The report of the WHT Subcommittee responded to the NCAB's request for an expert decision on the trial, and decisions on further support should be referred back to the DCPC BSC.

- The WHT investigators would like to continue to study the population's adherence to the diet over time.

- Many confounding factors, including the introduction of fat substitutes and a decline in fat consumption in the general population, would make it difficult for the WHT to detect a measurable case-control difference in fat intake.

- In general, future funding should be based on peer-reviewed proposals.

Mr. Richard Bloch made a motion to endorse the DCPC BSC's decision to discontinue the WHT as currently proposed. Dr. Howard Temin moved to table the motion, and 14 members voted to approve the motion to table. The Board expressed encouragement to the DCPC BSC to put out an RFA related to understanding the nature of the increase in breast cancer and the role of fat and other dietary factors.

VIII. Patient Accrual to Clinical Trials--Dr. Robert Wittes

By way of introduction, Dr. Chabner said that as the division concerned with treatment and research, DCT needs rapid clinical trial accrual to answer important treatment questions in a reasonable time, and accrual to Clinical Cooperative Group trials has been slow (e.g., 10 years to complete the colon cancer trial despite the high incidence of Dukes B and C colon cancer and much effort by researchers of the National Surgical Adjuvant Breast and Bowel Project). In addition, he noted the increasing competition for patients with the entrance of biological compounds to trial. He said the need to expand clinical trials to test compounds in a rapid fashion, as was done with IL-2/LAK, will magnify over the next 5 years, and DCT needs to prepare the clinical trials mechanism to accommodate these opportunities.

The second reason, according to Dr. Chabner, concerns the Institute as a whole as it deals with the problem of moving the best therapies to the community level to effect the greatest saving of lives and assure availability of these therapies to all patients. He added that there is a need to incorporate community physicians and their large numbers of patients into the clinical trials network.

Dr. Wittes began by describing the history and structure of the clinical trials program as an introduction to discussing problems with patient accrual and the Cancer Therapy Evaluation Program's (CTEP) project to increase accrual to high-priority trials. He stated that the Cooperative Group Program began in the mid- to late 1950s as the NCI Clinical Drug Development Program in which new agents could be tested reliably. From the late 1950s through the 1960s, the Program focused mainly on the hematologic

malignancies and several pediatric tumors. In the late 1960s and early 1970s, the Groups evolved toward the use of multimodal therapy, incorporating surgeons and radiotherapists in addition to medical and pediatric oncologists.

Dr. Wittes noted that the increasing availability of broad-spectrum agents created a need for Groups covering malignant diseases that had not been within the purview of the Cooperative Group Program. Thus, in the mid-1970s, DCT developed a contracts program focusing on multicenter trials in gastrointestinal, lung, brain, and later head and neck cancers. Continuous reevaluation of the Program toward the end of the 1970s resulted in the decision to convert the Cooperative Groups administratively from a mixture of grants and contracts to a system of cooperative agreements. Such agreements, Dr. Wittes explained, are an administrative mechanism through which investigators and NCI program staff share responsibility for protocol development. In particular, the terms of the award permit NCI program staff to disapprove trials that endanger patient safety, that are duplicative, or that are methodologically flawed. Dr. Wittes emphasized, however, that under such agreements ideas for trials are generated by the investigators, which is similar to the process under a grant award rather than a contract under which the NCI staff has the authority to generate the ideas. In response to comments from Drs. Korn and DeVita, Dr. Wittes clarified that all individual protocols undergo peer review for scientific merit within the Group structure.

Dr. Wittes then continued by explaining the current organization of the Groups along several different lines. He first illustrated various Groups with a multidisease, multispecialty orientation. Among such Groups treating adult cancers are Cancer and Leukemia Group B (CALGB), Eastern Cooperative Oncology Group, Southwest Oncology Group, and Southeast Cancer Study Group; all are national groups without a geographic focus. The two Children's Groups with a multidisease orientation are Children's Cancer Study Group and Pediatric Oncology Group.

Dr. Wittes then listed several groups organized with a disease-oriented focus: an intergroup devoted to the study of acute leukemia, groups devoted to brain tumors, gynecology, and lung cancer, and the National Surgical Adjuvant Breast and Bowel Project (NSABP). He pointed out that three Groups, including the Gastrointestinal Tumor Study Group, National Prostate Cancer Treatment Group, and National Bladder Cancer Collaborative Group A, had recently failed to compete successfully for funding. The failure of the latter two Groups had created a void in the area of urologic oncology, which CTEP is currently trying to fill. Pediatric disease-oriented Groups include Wilms' Tumor Study Group, and a Group focused on rhabdomyosarcoma.

Dr. Wittes stated that of several Groups organized regionally in the 1980s only the North Central Cancer Treatment Group, which is localized around the Mayo Clinic, had been favorably peer-reviewed. He noted that the California Oncology Program had continued to exist under largely private funding.

Dr. Wittes then referred to Groups organized around modality, notably the Radiation Therapy Oncology Group (RTOG), which has had a radiation orientation since its inception. He commented that the unsuccessful competition for funding of some of the Groups in each category had created the need to reaffiliate the stronger cancer centers, which were once part of Groups no longer funded, with continuously existing Cooperative Groups.

Dr. Wittes also described the organizational chart of a typical Cooperative Group, noting that none of the Groups is organized precisely the same way. He commented that the complicated structure of the Groups leads to an inherent slowness in the Group's function. He explained that most Groups have modality and disease committees, which work together on protocol development and review. He also pointed out that the Group members are most often spread geographically, which complicates the timely generation of protocols in response to initiatives. Describing the Group funding structure briefly, he stated that most Groups are funded via separate cooperative agreements from the NCI to the Group operations office; a statistical center responsible for data management and analysis; and institutional principal investigators located at cancer centers, university hospitals, or at community hospitals. In addition, many Groups have competed successfully for funding from the Cancer Control Outreach Program (CCOP), which was organized to encourage participation of community-based physicians in clinical trials. Some Groups also include physicians who participate in clinical trials on an unfunded basis.

Dr. Wittes stated that projected accrual to Phase III treatment studies for 1987 was in excess of 12,000 patients. Projected patient accrual to all therapeutic studies was 27,000. He then addressed the problem of accrual of patients to clinical trials, beginning by illustrating the duration of Phase III trials active as of October 1987. He pointed out that many of those trials had been activated more than 36 months prior to October 1987 and were still in the accrual phase of the trial.

Dr. Wittes presented new data evaluating the proportion of the estimated national incidence of cancers (obtained by SEER) that had been accrued to Cooperative Group Phase III studies in 1987. He noted that while proportional accrual of several pediatric diseases was fairly good (e.g., Wilms' tumor, 80 percent; neuroblastoma, 46 percent; localized rhabdomyosarcoma, 22 percent), that for the common epithelial cancers of adulthood was poor (e.g., localized bladder cancer, 1 percent; breast cancer $\leq$ 3 percent; localized colorectal cancer, 1 percent; melanoma, 0.9 percent). He expressed concern that the majority of cases of many malignancies are not being entered onto clinical trials. He also emphasized that the accrual rate of most trials is longer than the targeted accrual rate and often unacceptably slow. For example, CALGB had an 18 percent increase in its total accrual time for a collection of Phase III studies, the Gynecologic Oncology Group trials included some studies with actual accrual rates three to five times that of projected accrual rates, and studies of the Radiation Therapy Oncology Group have taken twice the length of time projected.

In assessing methods for increasing patient accrual, Dr. Wittes stated that CTEP had made several assumptions, including:

- Efforts to maximize accrual rates to clinical trials must consider maintenance of data quality.

- For physicians participating in the Group program, there is a substantial gap between the number of patients eligible for trials and the number actually entered.

- There is a large potential reservoir of clinical trials candidates among patients who are not now entered on trials.

- There is a large number of potential clinical trials participants among physicians who do not participate.

Dr. Wittes posed the question whether there is such a thing as too fast accrual. For Phase III studies, he stated that quick accrual was ideal provided the regimen included in the trial had been piloted adequately and likely toxicities were known. In situations in which severe toxicity may present problems in Phase III studies, the Groups often perform extensive Phase II piloting of the regimen or restrict the trial to selected institutions in the early stages of the Phase III trial.

Dr. Wittes also raised the issue of how many resources should be put into a trial to accelerate its accrual to the maximum possible rate. He noted that priorities of the clinical trials program must always be balanced against those of other NCI programs.

Dr. Wittes then reviewed the obstacles to increasing patient accrual to clinical trials, which he had described at the November 1987 Board meeting, as follows:

- Some physicians have a philosophical aversion to clinical trials and feel that physicians need to individualize patients' therapy and that randomizing patients to clinical trials is inimical to physicians' philosophy of medicine.

- Time commitments and complicated issues of informed consent, data management, and complexity of some protocols are involved in participation in clinical trials.

- Some physicians question the quality of the scientific questions of some protocols, sometimes stating that a given protocol is too vigorous or not vigorous enough.

- The inclusion in a clinical trial of an active control versus a no-treatment control is a major issue for diseases for which a no-treatment control can still be considered.

- Many practitioners have indicated that the Cooperative Groups are asking questions that are irrelevant to the major concerns

of practitioners, objecting mainly that protocols are too vigorous for practical office use.

- Many physicians comment on the political character of the Groups and the lack of community input, particularly objecting to the de facto exclusion of some key participants, especially surgical subspecialties, from funding in some Groups.

Dr. Wittes then reviewed the status of the initiatives that CTEP has been pursuing to increase patient accrual to high-priority clinical trials. CTEP had defined such trials as those that involve either common diseases or diseases for which exploitable therapeutic options exist and thus would have impact on mortality. The idea of increasing accrual to particular trials rather than to trials throughout the Cooperative Group Program was then discussed with the Group chairmen, who raised several issues related to the commitment of new participants identified for particular trials. Dr. Wittes stated that CTEP program staff had discussed the proposed trials with the Group chairmen and that the agreed-upon trials would be presented for approval at the February 18-19, 1988, Division of Cancer Treatment Board of Scientific Counselors meeting. Once these trials have been approved, all affiliates of the NCI-supported network, including the Groups, CCOPs, Cooperative Group Outreach Program (CGOP), and Centers, would be expected to participate, provided they have no other viable ongoing trials of comparable importance. However, Dr. Wittes cautioned that assessment of whether or not certain ongoing trials are of comparable importance may raise difficult issues.

Dr. Wittes explained that five of the high-priority trials identified by CTEP and the Group chairmen were adjuvant trials in common adult malignancies; the sixth trial would involve four different combination regimens in intermediate, high-grade non-Hodgkin's lymphoma. All of the trials have mortality endpoints.

To expand the number of participating physicians either by involving community physicians or the cancer centers, Dr. Wittes noted that affiliations could be created either with the Cooperative Groups or with CTEP as the coordinating center. For affiliation with the Groups, suggestions for additional participants would be made by the Groups based on documented ability of the proposed affiliates to accrue patients efficiently on particular high-priority trials. The affiliates would be funded through administrative supplements to the Groups. In response to a question from Mrs. Bynum, Dr. Wittes further explained that the Groups, not NCI, would evaluate the proposed affiliates' ability to accrue effectively under the peer-reviewed mandate of the Groups. He also stated that common intergroup toxicity criteria had been adopted recently, which should simplify participation in clinical trials.

Dr. Wittes raised the question to what extent the ratio of patients entered onto clinical trials to those who are eligible can be maximized. He expressed concern that many investigators believe that 30 percent is close to the theoretical maximum, and emphasized that minimizing protocol complexity and design, the number of required tests, and the data collection

requirements were all important factors in increasing study participation and accrual. He noted that although some investigators had indicated that increasing funding support to already funded participants might have a positive effect on accrual, analysis of per patient costs has suggested that current funding is appropriate. In response to a comment by Dr. DeVita, Dr. Wittes further explained that the Groups have objected strongly to previous CTEP proposals to fund the Groups on a per case basis. However, he commented that the CCOP program has been funded on a payment per case basis since its inception. He also suggested that providing explanatory material about informed consent and other general educational material about clinical trials to potential participants would be useful in increasing accrual.

Dr. Wittes described briefly the lengthy protocol generation review process, which has in many cases required more than a year from initial conception of a trial to submission to the NCI for review. He explained that protocols are developed by study chairmen or other Group members and are reviewed by the Groups' scientific committees, Group chairmen, statisticians, and principal investigators. The Group-approved protocols are then submitted to NCI for review. NCI-approved protocols then activated by the Group subsequently undergo review individually by participants' institutional review boards (IRBs).

Next, Dr. Wittes discussed several other factors that influence the clinical trials program. He stated that because increasing numbers of patients are obtaining care from HMOs and for-profit providers, CTEP had contacted several such providers about possible participation in clinical trials. Kaiser Permanente and Humana have expressed interest and are discussing active participation with representatives of the Groups.

Dr. Wittes also stated that publicity about clinical trials is also a key factor, and that the NCI Office of Cancer Communications (OCC) has launched a two-part publicity plan to increase awareness and understanding of clinical trials, first in several target populations and subsequently among prospective patient groups. For physicians and other health professionals, OCC publicity efforts will focus on placement of articles in professional publications, promoting a stronger presence of trials proponents at professional society meetings, including statements in PDQ on the importance of high-priority studies, conducting a needs assessment from physicians directly, and conducting orientation programs in clinical trials for oncology training programs.

Dr. Wittes went on to describe potential circumstances for CTEP's more direct involvement in clinical trials coordination than in the past. First is the increasing likelihood that CTEP will have more treatment INDs (Investigational New Drugs) than in the past as a result of FDA's liberalized regulations regarding treatment INDs but also as a result of NCI's Group C program. Secondly, CTEP could also coordinate trials directly in specialized studies of new approaches similar to the ongoing IL-2/LAK extramural trials or, at the opposite end of the spectrum, could coordinate large, relatively simple studies to assess the effect of given treatments on a population basis.

Dr. Wittes then raised the critical issue that most health insurance contracts explicitly exclude payment for therapy with investigational drugs and more recently for drugs used for non-package insert indications in clinical trials.

Major points raised in discussion following Dr. Wittes' presentation included the following:

- Insurance companies manage their risks over the long term with actuarial methods and manage their monies on a year-to-year basis. Most clinical trials, however, will produce a short-term loss even though they will produce a long-term gain. Thus, although a strong argument could be made to companies for payment for treatment during Phase III trials, the argument for short-term gain from Phase I and II studies would be much more difficult. Several Board members agreed that such economic issues are most critical impediments to increasing accrual to clinical trials.

- Study may be needed to determine whether or not the Cooperative Groups should be maintained as they currently exist or whether some different options for mechanisms for clinical research are needed.

- Further sociologic study of clinical trials mechanisms and participation would be useful, particularly in determining how much patient- versus physician-related obstacles influence accrual to clinical trials.

- Many Board members raised concern that practicing physicians do not enter patients on clinical trials due to personal and insurance-related economic issues and due to political issues of "not wanting to give patients away." These problems could be approached by increasing involvement of referring physicians in clinical trials and thus allowing them to retain purview over their patients.

- CTEP has made preliminary contacts with the VA Cooperative Study Center to explore further involvement of the Veterans Administration patient population in clinical trials. Other large Government groups such as Medicare, Medicaid, and the military, as well as private organizations such as Blue Cross/Blue Shield and companies providing separate cancer insurance, could also be approached.

- Dr. Fisher raised several points by illustrating the growth of the NSABP from 1971 to 1987 up to 179 participating institutions and a 1987 accrual of 2,262 patients to breast and colorectal protocols (i.e., an increase of 9 percent over 1986). Increasing numbers of patients, more promising treatments, and increased survival have led to increased patient followup and data management requirements. The costs linked to these

increased requirements, rather than solely to costs due to physician-provided care, must also be considered in efforts to increase accrual to clinical trials.

- Educational and publicity efforts on clinical trials could include more consensus conferences, which might promote better cooperation from physicians and insurance organizations that generally accept such consensus conferences as discussions of state-of-the-art treatment.

- Dr. Chabner proposed renegotiating a significant portion of Group funding to a per case basis and increasing CTEP's flexibility in directing and being an active partner in clinical trials as key steps in terminating protocols that are not meeting accrual goals and in redirecting the activities of the Groups.

- The cancer centers are greatly underutilized as a potential mechanism for patient accrual and participation in clinical studies. A Board Subcommittee is currently addressing this issue.

- Any consideration of abolishing or restructuring the entire Cooperative Group clinical trials mechanism must take into account the important issue of preserving the many good studies ongoing in the Group system. In addition, rebuilding an entirely new clinical trials system would require considerable start-up delays.

- Dr. DeVita stated that the issue of clinical trials accrual should remain under evaluation by the NCAB as a method of increasing the Program's visibility. He stated that periodic reports and accrual figures will be presented to the Board at future meetings.

The discussion concluded with many Board members reemphasizing several of the points raised as above. Dr. Wittes summarized by stating that approximately 25,000 patients per year are entered on therapeutic Cooperative Group studies. There are 1.3 million newly diagnosed cancer patients per year. Dr. DeVita informed the Board that NCI funding of this Program is $57 million per year.

IX. Closed Session

The second day of the meeting was closed to the public as it was devoted to the Board's review of grant applications. The applications reviewed numbered 1,183, requesting support in the amount of $172,045,510. Of these, 1,109 were recommended for funding at a total cost of $137,045,110.

X. Approval of Minutes--Dr. David Korn

The minutes of the November 16-17, 1987, meeting were unanimously approved.

XI. Report of the Subcommittee on Cancer Centers--Dr. John Durant

Dr. Durant reported that the Subcommittee had decided to ask all NCI Divisions to comment on the cancer centers through their Boards after the Subcommittee develops preliminary recommendations. The Subcommittee will meet during April to discuss the format of a Workshop to be held in either June or July to discuss the responses to the letter that was mailed to grantees. To date, 84 responses have been received.

The Subcommittee also heard a proposal from Dr. Lemuel Evans regarding a concept that had been approved by the DCPC BSC concerning minority career enhancement awards. The proposal is that 5 awards of at least $150,000 be made to responses to an RFA on how centers will address certain issues for minorities. Sample strategies to be addressed are how to target and facilitate the involvement of minority populations in cancer control research, how to investigate the impact of cancer therapy and control advances on minorities in community medical practice settings, and how to increase the involvement of minority and primary health care providers and other specialists in treatment and cancer control research, thereby providing educational opportunities for health care providers and facilitating interchange of information about current advances in cancer control research. These awards would be supplements to core grants, coming from a $1 million set aside in DEA's budget. Dr. Durant said the Subcommittee unanimously approved the recommendation of the DCPC Board and recommended approval of the minority enhancement program by the NCAB. It was pointed out that the program is not targeted to a specific minority but is intended for all minorities.

The Board unanimously approved the report of the Subcommittee on Cancer Centers.

XII. Subcommittee on Innovations in Surgical Oncology--Dr. Victor Braren

Dr. Braren reported that the Subcommittee had reviewed the curricula vitae of candidates for the position of Chief of the Extramural Surgical Section and discussed difficulties in filling the position. He said the Subcommittee continued to believe that surgical oncology in NCI would be best served by upgrading this position, preferably to the level of Associate Division Director and urged the Institute to take that action.

The Subcommittee also discussed the status of NCI-funded surgical training grants, including mechanisms, stipend structure, and budgetary concerns. In FY 1987, there were 8 active surgical T32s with 29 trainees, compared to 6 surgical trainees in 1975. It was noted that there is now one annual receipt date for these grant applications so that they can be reviewed by an ad hoc committee familiar with surgical oncology. Twelve surgical T32s are pending for the current round of review, which includes 2 renewals and 10

new applications. The Subcommittee also reviewed the K08 mechanism, for which there were 11 awards as of FY 1986. As there were 29 applications, the funding is about the same as for other grants in NCI.

In discussing new directions in surgical oncology, the Subcommittee recommended that NCI pursue the following areas: radio-immunoguided surgery, parenteral nutrition, transplantation, laser surgery, portable sonar devices, intraoperative magnetic resonance imaging (MRI), localized hyperthermia, anatomic precision surgery, and metastasis research as related to detection and surgical removal. The Subcommittee also urged that NCI undertake more clinical trials and include surgical representatives in the development and management of these trials.

In noting other business, Dr. Braren said the Subcommittee endorsed the upcoming American College of Surgeons cancer management courses. The SORDS Committee will meet on February 17 and the meeting will be attended by a member of the Subcommittee as well as NCI staff. In conclusion, Dr. Braren commended Dr. Michael Friedman for his support to the Subcommittee.

In discussion it was pointed out that the person recruited as Chief of Extramural Surgery would be a section head within the Cancer Therapy Evaluation Program (CTEP). Dr. Chabner stated that position level was consistent with the size of the program and the individual's responsibilities.

The Board unanimously approved the report of the Subcommittee on Innovations in Surgical Oncology.

XIII. Subcommittee on Planning and Budget--Dr. Louise Strong

Dr. Strong reported that the Subcommittee had met in closed session to review the President's FY 1989 budget. A general question was raised about the stability of the budget and deficit reduction considerations. No additional reductions are expected for FY 1988, but more deficit reduction is a possibility in FY 1989.

During the open session, the status of the NCAB biennial report was discussed. A draft will be ready for Subcommittee review in late February, and it is expected that a final draft will be available for NCAB review at the May 1988 meeting.

The Board unanimously approved the report of the Subcommittee on Planning and Budget.

XIV. Subcommittee on Cancer Information and Subcommittee on Cancer Control for the Year 2000--Mrs. Helene Brown

Mrs. Brown presented the report of the joint meeting of the Subcommittee on Cancer Information and the Subcommittee on Cancer Control for the Year 2000. Mr. Bloch had presented suggestions for increasing PDQ usage by simplifying the language and use of the system. Specific suggestions were that the patient receive stage-specific information and the physician's

portion, if requested; physicians be sent protocols along with the information requested; references be offered separately; state-of-the-art statements and patient summaries be combined; the materials be reviewed by a physician for accuracy; and the Cancer Information Service (CIS) audit the time lapse from the receipt of the request to mailing. Mrs. Brown said that NCI had begun to develop a patient information file from PDQ and that she had been asked to chair the editorial board. She suggested that most of the issues raised by Mr. Bloch will be handled by the editorial board.

Mrs. Brown said the Subcommittees heard reports on the NCAB public participation hearings in Los Angeles and Atlanta and plans for hearings in Miami on February 11, Dallas on April 7, and Philadelphia on April 19. The Subcommittees also discussed the recompetition of the Cancer Information Service, with respect to the fact that the RFP requires some element of cost-sharing, which may pose a problem for cancer centers. Because of the importance of the CIS, Mrs. Brown requested assurance that the DCPC Board would further discuss and approve the concept before proceeding with the recompetition.

At a future meeting, the Subcommittees will consider the establishment of a prize, similar to the General Motors Prize, for advances in prevention, screening, and detection. Another issue to be addressed is attention to the handicapped. In discussion of the report, the following points were raised:

- Guidelines for the proposed prize should be carefully defined and care taken in accepting corporate support.

- The Subcommittee will bring to the NCAB the report on progress toward reaching the year 2000 goals.

- An evaluation report will be prepared and presented to the Board after the completion of the first five public participation hearings.

The Board unanimously accepted the report of the Subcommittees on Cancer Information and Cancer Control for the Year 2000.

XV. Black Leadership Initiative--Dr. Louis Sullivan

Dr. Sullivan recalled that the Black Leadership Initiative originated as a result of discussions at the NCAB in September 1986 on involving the Nation's Black leadership in a more visible way in supporting and advocating programs for cancer control. At that time, it was proposed that a series of six hearings be held around the country in major population centers with large Black populations. The hearings were to serve as regional forums for Black leaders to address these problems. Dr. Sullivan reported that the first hearing had been held in Atlanta on November 20, and he called Board members' attention to the proceedings of that hearing. Approximately 68 individuals from 8 southern states attended the hearing. The Board members then viewed a videotape of the hearing.

Dr. Sullivan said hearings are being planned in other cities with local chairpersons identified: March 10-11 in Los Angeles, Dr. Walter LaVelle, Chairperson; April 14-15 in Chicago, Dr. Clyde Phillips, Chairperson; June in New York, Dr. Harold Freeman, Chairperson; September in Washington, D.C., Dr. Kenneth Olden and Dr. LaSalle Leffall, Chairpersons; and September 29-30 in Houston, Dr. Dezra White, Chairperson. Based on the experience with the Atlanta hearings, Dr. Sullivan recommended that an individual be hired in each city to ensure the followup and implementation of recommendations. He said a report on all the hearings, their outcomes and recommendations, would be presented at the December NCAB meeting.

As an item of interest, Dr. Sullivan announced that on March 28-29, a Conference on Tobacco Use Among Blacks and Hispanics would be held in Washington at the Omni Shoreham Hotel. This conference is aimed at attracting the attention of Congress and state legislators. Dr. Sullivan also reported that Johnson Publications will feature an article on the National Black Leadership Initiative in Ebony magazine. In discussion, it was agreed that the videotape of the Atlanta hearing should be distributed to the Congressional Black Caucus and other members of Congress, as appropriate.

XVI. Subcommittee on Environmental Carcinogenesis--Dr. Roswell Boutwell

Dr. Boutwell stated that the meeting of the Subcommittee on Environmental Carcinogenesis, which lasted more than two hours, had begun with a review of the charge, which is to study the national needs and problems in environmental carcinogenesis and monitor progress in the area. The Subcommittee then reviewed the numerous changes that have taken place in cancer etiology and prevention since 1980. Dr. Adamson said that the Subcommittee was asked to consider the changes not only as part of its normal oversight responsibility, but also because of the article by Dr. Samuel Epstein in the Congressional Record last September. He said he hoped the Subcommittee would point out gaps or deficiencies in the etiology program and offered to arrange for presentations on topics of interest by NCI/NIH staff or scientists from other Federal agencies, academic institutions, and other organizations.

Dr. Adamson also described a concept for a large case-control study on childhood leukemia intended to try to find etiological factors. Dr. Susan Sieber, Deputy Director of the Division of Cancer Etiology, presented to the Subcommittee an overview of the history of the NCI carcinogenesis bioassay program and its transfer to the National Toxicology Program. Dr. Dorothy Canter from the National Institute of Environmental Health Sciences emphasized that NCI remains very important to the National Toxicology Program and has nominated the largest number of chemicals for testing. After a review by Dr. Adamson of the organization and programs of the Division of Cancer Etiology and changes in the Laboratories and Branches since 1980 in the Chemical and Physical Carcinogenesis Program, Dr. David Longfellow, Chief of the Chemical and Physical Carcinogenesis Branch, presented an overview of that Branch and its grants and contract program to the Subcommittee.

Dr. Boutwell reported that Dr. Greenwald had also addressed the Subcommittee and discussed the scientific findings that laid the groundwork for DCPC and the evolution of the concept of cancer control. Dr. Greenwald noted milestones in cancer prevention, including human intervention trials, the development of the Community Clinical Oncology Program, the development of cancer prevention and research units, the Cancer Prevention Fellows Program, the NCI goals for the year 2000, the Black and Hispanic cancer control program, the Public Health Agency initiative, the Cancer Prevention Awareness Program, the diet, nutrition, and cancer laboratory, and the development of working guidelines for early cancer detection. Dr. Boutwell said that Dr. Joseph Fraumeni was not able to give a presentation on the DCE Epidemiology and Biostatistics Program because of the lack of time. He said the Subcommittee had hoped to review the Epidemiology Program and to discuss with Dr. Fraumeni his views on the possible relocation of his program to DCPC. Dr. DeVita said any reorganization would be presented to the Board before implementation. He expressed the hope that the Board would consider the overall program in environmental carcinogenesis.

Dr. Boutwell suggested that topics for future discussion are a review of the Epidemiology Program, studies on the etiology of breast cancer, and studies on the potential hazards of pesticides.

The Board unanimously approved the report of the Subcommittee on Environmental Carcinogenesis.

XVII. Subcommittee on AIDS--Dr. Gertrude Elion for Dr. Howard Temin

Dr. Elion said that Dr. Temin proposed that the Subcommittee on AIDS adopt the following resolution:

> The NCAB notes the pivotal role that NCI intramural and grantee scientists have played in coping with the AIDS epidemic. The program in place in NCI in epidemiology, immunology, virology, and drug development provided the foundation on which many scientists built their early work and discoveries in AIDS. The NCAB supports the continuation of these efforts both for their importance in controlling AIDS and for the information that they will develop relevant to controlling cancer.

The Subcommittee adopted the resolution.

Dr. Roper had presented to the Subcommittee a review of the AIDS budget for FY 1988 and the process used by NCI, NIH, and PHS in developing the AIDS budget. She stated that the budget was planned on the basis of 5 functional categories: pathogenesis and clinical manifestations, therapeutics, vaccine development, public health control measures, and patient care and health needs. Each NCI Division is asked to summarize its ongoing needs in AIDS research on a project-by-project basis and to classify each project into one of the functional categories. This compilation is then reviewed in the Office of the Director, NCI, and priorities are established within the Divisions and the Institute. Each Institute then prepares a

summary budget document describing its high priority projects and support requirements. Dr. Roper said that discussion of the budget proposal centers on establishing scientific priorities, identifying unnecessary duplication, and noting gap areas of scientific opportunities. A similar process occurs at the PHS level, involving all the PHS agencies.

Dr. Elion said the FY 1988 AIDS budget for NCI was approximately $90 million, and it was not spared from deficit reduction. The distribution of the budget reflects the scientific priorities within NCI, with the largest share of money designated for drug development ($38 million), followed by research on pathogenesis and clinical manifestations of AIDS ($30 million), and vaccine development ($19 million). Dr. Chabner pointed out to the Subcommittee that the continued growth of the AIDS effort will be related to the ability to get full-time employee slots and construction money for new and renovated laboratory space. The current AIDS budget includes no money to support construction.

The Subcommittee discussed the opening of the 12-East Ward at the Clinical Center for treatment of both cancer and AIDS patients. Dr. Chabner had reiterated that the major problem was the shortage of nurses and that all steps to improve salaries had not yet been taken. The Subcommittee requested that they be kept informed on progress in hiring nursing personnel. The Subcommittee also received an update on the status of the infected laboratory workers and the safety surveillance program to be implemented at NIH. Two laboratory workers remain clinically asymptomatic and seropositive. Dr. Roper reported that it appears that an attempt to grow live virus from a second sample from the first worker has been successful; this should provide valuable information on the course of viral infection in this worker.

Dr. Elion said the final topic considered by the Subcommittee was new initiatives being undertaken by DCE and DCT. DCE is issuing RFAs for further study of the relationship between HIV and HIV-associated malignancies and for investigating animal models for AIDS. DCT is issuing RFPs for clinical pharmacokinetic studies and processing viral samples from patients. It was noted in discussion that because of the grant referral guidelines, most AIDS grants are referred to NIAID.

The Board unanimously approved the report of the Subcommittee on AIDS.

XVIII. Subcommittee on Organ Systems--Dr. Bernard Fisher

Dr. Fisher said the Subcommittee on Organ Systems had met to synthesize information compiled from the December 3 hearing and prepare a position for presentation to the NCAB. The Subcommittee agreed that there is a need for an organ systems focus, there needs to be better advocacy by program relative to the people who are doing the research, and there is a need for the best possible intramural and extramural scientific input. Dr. Fisher said there was also a consensus of praise for the Organ Systems Program (OSP).

The two issues addressed by the Subcommittee were the recompetition of the Coordinating Center and the grant portfolio management of the OSP. Dr. Fisher said the Subcommittee had unanimously agreed that the portfolio issue is a managerial problem that should be handled internally by NCI. With respect to the Coordinating Center, Dr. Fisher emphasized that the Committee completely agreed that there must be a focus on the OSP because the heterogeneous nature of the diseases precludes overall, unified approaches. Therefore, the question actually raised was whether the OSP, as it exists, adequately provides needed visibility.

Dr. Fisher said the plan to revise the OSP, developed by the NCI Executive Committee, pulls it closer into NCI, and the working groups, retaining their extramural scientific expertise, would be maintained as chartered committees. There would be close coordination among the scientists in the working groups, intramural scientists, and the divisional Boards of Scientific Counselors. Dr. Fisher said that 3 members of the Subcommittee had agreed that within the revised structure, an external coordinating center was not justified. Two other members of the Subcommittee felt strongly that the external headquarters should remain at least until the effect of other changes in the program could be evaluated. With respect to other issues, Dr. Fisher said the Subcommittee agreed that cancer control must be a major aspect of the OSP no matter how it is structured. No action was taken with respect to mechanisms for adding or eliminating working groups, as the criteria are still being formulated.

In discussion, it was noted that the annual savings of internalizing the OSP would be about $300,000. Adequate internal communication would be ensured by the establishment of an Organ Systems Program Committee, the designation of a coordinator in each Division to attend all working group meetings, preparation of an annual report for each organ system, and continuation of concept reviews by the Executive Committee and BSCs.

A motion was made and unanimously approved that NCI determine how best to distribute and manage the OSP grants portfolio.

A motion to recommend that the functions of the Organ Systems Coordinating Center be internalized within NCI was approved by a vote of 12 in favor, 3 opposed, and 1 not voting.

XVIX. New Business

As required by the reauthorization statute, the Board unanimously approved the following delegation of authority:

> In accordance with stated policies of the Public Health Service and the National Institutes of Health, the Director of the National Cancer Institute may:
>
> (1) appoint not more than 151 special experts; and

(2) establish, and appoint members to, one or more advisory committees composed of scientifically and professionally qualified private citizens and officials of Federal, State, and local governments, to advise the Director, NCI with respect to the Director's functions.

Also unanimously approved were the guidelines for NCI staff in negotiating desirable adjustments in grant amounts and times.

Dr. Korn next asked the Board to endorse a resolution from the DCPC BSC regarding the lack of funds for construction. They unanimously voted to endorse the following resolution:

> "whereas construction issues have come up year after year, it is important that this board convey to the NCAB and to the NCI/NIH management that cancer research in the biomedical area will be (increasingly) impeded...by outmoded plans...if the Office of Construction is not maintained with proper authority to...(receive) funding; that...(the Office) be within the NCI...that Congress be urged to move on with this important task of funding construction...and that construction facilities undergo peer review."

With respect to future agenda items, the following suggestions were made:

- Policy on funding of grants (review of issues to be presented at May 1988 meeting)
- OMB presentation on privatization of NIH research results
- Schedule presentation on linkage of the goals for the year 2000 with the bypass budget for the fall of 1988
- Health effects of exposure to radon.

It was also suggested that the closed session of NCAB meetings include discussion of some interesting or exemplary RFPs or RFAs to increase awareness of Agency activities.

The Board next discussed whether and how NCI should respond to comments and criticism that may be expected as a result of the publication of the Annual Cancer Statistics Review. Discontinuing the Women's Health Trial at the same time that breast cancer incidence is reported to be increasing was cited as an issue that could produce comments and questions. NCI will continue to investigate ways of improving public relations.

In conclusion, Dr. Korn recognized the contributions of departing Board members, Mr. Richard Bloch, Dr. Victor Braren, Dr. Edward Calhoon, Dr. Geza Jako, and Mrs. Barbara Ingalls Shook. All present observed a moment

of silence in memory of deceased members Mrs. Angel Bradley and Dr. Tim Lee Carter.

XX. Adjournment

The 65th meeting of the NCAB adjourned at 10:55 a.m. on Wednesday, February 3, 1988.

APR 26 1988

Date

David Korn, M.D.