Department of Health and Human Services

Public Health Service

National Cancer Institute

National Cancer Advisory Board

Summary of Meeting
November 16-17, 1987
Building 31, Conference Room 6
National Institutes of Health
Bethesda, Maryland

Department of Health and Human Services
Public Health Service
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Minutes of Meeting
November 16-17, 1987

The National Cancer Advisory Board (NCAB) reconvened for its 64th regular meeting at 8:30 a.m., November 16, 1987, in Building 31, 6th floor, Conference Room 6, National Institutes of Health (NIH). Dr. David Korn, Chairman, presided.

Board Members Present

Mr. Richard A. Bloch
Dr. Victor Braren
Mrs. Nancy G. Brinker
Mrs. Helene G. Brown
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
Dr. Louise C. Strong
Dr. Louis W. Sullivan
Dr. Howard Temin

Absent

Dr. Roswell K. Boutwell
Dr. Ed L. Calhoon

President's Cancer Panel

Dr. William P. Longmire

Absent

Dr. Armand Hammer
Dr. John A. Montgomery

Ex Officio Members

Dr. David P. Rall, NIEHS
Dr. Dorothy A. Canter, NIEHS
Dr. Ralph E. Yodaiden, DOL
Captain Stephen R. Veach, DoD
Dr. Richard J. Greene, VA
Dr. Lakshmi Mishra, CPSC
Dr. Mary Ann Danello, FDA
Mr. Richard A. Lemen, NIOSH

Chairmen, Boards of Scientific Counselors, National Cancer Institute

Division of Cancer Biology and Diagnosis--Dr. Arnold J. Levine, Chairman and Professor, Department of Molecular Biology, Princeton University, Princeton, New Jersey.

Division of Cancer Etiology--Dr. George F. Vande Woude (for Dr. G. Barry Pierce, Former Chairman), Director, BRI - Basic Research Program, Frederick Cancer Research Facility, National Cancer Institute, Frederick, Maryland.

Division of Cancer Prevention and Control--Dr. Paul F. Engstrom, Vice President for Cancer Control, Fox Chase Cancer Center, Philadelphia, Pennsylvania.

Division of Cancer Treatment--Dr. John Niederhuber, Professor of Surgery, Division of Surgical Oncology, Johns Hopkins University School of Medicine, Baltimore, Maryland.

Frederick Cancer Research Facility--Dr. Dante G. Scarpelli (for Dr. Werner Kirsten, Chairman), Chairman, Department of Pathology, Northwestern University Medical School, Chicago, Illinois.

Liaison Representatives

Ms. Jane Blash, Member, Government Relations Committee, Frederick Memorial Hospital, Frederick, Maryland, representing the Oncology Nursing Society, Cambridge, Massachusetts.

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.

Ms. Elaine Locke, Associate Director for Practice Administration, American College of Obstetricians and Gynecologists, Washington, D.C., representing the American College of Obstetricians and Gynecologists.

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

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

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

Dr. Harold Segal, Program Director, Biochemistry Program, National Science Foundation, Washington, D.C., representing the National Science Foundation for Dr. M. V. Parthasarathy.

Dr. John Stevens, Research Administrator, American Cancer Society, New York, New York, representing the American Cancer Society for Dr. John Laszlo.

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

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 September 28-30, 1987, NCAB Meeting Minutes--Dr. David Korn**

Dr. Korn, Chairman, called the 64th meeting of the National Cancer Advisory Board (NCAB) to order and welcomed members of the Board and the President's Cancer Panel (PCP), Chairmen of the Divisional Boards of Scientific Counselors, 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. Bynum, Executive Secretary of the Board, within 10 days after the meeting.

Approval of the September NCAB minutes was postponed until the Tuesday, November 17, session.

Dr. Korn noted the death of Dr. Elizabeth Miller and said that an expression of sympathy from members of the Board was sent to her husband, Dr. James Miller. It read as follows:

> The members of the National Cancer Advisory Board were deeply saddened by the death of your wife, Elizabeth. It is impossible to overstate the importance of her scientific contributions to the field of chemical carcinogenesis. Her efforts, notable not only for their intrinsic excellence, but also for the practical importance of this body of work in defining approaches to cancer prevention, are widely known, and appropriately, were frequently rewarded.
>
> The range of her accomplishments and character is not fully defined by her research, however. Betty was also a fine teacher, a productive and valued member of the President's Cancer Panel, and a perceptive observer and adviser in the complex arena in which science and politics come together.
>
> All of us feel a sense of great loss and join her many friends and colleagues in extending to you and your family our deepest sympathy.

II. **Future Board Meeting Dates**

Dr. Korn called the Board members' attention to the following confirmed future meeting dates: February 1-3, 1988; 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. Longmire presented the report of the President's Cancer Panel (PCP), prepared by Panel Chairman Dr. Armand Hammer for this meeting. Dr. Hammer reported that the PCP met on October 23, 1987, at the University of Pittsburgh Medical School to hear the results of the National Surgical

Adjuvant Breast and Bowel Project (NSABP) 10-year study on colon and rectal cancer, which was carried out at 21 institutions under the direction of Dr. Bernard Fisher. Dr. Hammer said that the results, as reported by Dr. Fisher and Dr. Norman Wolmark, clearly demonstrate the benefits of adjuvant therapy in colon and rectal cancer cases and suggest that chemotherapy should be considered in treating all patients with the disease, particularly in clinical trials. He noted that although this study confirms the efficacy of adjuvant therapy in treating this second most common form of cancer, only 1,000 of the 100,000 eligible patients are accrued to these trials each year. Dr. Hammer suggested that a lack of understanding and information concerning the trials might be part of the problem in attracting patients to the clinical trials. On behalf of the Panel, he expressed satisfaction with the steps that were taken recently to ensure the widespread dissemination of information about the NSABP colon and rectal cancer trial. In particular, he noted that the Editorial Board of the Physicians' Data Query (PDQ) has revised the state-of-the-art statement to refer specifically to patient participation in the trials and also has fully referenced each trial. In addition, the PDQ News Bulletin includes information on the trials. Dr. Hammer expressed the Panel's hope that PDQ's role in promoting awareness of the trials will lead to increased patient participation. He added that the Panel also hopes to play a role in promoting awareness of the clinical trials program and its potential benefit for cancer victims, and he invited NCAB members to become involved.

In another presentation at the Pittsburgh meeting, Dr. Robert Wittes of NCI identified general surgeons as probably the most important target group in the effort to increase patient accrual to clinical trials. Dr. Hammer commended ongoing NCI efforts in this area.

Continuing his report on the October PCP meeting, Dr. Hammer noted that preclinical studies of methyl CCNU and related compounds were the subject of a presentation by Panel member Dr. John Montgomery, who is well known for his contributions to this field of study. Dr. Hammer expressed confidence that the adverse side effects that complicate present use of methyl CCNU will be overcome by advancing technology, and methyl CCNU will join the ranks of effective anticancer drugs.

In the final presentation at the October meeting, Dr. Charles Meyers, Chief of NCI's Clinical Pharmacology Branch, discussed the biochemical basis for drug resistance in colon cancer. Dr. Hammer said that the NCI approach to the problem, as outlined by Dr. Meyers, appeared sound and worthy of support.

The next PCP meeting is scheduled for November 20, 1987, at NCI on the NIH campus. Dr. Hammer noted that the Panel plans to continue the informative meetings at cancer centers around the country. However, the Panel believes that an opportunity to hear from the various Division Directors of NCI about the problems and opportunities in their fields also will be beneficial.

Dr. Hammer indicated that the pending reauthorization of the National Cancer Act will be on the PCP's November meeting agenda. He expressed the opinion that a longer period between the reauthorization process (perhaps 5 years instead of 3) might benefit all concerned. A related issue is the gradual decrease in special authorities that were originally granted to NCI in 1972. Dr. Hammer said that the Panel considers these authorities important for enabling NCI and its Directors to efficiently and effectively discharge their duties and believes that this issue is relevant to the mandate set forth in the National Cancer Act--to review and oversee the National Cancer Program as operated by NCI. He also said that the Panel has requested a written report from Dr. DeVita and plans to study the issues involved and present their views to the appropriate administrative officials and Congress.

A discussion of the Panel's plans and priorities for the coming year also will be on the November meeting agenda. Dr. Hammer noted that the 12 years remaining in this century will be a crucial period for everyone involved in the fight against cancer, if the year 2000 goals are to be realized.

Dr. Hammer concluded his report of the Panel's activities with the announcement that Dr. Bernard Fisher was chosen to receive one of the 1987 Hammer cancer awards for his distinguished accomplishments in the field of cancer research and in recognition of his outstanding work in clinical trials and research in breast and colorectal cancer.

Dr. Korn thanked Dr. Longmire for presenting Dr. Hammer's report and offered congratulations to Dr. Fisher on behalf of the Board.

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

Before the Director's report, a videotape summary of the second Public Participation Hearing held in Atlanta, Georgia, on November 5, 1987, was shown to the Board. Dr. DeVita congratulated Dr. Sullivan, who chaired the Hearing, and other members of the Board for their outstanding efforts. He said that the Hearings were proving to be effective vehicles for NCI to learn about local communities and for communities to learn about NCI. Dr. DeVita suggested that this improved communication may be helpful to NCI's efforts to get more patients enrolled in clinical trials.

As a preface to the program overview, Dr. DeVita pointed out that following the passage of the National Cancer Act, the Institute was reorganized by divisions according to basic thrusts of etiology, treatment, biology, and diagnosis. In addition, the Act established the NCAB as a Presidentially appointed Board and added a meeting--the annual program review--which is not held by Councils for other Institutes. NCI established a format for the program review in 1980, which has been continued with the approval of the NCAB. The usual format includes a presentation of the annual statistics report from the Surveillance, Epidemiology, and End Results (SEER) Program; however, Dr. DeVita said that because the format of the report was being revised, the report would not be presented until the February 1988 NCAB meeting. The major focus of the program review is on the divisional reports

from the Division Directors and Chairmen of the Boards of Scientific Counselors. The program review also includes the annual report of the Organ Systems Program. The second day of the program review meeting is devoted to highlights of scientific segments of the NCI program. Dr. DeVita said that because of the pressure of the AIDS epidemic, this program review would focus on AIDS and NCI's AIDS program.

Dr. DeVita first reported on the status of the Unconditional Gift Fund. In general, the gifts are small donations from individuals, but in some cases special programs are supported by donations. For example, Dr. Hammer has donated funds for IL-2/LAK research and Mr. Leonard Abramson has donated funds for research on breast cancer. Some of the money also is used for a summer students program and some is contributed to the Clinical Center Patient Emergency Fund. Dr. DeVita said that $2.6 million had been received over the past 2 years.

In describing the organization of NCI, Dr. DeVita began with the Office of the Director, which includes the Office of Program Operations and Planning, headed by Ms. Iris Schneider; the Office of Cancer Communications headed by Mr. Paul Van Nevel; the Office of International Affairs headed on an acting basis by Mr. Ihor Masnyk; and the Office of Administrative Management headed by Mr. Phillip Amoruso. Dr. Elliott Stonehill serves as Assistant Director and Executive Secretary of the President's Cancer Panel. Dr. DeVita said that the Executive Committee, the central governing body of the Institute, makes corporate decisions on both science and policy matters and allocates resources with the assistance of Advisory Committees. Decisions are implemented through administrative meetings of divisional administrative staff and by Division program directors. The Executive Committee also participates in scientific seminars, which focus on areas that require special attention. At their January retreat, the Executive Committee makes broad plans for the allocation of resources and at the July retreat develops planning levels for each Division.

Dr. DeVita pointed out that the Boards of Scientific Counselors had been organized in 1980 to review the policies and decisions related to budget for each Division. The Boards are composed of experts related to the main subject area addressed by the Division, but they represent many different disciplines. The Boards review both the intramural and extramural program budgets, as well as concepts for all new and current contracts, interagency agreements, and RFAs. In addition, the Boards are responsible for the intramural site visit process and are involved in program planning and evaluation. The Boards are linked to the NCAB through the submission of the minutes of their meetings and the listings of contracts awarded.

Dr. DeVita reiterated that the NCAB is responsible for the overview of the Institute and has the legal authority to approve the funding of grants. He noted that the NCAB, by assuring that resources are allocated on the basis of peer review, is also the guardian of the peer review system. The National Cancer Act affords management oversight responsibilities to the President's Cancer Panel. The Panel also will identify and address any blocks in the implementation of the National Cancer Program.

In continuing the organizational review, Dr. DeVita noted that the Division of Extramural Activities (DEA), directed by Mrs. Barbara Bynum, does not have a Board because it is the review division. The Frederick Cancer Research Facility (FCRF) has a Board (called the FCRF Advisory Committee) but is not an extramural program. From a functional perspective, Dr. DeVita said it can be seen that 80 percent of NCI's resources supports basic research and the remainder supports programs that apply the results of basic research. The Cancer Centers, for example, perform basic research and apply it through clinical trials. In addition, NCI sets goals for itself, i.e., the goals for the year 2000, through programs such as the Cancer Control Program as well as the entire NCI network. The International Cancer Research Database (ICRDB) and the PDQ collect and disseminate information, and the SEER program monitors incidence, mortality, and survival.

Dr. DeVita next turned to a discussion of the budget, noting that there was still uncertainty about the FY 1988 budget although the House level is $1.542 billion, which is slightly higher than the Senate level. If the actual amount is less, adjustments are made, usually directly by Congress.

In concluding his remarks, Dr. DeVita announced the presence of Mr. David Stevenson from the General Accounting Office (GAO) and that a representative from the Office of Management and Budget (OMB) might attend part of the meeting. He also announced that Dr. Maryann Roper would serve as Acting Deputy Director while Dr. Fischinger serves as the AIDS Coordinator for the Public Health Service.

The following points were raised in the discussion:

- Obstacles to the realization of the year 2000 goals are not solely related to implementation or resources, but also to issues such as the general practice of medicine. This is illustrated by such things as the low number of patients in clinical trials and the small proportion of women getting mammography.

- Lack of information is not a problem. The problem is to get people to use the available information, which was an important reason for announcing the year 2000 goals.

- A cross section of both the professional and lay community was present at the Atlanta Public Participation Hearing, and the media coverage served to heighten awareness of the cancer problem.

- Consideration should be given to including DEA in the annual program review.

V. <u>Division of Cancer Etiology Program Review--Dr. Richard Adamson</u>

Dr. Adamson began by stating that, because Dr. Barry Pierce was unable to attend the meeting, he and Dr. Vande Woude would present the review. Dr. Adamson explained that the Division of Cancer Etiology (DCE) is responsible for planning and conducting NCI's program of coordinated research

on cancer causation and its basic research on cancer prevention. The Division supports both intramural laboratories and extramural programs that seek to elucidate the mechanisms of cancer induction at each step of the cellular process from initiation to the transformation of normal cells to malignant cells. Epidemiologic studies of human populations also are performed to identify risk factors that predispose individuals to various cancers. Studies are aimed at the prevention, interruption, or reversal of initiation or transformation prior to the development of clinical disease.

Dr. Adamson then briefly commented on the organizational structure of the Division and noted that there are three program areas: the Biological Carcinogenesis Program, the Chemical and Physical Carcinogenesis Program, and the Epidemiology and Biostatistics Program. Dr. Susan Sieber serves as the Deputy Director and Dr. Elizabeth Weisburger serves as the Assistant Director for Chemical Carcinogenesis. There was one organizational change during the past year: the Laboratory of Tumor Cell Biology was transferred from the Division of Cancer Treatment to DCE. This change was based on the fact that the Institute's viral oncology program is focused within the Biological Carcinogenesis Program of DCE. Dr. Adamson also stated that recruitment was underway for an Associate Director for the Biological Carcinogenesis Program.

Dr. Adamson referred Board members to the DCE section of the Board book, which listed the current studies in each Program and provided additional details on three studies.

The Biological Carcinogenesis Program has undertaken a 3-year prospective study of adult leukemias and lymphomas in Jamaica, which has clarified the spectrum of T-cell malignancies linked to human T-cell lymphotrophic virus type I (HTLV-I) and confirmed the connection between this virus and the neurological disorder, tropical spastic paraparesis. People who are serum-positive for the HTLV-I antigen are 30 to 40 times more likely to develop T-cell leukemia. He added that isolates of HTLV-II have recently been found in hairy cell leukemia and lymphocytic leukemia T cells. These isolates have been shown to have the ability to immortalize normal blood leukocytes in culture. Dr. Adamson stated that the repeated isolation of these viruses from various patients confirms that HTLV-II is a human tumorigenic retrovirus.

Dr. Adamson next described, from the Chemical and Physical Carcinogenesis Program, human mesothelial cell carcinogenesis studies. In culture, human mesothelial cells have been shown to be much more sensitive than human fibroblasts to the induction of structural chromosomal aberrations when exposed to asbestos fibers. These fibers disrupt the mitotic spindle apparatus by direct physical interaction. The human mesothelial cell lines also produce both PDGF and tumor growth cell factor beta in greater amounts than normal cells. This suggests the possibility of an autocrine mechanism in the generation of human mesothelioma.

Dr. Adamson continued his review by discussing the Epidemiology and Biostatistics Program's updated atlas on cancer mortality. In response to Dr. DeVita's comment on the study of exposure to chlorinated water and the development of bladder cancer, Dr. Adamson noted that some studies,

particularly in Iowa, have shown that people who drink chlorinated water have a higher risk of developing bladder cancer than those who drink nonchlorinated surface water. He stated that the risk is approximately one-and-one-half times higher for chlorinated-water drinkers, although the risk is considerably lower than the major bladder cancer risk factor, cigarette smoking. Whether this risk is related to the trihalomethanes or to other organics is a current research subject.

Dr. Adamson continued his discussion of the cancer mortality atlas. He noted that the atlas describes the U.S. cancer mortality rate for whites, and that an atlas addressing cancer mortality rates among minorities is expected to be published in 1988. The atlas focuses on time trends over the 30-year period from 1950 to 1980. Among the noteworthy new geographic patterns were areas of high risk for lung cancer among women in Florida and on the west coast and apparent clusters of high rates of non-Hodgkin's lymphoma in the north central and midwestern states.

Dr. Adamson next pointed out that advisory panels have been established for occupational cohort studies of acrylonitrile and methylene chloride. The advisory panels are chaired by a member of the DCE Board of Scientific Counselors and meet in scheduled public sessions. There are also liaison panels that consist of individuals from interested companies and unions. These panels were created because of the misunderstandings concerning the formaldehyde study, which had an advisory committee but not a formally chartered one.

Dr. Adamson noted that two RFAs were funded in FY 1987: one on transformation mechanisms of human polyomaviruses and the other on application of shuttle vector technology to study mechanisms of DNA damage repair and cell sensitivity to X-ray radiation. One cooperative agreement, the National Collaborative Chemoprevention Project, also was funded, which allows investigators from various disciplines and affiliations to work together to generate new approaches toward the biological and chemoprevention of cancer.

The planning budget for FY 1988, which reflects the House of Representatives level and does not take into account possible reductions, reflected an 11 percent ($31.8 million) increase for the DCE as a whole. The intramural budget received a 9 percent increase, contracts an 11 percent increase, grants a 9 percent increase, and RFAs and cooperative agreements a 4 percent increase. Dr. Adamson explained that the largest part of the contracts program is the epidemiology program, which requires personnel to go out in the field to conduct interviews. The $6 million that is budgeted for AIDS vaccine resources and some research contracts for the Frederick Cancer Research Facility will be transferred to DCE. Within DCE, the Biological Carcinogenesis Program received an 11 percent increase, the Chemical and Physical Carcinogenesis Program a 9 percent increase, the Epidemiology and Biostatistics Program a 15 percent increase, and the Office of the Director a 10 percent increase.

Dr. Adamson concluded his presentation by thanking the Board of Scientific Counselors for their many efforts during the past year.

Board of Scientific Counselors, Division of Cancer Etiology--Dr. George Vande Woude (for Dr. G. Barry Pierce)

Dr. Vande Woude briefly reviewed the history of the Board of Scientific Counselors for the Division of Cancer Etiology. Since its first meeting on October 17 and 18, 1978, the Board has met 23 times. Dr. Vande Woude described the role of the Board as providing budgetary advice, participating in site visits to intramural laboratories, participating in special ad hoc subcommittees on areas of importance, and performing concept reviews of contracts, RFAs, cooperative agreements, and interagency agreements. On October 1, 1987, Dr. Hilary Koprowski replaced Dr. Pierce as chairperson.

Dr. Vande Woude reported that there had been one site visit since November 1986, to the Laboratory of Viral Carcinogenesis, headed by Dr. Steven O'Brien, on September 25, 1987. Eight site visits are scheduled for FY 1988, including the Laboratory of Tumor Virus Biology, Biostatistics Branch, Environmental Epidemiology Branch, Clinical Epidemiology Branch, Laboratory of Biology, Laboratory of Cellular and Molecular Biology, Laboratory of Molecular Carcinogenesis, and Radiation Epidemiology Branch.

Dr. Vande Woude reported that in October 1986, eight concept reviews were presented to the Board and all of them had been approved. At the March 1987 Board meeting, 6 concepts were presented and approved, and at the June 1987 meeting, 10 concepts were presented and approved.

Dr. Vande Woude then stated that it was the general opinion of the Board that both the intramural and extramural programs of the Division of Cancer Etiology were functioning well.

The following points were raised in the discussion:

- In the model of the mdr gene, both regenerating livers and primary hepatocytes become resistant when exposed to a carcinogen and the p-glycoprotein is expressed in response to the carcinogen. Work is continuing to identify the initiation and promotion phases.

- Intramural site visits are designed to be comparable to extramural site visits. Intramural site visits are oriented toward retrospective activities, and there has been an effort to evenly balance retrospective and future considerations.

- Autocrine factors from transformed cells may stimulate normal cells to transform. A number of factors, including the growth factor, require receptors for cell proliferation. A number of factors potentially involved in carcinogenesis, particularly nutritional and endocrine factors, remain to be elucidated (the Board book for the February meeting will include information on mutagens and carcinogens in food).

- DCE is responsible for only the basic studies of chemopreventive compounds. The Division of Cancer Prevention and Control (DCPC) has the responsibility, once an agent and its mechanism of action are identified, of investigating toxicity, getting an IND, and taking the compound to clinical trial.

VI. **Division of Cancer Biology and Diagnosis Program Review-- Dr. Alan Rabson**

Dr. Rabson stated that the Division of Cancer Biology and Diagnosis (DCBD) is divided into an Extramural Research Program under the Associate Director, Dr. Brian Kimes, and an Intramural Research Program, which is composed of 12 laboratories. He described himself, Deputy Director Dr. Ihor Masnyk, Administrative Officer Mr. Larry Willhite, and Chief of Planning and Analysis Ms. Sue Ficker as facilitators for both the intramural and extramural programs. He described the intramural laboratory chiefs as the driving forces of the science in their laboratories and summarized their major research areas as follows:

- Molecular Biology (Dr. Ira Pastan) -- multidrug resistance; molecular genetic techniques to develop immunotoxins for the treatment of cancer; and bacterial genetics

- Biochemistry (Dr. Maxine Singer) -- repetitive DNA and gene regulation

- Mathematical Biology (Dr. Jacob Maizel) -- supercomputer; computer approaches to modeling genetic material with possible application to developing antiviral drugs and vaccines

- Tumor Immunology and Biology (Dr. Jeffrey Schlom) -- use of monoclonal antibodies for cancer diagnosis and treatment; oncogenes associated with mouse mammary tumor virus

- Metabolism Branch (Dr. Thomas Waldmann) -- characterization and clarification of the IL-2 receptor

- Cellular Oncology (Dr. Douglas Lowy) -- ras-oncogenes; papillomaviruses

- Dermatology Branch (Dr. Steven Katz) -- application of immunology to the study of skin diseases

- Pathology (Dr. Lance Liotta) -- metastases research; autocrine motility factor

- Immunology Branch (Dr. David Sachs) -- organ and bone marrow transplantation

- Immunobiology (Dr. Tibor Borsos) -- molecular genetics of cancer; interaction of antibodies, antigen, and complement

- Genetics (Dr. Michael Potter) -- plasma cell tumor induction; oncogenes

- Cell Biology (Dr. Lloyd Lar) -- tumor-specific transplantation antigens.

Dr. Rabson next showed a slide that listed the members of the DCBD Board of Scientific Counselors. The new Chairman is Dr. Arnold Levine, Chairman of the Department of Molecular Biology at Princeton. In FY 1987, site visits were made to the Laboratories of Cell Biology, Cellular Oncology, Genetics, and Molecular Biology. Site visits in FY 1988 will be made to the Laboratory of Immunobiology, the Dermatology Branch, and the Immunology Branch.

The following intramural scientific highlights were identified by Dr. Rabson: 1) characterization of the autocrine motility factor, that stimulates motility and can be inhibited by phospholipase inhibitors; 2) improved methods for constructing immunotoxins for cancer therapy; 3) T-cell epitopes as a new approach to vaccine development; 4) uromodulin, an immunosuppressive glycoprotein isolated from the urine of pregnant women, is an inhibitor of IL-1; 5) repetitive DNA in the human genome can be human "transposons;" 6) identification of a new regulatory protein in gene expression; and 7) characterization of the IL-2 receptor as a multichain receptor. Among the extramural scientific highlights, Dr. Rabson particularly noted the establishment of the Cooperative Human Tissue Network as a result of a suggestion from the NCAB. This network provides highly characterized human tissues to investigators all over the country and should serve to promote more rapid progress in basic cancer research and diagnosis.

Dr. Rabson said that the estimated FY 1988 DCBD budget was $275.9 million, with about $50 million for the intramural program and about $226 million for the extramural program. The small contract program provides animals and resources for the intramural program, and the two current RFAs are intended to stimulate the use of cytogenetics in cancer diagnosis. The one cooperative agreement is for the Human Tissue Network. Dr. Rabson noted that DCBD reviews concepts for the Organ Systems Program, two of which were approved in FY 1987. The contract in the diagnosis program, for the evaluation of hemocult screening as a means of detecting early cancer of the bowel, was renewed.

Board of Scientific Counselors, Division of Cancer Biology and Diagnosis--Dr. Arnold Levine

Dr. Levine first discussed the Board's role in the review and evaluation of the scientific progress made in the intramural program through site visits. The Board also identifies and suggests new directions for future research, often by inviting scientists to make presentations at Board meetings. In addition, the Board reviews and approves support contracts for the intramural program and reviews the extramural research program. Dr. Levine said that the Board was enthusiastic about two new grant programs: one for young investigators who are applying for their first research grant and the other to recognize senior investigators by awarding long-term grants.

Finally, Dr. Levine said that the Board of Scientific Counselors (BSC) evaluates concept proposals for program announcements and RFAs for the Organ Systems Program.

In elaborating on the Board's efforts to explore new areas for research, Dr. Levine cited the presentation to the Board by Dr. David Houseman from MIT on familial melanoma and hereditary predispositions in cancer. Dr. Levine described this research as a promising new approach to studying familial associations using molecular biological techniques. Such approaches are supported by research that was described in the October 1987 issue of Cell. Two groups, by putting together a series of 220 molecular probes across all 23 chromosomes of the human genome, had for the first time produced a genetic map of the entire human genome. Dr. Levine cited this research as an important advance that will enable the intensive study of familial associations with different kinds of cancer. The information can be used to map the DNA and determine the location of the gene for familial cutaneous melanoma, for example, and identify and characterize the gene. Dr. Levine pointed out that Dr. Zbar in the Laboratory of Immunobiology had found that people with renal carcinomas and small cell lung carcinomas have an abnormality on chromosome 3. When the genes from chromosome 3 that are involved in the abnormality have been cloned and sequenced and the proteins that they code for have been characterized, the information may lead to new approaches to cancer treatment.

As his concluding statement, Dr. Levine described a research project on drug resistance conducted by the Laboratory of Molecular Biology. One type of drug resistance is associated with the P170 protein. Drs. Gottesman and Pastan found that the genetic information for that protein in the cell is often amplified when high levels of the protein are found on the cell membrane. In studying the mechanism of action of the protein, they found that the protein causes the cell to excrete some of the drugs used for cancer chemotherapy, thus permitting the cell to escape from the effects of the drugs. Therefore, Dr. Levine said, there is a need to identify agents to block this excretion of drugs and thus prevent drug resistance.

The following points were raised in the discussion:

- Research on familial susceptibilities to cancer will help to identify people at risk so they can receive early intervention and also lead to the identification of a rational basis for chemotherapy.

- The relatively low increase of 1 percent in DCBD's intramural budget is attributed to nonrecurring expenses that occurred in FY 1987; the real increase is approximately 4 to 5 percent.

- The Center for the Study of Human Polymorphisms in Paris is acting as a reference center and collecting information from numerous sources, including for-profit institutions, on molecular probes and genetic mapping.

- The application of cytogenetics to diagnosis is widely used for lymphomas and leukemias, and molecular genetics may become very important for cancer diagnosis within the next few years.

VII. **Division of Cancer Treatment Program Review--Dr. Bruce Chabner**

Dr. Chabner said that the mission of the Division of Cancer Treatment (DCT) is to discover new and better treatments for cancer, both in terms of basic research and transfer to clinical practice. Program areas include the disciplines of surgery, chemotherapy, radiation therapy, immunotherapy, and the use of biological compounds. Organizationally, DCT includes the Deputy Director (Dr. Gregory Curt) and Special Assistant for Clinical Affairs (Dr. Marcia Brown) in the Office of the Director; the Board of Scientific Counselors (Dr. John Niederhuber, Chairman); the Administrative Management and Planning Branch (Mr. Lawrence Ray); and five operating Programs--Clinical Oncology (Dr. Samuel Broder), Cancer Therapy Evaluation (Dr. Robert Wittes), Drug Development (Dr. Michael Boyd), Radiation Research (Dr. John Antoine), and Biological Response Modifiers (Dr. Dan Longo). Dr. Chabner commended the work of Dr. Eddie Reed, former Special Assistant for Preclinical Affairs, who has rejoined the intramural staff.

Dr. Chabner said that a major task for this year was to clarify the role of DCT in the AIDS drug development program and alluded to the key role played by Dr. Broder, who was responsible for the development of AZT and the dideoxy compounds for treating AIDS. Dr. Chabner noted that a number of compounds have either entered or are soon to enter the clinical trial phase (dideoxycytidine in early 1987), creating the dilemma of trying to accommodate both AIDS and cancer patients in the DCT complement of beds in the Clinical Center. He said that the new ward recently reallocated to DCT would ease this situation as soon as it is staffed.

Turning next to a review of Program areas, Dr. Chabner listed the Branches of the Clinical Oncology Program (COP), selected research highlights, and Branch heads as follows: Medicine--adult oncology with an emphasis on ovarian and testicular cancer and the lymphomas (Dr. Robert Young); Pediatric Oncology--studies showing that infusional regimens of AZT have mediated improved immune function (Dr. Philip Pizzo); NCI-Navy Medical Oncology--studies on deletion to homozygosity in one arm of the third chromosome, amplification of the c-*myc* gene, and discovery of a new *onc* gene in small cell lung cancer patients (Dr. John Minna); Radiation Oncology--the role of glutathione in drug and radiation sensitivity, the use of porphyrins in photodynamic therapy, and studies using radiolabeled monoclonal antibodies (Dr. Eli Glatstein); Surgery--continued development of the IL-2/LAK regimen (Dr. Steven Rosenberg); and Clinical Pharmacology--studies of drug resistance and the MDR gene and anti-HIV drug development (Drs. Samuel Broder and Charles Myers). Dr. Chabner noted that the Clinical Pharmacology Branch has identified an amplification of mechanisms for drug detoxification in both drug-resistant cells and preneoplastic nodules during carcinogenesis that promises to be important to the understanding of drug resistance. Recently published research showing that the anticancer drug trimetrexate is an effective agent for treating *Pneumocystis carinii* has led to a collaborative trial with the National Institute of Allergy and

Infectious Diseases (NIAID) and efforts to secure FDA release of the drug on a treatment IND basis.

The entirely extramural Radiation Research Program (RRP) has both a radiation therapy and a diagnostic imaging component. Dr. Chabner noted that a major accomplishment of the Diagnostic Imaging Research Branch was the creation of a national cooperative diagnostic imaging group that was organized to study and compare the various imaging modalities and determine the most appropriate test for the various cancers. The first series of studies is targeted at prostate and lung cancer.

The Cancer Therapy Evaluation Program (CTEP) has an Investigational Drug Branch, which is responsible for early clinical trials, and a Clinical Investigation Branch, which oversees the Clinical Cooperative Group program, and two support branches, Biometric Research and Regulatory Affairs. Dr. Chabner noted that the positive results seen in adjuvant IL-2/LAK trials have generated an interest in increasing patient accrual to a second generation of trials that are underway.

Dr. Chabner noted that the Developmental Therapeutics Program (DTP) has been reorganized to simplify its structure and to place grants and contracts in a single operating branch. Research activities in the four intramural laboratories are related to both AIDS and cancer, with the AIDS-related work located mainly in the Biochemical Pharmacology and Medicinal Chemistry Laboratories. He said that the Laboratory of Biological Chemistry, in collaboration with the Laboratory of Molecular Biology in DCBD, produced the photoaffinity labels that identified the drug binding function of the P170 protein, which is important in understanding drug resistance. DTP also has eight extramural branches that are primarily concerned with preclinical drug development, drug screening, toxicology, and the various other phases of drug development that precede clinical testing.

The Biological Response Modifiers Program (BRMP), located at the FCRF, has intramural branches with major interests in lymphokines and cell-mediated immunology. Dr. Chabner noted that IL-1, which has been shown to mediate bone marrow growth, is due for a clinical trial in the near future. Extramural branches include the Biological Resources Branch, which is responsible for organizing and supporting extramural clinical trials, and the Clinical Research Branch, operated through FCRF, which provides clinical support to the intramural laboratories. The newest addition to the BRMP is the Laboratory of Biochemical Physiology under Dr. Kung, which conducts research in molecular biology and serves as a resource for the entire program.

In response to a question about the difference between the DTP extramural Pharmacology and Pharmaceutical Research Branches, Dr. Chabner explained that the first administers contracts for the pharmacokinetic study of identified actives from the drug screen that cannot be handled in the intramural laboratories, while the latter is primarily responsible for the formulation of drugs prior to clinical trials.

Turning to the budget, Dr. Chabner noted that the FY 1987 budget of $400 million was spent equally between grants and the other parts of the program, including about 15 percent for in-house cancer expenditures and 15 percent for contracts in support of drug development and Phase I/II new drug trials. Dr. Chabner pointed out that the in-house AIDS budget for FY 1987 is 12 percent of the in-house cancer amount and estimated that it would double in FY 1988.

Referring to the FY 1988 projection of less than a 1 percent change for in-house cancer expenditures compared to an 83 percent increase for in-house AIDS, Dr. Chabner said that the AIDS money is new money to DCT, and he pointed out the extensive cooperation that exists in all phases of AIDS and cancer research and drug and biologics development. He noted that the DCT Board had discussed the possible impact on cancer research of the added major responsibility for AIDS research and reached the consensus that DCT was nevertheless the most appropriate organization for it. He acknowledged the impact of AIDS research on the intramural program but stated that it is an important national priority and an area of great scientific interest.

According to Dr. Chabner, the major managerial initiatives of the DCT were the establishment of the new ward in the Clinical Center for cancer and AIDS research, the establishment of the AIDS drug screening program, and the consolidation of the new cancer drug screening effort at the Frederick Cancer Research Facility.

Dr. Chabner listed the following areas of significant progress in cancer treatment in the extramural program:

- MVAC combination therapy in bladder cancer showed a 70 percent response rate (20 percent complete response); adjuvant trials are planned.

- Fluoro-ara-AMP was found to be active in CLL and nodular lymphomas when administered at lower, less toxic doses.

- Radioprotector WR-2721 interacts with cis-platin to produce a response rate of almost 30 percent in patients with malignant melanoma; confirmation trials are imminent.

- 5-FU and leucovorin were found to produce improved responses in patients with colon cancer; adjuvant trials are planned.

- Ifosphamide, when used with cis-platin, was found to be curative in a significant fraction of patients who fail standard therapy for testicular cancer; Group C status is being sought.

- Positive results were achieved in adjuvant trials (some confirming earlier results; some new) in colon cancer, rectal cancer, node-negative/high-risk breast cancer, and stage II adenocarcinoma of the lung.

Dr. Chabner reported that a number of biological agents have shown activity in clinical trials during the past year: 1) the colony stimulating factors GM-CSF and G-CSF in bone marrow reconstitution; 2) interferon-alpha in hairy cell and chronic myelocytic leukemia; 3) IL-2 in melanoma; 4) IL-2/LAK in renal cell carcinoma, melanoma, and colon cancer; 5) intraperitoneal IL-2/LAK in ovarian cancer; and 6) monoclonal antibodies in melanoma.

Dr. Chabner then reviewed the progress of ongoing studies of IL-2/LAK and IL-2 alone. The Surgery Branch randomized trials comparing the two regimens produced higher response rates for IL-2/LAK in patients with renal carcinoma, no clear difference in melanoma, and low response rates (15 percent) in both arms for colorectal cancer and non-Hodgkin's lymphoma patients. Dr. Chabner noted, however, that complete responses were seen in both arms for renal carcinoma and the IL-2/LAK arm for melanoma, and 13 of the 16 patients who achieved a complete response are still in remission. He said that the persistence of these complete responses was the basis for the application to the FDA for group C status for IL-2/LAK to expand its use to 38 clinical and comprehensive cancer centers.

Dr. Chabner said that the BRMP trial of intraperitoneal IL-2/LAK achieved partial responses in both ovarian and colorectal cancer patients, but intraperitoneal fibrosis was present when the patients were biopsied. He said that the problem probably relates to the fact that the gamma-interferon released during intraperitoneal administration of IL-2 stimulates proliferation of fibroblasts and noted that the BRMP is attempting to inhibit the gamma-interferon release biochemically.

Dr. Chabner said that the first extramural confirmatory trial of the Surgery Branch regimen also demonstrated activity in renal and colorectal cancer and melanoma, with about the same response rate as Dr. Rosenberg found in colorectal cancer and melanoma but only half the renal response rate. Future directions in these studies include: 1) Phase II screening of a wider range of tumor histologies using the Rosenberg regimen, beginning with lymphoma and breast cancer; 2) a randomized trial of Dr. Rosenberg's regimen versus a higher dose continuous infusion regimen in renal cell carcinoma and melanoma; 3) expanding the cancer center IL-2/LAK programs in group C; 4) initiating trials of IL-2/LAK with other chemotherapeutic or biological agents; 5) supporting innovative preclinical and clinical research through task order mechanisms and the grants program.

In the discussion following Dr. Chabner's review the following issues were raised:

- In assessing the speed with which biologicals are being developed as compared to chemotherapeutics, it is necessary to note that their use is essentially confined to unresponsive diseases or patients who failed other therapy. However, progress is being made and biologicals, as they become available, will be useful in clinical chemotherapy.

- Study of animal tumors and some patient material suggests a correlation between expression and histocompatibility antigens and their ability to respond, which might explain the differences in patient responses to the IL-2/LAK regimen.

- The variation of clinical responses to IL-2/LAK could be related to differences between individuals and their suppressor systems. This theory is being tested with a protocol for using cyclophosphamide to inactivate the suppressor cell population.

- In general, AIDS grants are administered by NIAID. DCT began the grant-supported AIDS cooperative drug discovery program about 3 years ago then agreed to the transfer of that responsibility to NIAID along with several million dollars worth of grants.

Board of Scientific Counselors, Division of Cancer Treatment--Dr. John Niederhuber

Dr. Niederhuber briefly reviewed the role of the DCT Board of Scientific Counselors (BSC) and listed the standing subcommittees: Surgical Oncology Research and Development (SORDS), Diagnostic Imaging, and Radiotherapy. He explained that SORDS represents the efforts of the surgeons who make up the committee to bring surgical oncology into a more central role in cancer treatment research. He noted that the committee has been instrumental in developing the T-32 grant for the training of young academic surgical oncologists. Dr. Niederhuber then introduced the members of the BSC and noted that they represent disciplines in molecular biology, molecular genetics, biology, tumor immunology, tumor cell biology, and medical, radiation, and surgical oncology.

During FY 1987 the Board appointed site visit teams to conduct three major reviews of intramural programs: Laboratory of Tumor Cell Biology (Dr. W.H. Kirsten, Chairman); Surgery Branch (Dr. Niederhuber, Chairman); and NCI-Navy Medical Oncology (Dr. John Mendelsohn, Chairman). In his brief summary of the reviews, Dr. Niederhuber noted that the decision to transfer the Laboratory of Tumor Cell Biology to DCE was made at the staff level; however, it was endorsed by the site visit team. He said that these three programs received commendation for their work along with specific recommendations from the teams. Site visits scheduled for FY 1988 include the recently completed review of the Clinical Pharmacology Branch (Dr. Yung-chi Cheng, Chairman), and the Laboratories of Biological Chemistry, Molecular Immunoregulation, Biochemical Pharmacology, and Medicinal Chemistry.

Dr. Niederhuber presented a list of concepts that was reviewed by the Board during the fiscal year and pointed out the high approval rate and the large number approved at the February meeting, including 18 AIDS concepts. Cooperative agreements were awarded for multi-institutional collaborative diagnostic imaging trials, an initial effort in this area; biochemical modulation; and National Cooperative Drug Discovery Groups (lung and colon).

Dr. Niederhuber showed slides of the scientific highlights that were presented by DCT staff at each of the FY 1987 meetings and expressed the opinion that the Board provides an important link between the Division of Cancer Treatment and the academic and industrial communities. In his final comments on the review process as it relates to Board responsibilities, Dr. Niederhuber noted that the teams are conducting rigorous reviews of the intramural program, similar to those for extramural P01 programs or cancer centers. He added that the positive response of DCT staff has been an affirmation of the Board's advisory function.

In the discussion period following his presentation, Dr. Niederhuber was asked to comment on the Board's views in relation to the increased research emphasis on AIDS in the DCT. He noted that the Board initially questioned whether DCT was the appropriate Division for the effort and whether the increased effort in terms of financial support and manpower would not detract from the cancer research program. He said that the Board is satisfied, on the basis of its ongoing discussion, that the effort is appropriately placed and that additional funding and staff are forthcoming.

Dr. Longmire called attention to the issues that surround the training of surgical oncology researchers. The following points were made in the ensuing discussion:

- NCAB has a special interest in surgical oncology and the training of surgical oncological researchers.

- DCT staff and the SORDS Committee are to be commended for significantly increasing the number of surgical research training programs and for providing a review mechanism that assures careful review of the grants that are awarded.

- Academic surgeons have a broad point of view that encompasses many different fields as well as cancer research. Their efforts to prepare young research surgeons in the various categories have run counter to Institute requirements as they relate to awarding grants. There is no satisfactory solution to this problem at the present time; however, a change in outlook may be necessary if NCAB is to successfully broaden the base of surgical research to attract increasing numbers of surgical research trainees.

- Over the past several years, the majority of research grant applications that relate to surgical oncology have been in the area of immunology. Since medical oncologists and immunologists also compete in this area, it is important to evaluate and revise the area where surgeons can be effective in doing basic and applied research in the field of cancer science.

VIII. <u>Increasing Patient Accrual in Clinical Trials--Dr. Roberts Wittes</u>

Dr. Wittes began by explaining the rationale for the proposed expansion of the clinical trials program. He first outlined positive studies

in advanced cancer and in the adjuvant setting, citing progress in pediatric cancer, hematologic malignancies in adults, and testicular cancer, as well as in large bowel cancer, advanced bladder tumors, and refractory testicular cancer. He emphasized that these positive studies inevitably lead to further research questions and thus a need for expansion of the clinical trials mechanism.

Dr. Wittes briefly reviewed the positive results in early clinical trials, which will generate leads that will require future expansion in larger studies. For example, a good response rate in very refractory malignancies has been seen in the IL-2/LAK study. Deoxycoformycin and fluoro-ara-AMP have shown evidence of activity in chronic lymphocytic leukemia. The cis-platinum analog carboplatin has shown activity in acute leukemia, while the parent compound has not. Ifosphamide has shown striking results in testicular cancer and, in combination with VP16, in children with Ewing's sarcoma.

Dr. Wittes also noted the results of early studies in advanced metastatic melanoma. The radioprotector WR-2721 appears to increase the antitumor activity of cis-platinum in melanoma, and plans for a Phase III trial that includes this combination are ongoing. The natural product taxol also has shown some activity in melanoma.

Dr. Wittes then proceeded to discuss the issues related to the overall clinical trials mechanism and the expansion of the program's structure. He reviewed the efforts of the Clinical Investigations Branch (CIB) to ensure optimum coordination of the program by the Clinical Cooperative Groups and the Cancer Therapy Evaluation Program. Over the previous 18 months, the CIB had hosted a series of meetings of the Groups and the CTEP staff to avoid duplication of efforts and coordinate trials on a variety of malignancies, including breast cancer, non-Hodgkin's lymphomas, hairy cell leukemia, and colorectal cancer. These strategy meetings have resulted in integrated activity of the Groups, intergroup trials, and the establishment of some common criteria for response or toxicity. He noted that refinements in the Cooperative Groups' management had in many cases resulted in on-time or early completion of accrual target goals, but that patient accrual was still delayed in some studies.

Stressing that patient accrual to studies should be accomplished as quickly as possible while maintaining adequate quality control of the study parameters, Dr. Wittes suggested that the increasing number of promising new drugs and biologics threatens to overwhelm the capacity of the current clinical trials mechanism. He reported that only about 10 to 40 percent of eligible patients within the clinical trials mechanism are accrued to clinical trials in most Cooperative Groups. He also emphasized that the patients of nonparticipating physicians represent a large potential group of clinical trials participants.

Turning to the issue of specific methods for increasing accrual to high-priority studies, Dr. Wittes defined these studies as those that involve common diseases or diseases for which exploitable therapeutic options exist and thus would have impact on mortality. He stated that the CTEP had

proposed to identify an initial list of high-priority trials for the Cooperative Groups' chairmen, which would be reviewed by the chairmen and then presented to the DCT Board of Scientific Counselors for further discussion at their February 1988 meeting. Dr. Wittes also noted the general impression that some physicians are not interested in participating in clinical trials because they are more concerned with the need to individualize therapy on a patient-to-patient basis than with participating in structured studies, which involve complex issues such as informed consent, data management, and protocol design. To increase accrual to clinical trials would involve improving the efficiency of present participants and/or increasing the scope of the mechanism and participants.

Outlining approaches to enlarge the clinical trials network, Dr. Wittes discussed the possibilities of involving HMOs, more non-HMO for-profit providers, more community-based physicians, and possibly more university participants. He described a CTEP proposal to increase community involvement by allowing centers and community physicians to affiliate with the Cooperative Groups for high-priority trials and to provide NCI funding to the Groups for such participants. This type of arrangement would, Dr. Wittes noted, be facilitated by a relatively simple study design and by the adoption of common intergroup forms and toxicity criteria.

Dr. Wittes also raised the possibility that direct affiliation of community physicians or institutions with CTEP also could accomplish the goal of increasing patient accrual. This mechanism could be applied, for example, in specialized trials of new approaches such as with IL-2/LAK extramural trials at six institutions that are directly coordinated by CTEP or in large, relatively simple studies designed to examine the effect of a treatment on a population basis rather than on a standard clinical trial basis. Dr. Wittes emphasized that this approach would not be designed to compete with the Cooperative Groups but rather to allow participation by community institutions that are not ordinarily eligible for participation in Group trials.

Dr. Wittes concluded by summarizing the current efforts of CTEP to address the issues involved in the expansion of the clinical trials program as follows:

- CTEP's definition of the high-priority studies and discussion of these studies with the Cooperative Group chairmen of both current and past functioning groups.
- Examination of administrative mechanisms for the process of reimbursing community-based participants.
- Evaluation of methods to expedite the process of protocol writing and review, including experimentation with using electronic mail devices in the process.
- Focusing more attention on avoiding unnecessary protocol complexity in the review process.

- Contacts with several large U.S. HMOs to seek participation in the clinical trials program.

- Drafting a plan with NCI's Office of Cancer Communications to increase publicity about clinical trials and their value both to physicians and the lay public.

- Direct coordination of trials (e.g., deoxycoformycin) by CTEP and use of an innovative IND procedure to make a specified treatment available to patients who cannot participate in clinical trials.

- Investigation of the issue of third-party coverage of the cost of investigational therapy involved in clinical trials participation, which is currently excluded from coverage by almost all carriers.

Dr. Korn suggested that a discussion of the expansion of the clinical trials program be put on the agenda of a future Board meeting. Dr. DeVita raised the issue of whether the problems with patient accrual within the Group system were solvable. He stressed that proposals to expand the program, which is currently funded at $57 million per year, should be approached with the possibility that the clinical trials mechanism may need revision. Dr. Chabner also noted that expansion of the clinical trials program involves the ongoing evaluation of the cancer centers, which are not integrated in the clinical trials network.

The Board concurred that a major discussion of the expansion of the clinical trials program should be included on the agenda of the February 1-3, 1988, NCAB meeting.

IX. **Division of Cancer Prevention and Control Program Review--Dr. Peter Greenwald**

Dr. Greenwald said that the organization of the Division of Cancer Prevention and Control (DCPC) includes within the Office of the Director the Smoking, Tobacco, and Cancer Program headed by Dr. Joseph Cullen. This smoking prevention program has established a network of scientists across the country, with 57 trials in progress in 25 states and 200 communities, involving more than 10 million people. Many approaches are used, including stimulating local leadership, building statewide programs, using the media, developing programs for schools, teaching self-quitting techniques, involving health professionals as interveners, and targeting special populations.

The Surveillance and Operations Research Branch, headed by Dr. Edward Sondik, tracks the progress of the National Cancer Program in terms of both research progress and the application of research to clinical practice. This Branch also includes the SEER program. Dr. Greenwald said that during the past year the Branch had been analyzing a new set of data on the knowledge, attitudes, and practices of 52,000 people from a survey conducted by the National Center for Health Statistics. NCI supported a cancer control section of the survey to find out about changes in smoking,

diet, and screening practices. Dr. Greenwald said that the Biometry Branch, headed by Dr. David Byar, conducts independent research and much of it is mathematical modeling. The Branch also assists in many clinical trials, including the Women's Health Trial, the Lung Cancer Study Group, and the Brain Cancer Study Group.

Dr. Greenwald next discussed the Division's three program areas: Cancer Control Science headed by Dr. Lillian Gigliotti, Centers and Community Oncology (a new Associate Director is being sought), and Cancer Prevention Research headed by Dr. Dan Nixon. He began with the Cancer Control Science Program, noting the four extramural branches: Cancer Control Applications, Health Promotion Sciences, Special Population Studies, and Cancer Training. The Cancer Control Applications Branch has expanded cancer control efforts to state health agencies in an effort to increase the technical competency for performing prevention and control program activities and research. Dr. Greenwald said 15 health agencies are being funded. The Cancer Prevention Fellowship Program is aimed at bringing new scientists into the field of cancer prevention. Dr. Greenwald said that the Health Promotion Sciences Branch performs research aimed at achieving wide effects from what has been learned through basic clinical research. This program includes the Cancer Communications System and the Eat for Health project with the Giant Food Corporation to see whether point of purchase information will affect consumers' food choices. In addition, a school lunch manager's guide has been developed to provide nutrition guidelines to primary care physicians, and an RFA has been released on modification of eating behavior in the community.

Also in the Cancer Control Science Program is the Special Population Studies Branch, which Dr. Greenwald said had completed the feasibility phase of research contracts for cancer control in the black population. The two major thrusts of activity are smoking and avoidable mortality. The Branch also will be starting new cancer control research programs for Hispanics and Native Americans. Dr. Greenwald said that the Cancer Training Branch oversees much of the training for all of NCI, including programs for research training and postdoctoral fellows. There are a total of 47 awards, including the revision of the Clinical Education Program to emphasize prevention and control, nutrition curriculum development for medical and other health science schools, and short-term training for minority and other groups.

Dr. Greenwald identified the components of the Centers and Community Oncology Program: the Cancer Centers Branch, which includes the Organ Systems Program; the Community Oncology and Rehabilitation Branch, which includes the Community Clinical Oncology Program (CCOP); the Research Facilities Branch; and the Early Detection Branch. He pointed out that the CCOPs include both cancer prevention trials as well as continuation with accrual to clinical trials. There were 53 awards to community hospital physicians, and there are now 8 Clinical Cooperative Groups and 8 cancer centers. Dr. Greenwald identified the fact that a zero budget is projected for the Research Facilities Branch as a key problem.

Dr. Greenwald described the Cancer Prevention Research Program as one of the major thrusts of the Division. The extramural Diet and Cancer

Branch has sponsored research related to analytical methods for dietary fibers, studies of the chemistry and function of dietary fiber and how these might affect biological markers, especially for colon cancer, and international food consumption analysis. Dr. Greenwald noted that the Division is in the process of developing an intramural laboratory for nutrition and cancer research and is searching for a laboratory director. The intramural Cancer Prevention Studies Branch performs a number of prevention trials and clinical metabolic studies in collaboration with the Department of Agriculture.

Dr. Greenwald elaborated on the activities of the extramural Chemoprevention Branch, within the Cancer Prevention Research Program. Basic research, including research on chemicals that may inhibit cancer, is performed at DCE. DCPC picks up the leads from basic science or epidemiology and proceeds through a structured series of stages from the laboratory through to human intervention. Dr. Greenwald said that during 1987, 54 of the 600 compounds reviewed were started on in vitro studies. The results are reviewed according to specific criteria to determine which compounds should go into a battery of animal efficacy studies and chronic toxicity studies. The agents include both naturally occurring substances and synthetics such as pharmaceuticals. Dr. Greenwald cited several examples of trials including a study conducted at Dartmouth by Dr. Robert Greenberg using beta-carotene to prevent new primary skin cancers. A trial involving an intramural group and investigators in Finland is studying beta-carotene and vitamin E in the prevention of lung cancer in 26,000 smokers. Another trial involving collaboration between DCPC and DCE with Chinese investigators is testing four combinations of agents--vitamin A, beta-carotene, and zinc; riboflavin and niacin; vitamin C and molybdenum; and selenium and vitamin E--for the prevention of esophageal cancer in 30,000 subjects.

In turning to discussion of the budget, Dr. Greenwald noted that there is a line item for cancer prevention and control that includes RFAs and contracts to support the cancer control programs in blacks, the cancer communications systems, the heavy smoker trial, CCOP evaluations, and interagency studies with the Department of Agriculture. He referred Board members to the information provided in the Board books for additional details.

Board of Scientific Counselors, Division of Cancer Prevention and Control--Dr. Paul Engstrom

Dr. Engstrom reviewed the membership of the Board and commented that the Board included cancer center directors, directors of CCOP programs, a medical school president, deans or professors from schools of public health, epidemiologists, health management researchers, corporate medical program directors, and clinical oncologists. The Board has subcommittees on Cancer Prevention Research, Cancer Control Science, and Centers and Community Oncology. Dr. Engstrom said that the ad hoc committees were the Policy Advisory Committee (PAC) for the Women's Health Trial and a subcommittee to examine the PAC's recommendations and a Cancer Detection Committee to develop recommendations for cancer screening and detection in clinical practice. The

Board made site visits to the Surveillance and Biometry Branches in 1987 and will visit the Prevention Branch in 1988.

Dr. Engstrom highlighted the significance of reports to the 1987 BSC. The Board endorsed the recommendations to establish an intramural nutrition laboratory. The Steering Committee on Early Detection developed guidelines for the practicing physician for screening for skin, uterine, cervix, colorectal, testes, prostate, and breast cancer. The Board supported the Cancer Centers Program and encouraged the activity of an NCAB subcommittee to review the location and function of the Program. Dr. Engstrom said that the DCPC Board considered that the guidelines for the cancer education grant program establish a sound basis for developing a cadre of investigators to accomplish NCI's cancer control and prevention goals. He also noted that the Board unanimously passed a resolution on involuntary smoking.

Other activities that were addressed by the BSC were the Women's Health Trial, the Cancer Information Service, and the establishment of Cancer Prevention Research Units.

Points raised in discussion included the following:

- The prevention and control activity includes consultation and advice to scientists throughout the country and requires widespread interactions.

- The allocation of FTEs for the National Research Service Awards is done on an NIH-wide basis.

- Consideration will be given to reannouncing the guidelines for cancer education (R25) grants to encourage the application of minority students at the predoctoral level.

- The committee to review the PAC recommendations is chaired by Dr. Phillip Cole and includes Drs. Roswell Boutwell, Malcolm Pike, and Edward Bresnick.

- The SEER program budget is about $10.5 million and is included under other DCPC contracts.

X. <u>Frederick Cancer Research Facility--Dr. Peter Fischinger</u>

In noting that this would be his last report on the Frederick Cancer Research Facility (FCRF), Dr. Fischinger stated that the FCRF is now well integrated into the structure and fabric of NCI and able to quickly deploy its resources. In addition, there is a sense of stability at FCRF and a commitment to continuing its high-quality work. However, despite these positive features, Dr. Fischinger suggested that there is some built-in fragility to the program because the Institute does not have the same degree of control that it has over its intramural programs.

The new organization will include in the Office of the Director a specific NCI Associate Director for Frederick who serves on the NCI Executive

Committee. The contractors' operations include the Basic Research Program headed by Dr. George Vande Woude of Bionetics Research, Inc., Operations and Technical Support headed by Dr. Raymond Gilden of Program Resources, Inc. (PRI), Animal Production headed by Dr. Robert Russell of Harlan Sprague Dawley, Inc., and Computer Services and Scientific Library support headed by Mr. Larry Callahan and Ms. Susan Wilson, respectively, of Data Management Services, Inc. Dr. Fischinger showed slides of new buildings: number 549, the conference facility and library; number 432, where much of the in vitro screening will be done; number 431, where AIDS and cancer chemotherapeutic agents will be screened; number 470, which NCI recently acquired; and number 426, which is being renovated. Some relatively new components of FCRF include three laboratories and an Office of Scientific Director operated by the National Institute of Allergy and Infectious Diseases (NIAID) and a laboratory operated by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS).

Dr. Fischinger next focused on the Operations and Technical Support Program. The support groups under the direction of Dr. Gilden include Research Support, the Laboratory of Animal Sciences, the Advanced Scientific Computing Laboratory, the AIDS Vaccine Development Program, Contracts and Administration, Environmental Control and Research, and the Facilities Maintenance and Engineering Program. Shared services include chemical synthesis and analysis, a central repository, fermentation production, biological products unit, clinical immunology services, clinical services and testing, recombinant DNA technology, microbial mutagenesis, and nucleic acid and protein synthesis. Dr. Fischinger noted the progressively growing demand for shared services. Other support services provided by PRI include the operation of the supercomputer, the LAK cell project, in vitro anti-cancer and anti-AIDS drug screening, and the establishment of a natural product extraction laboratory. New areas identified by Dr. Fischinger include the clinical monitoring of AIDS patients, epidemiologic studies on human retroviruses, various aspects of AIDS vaccine development, and the establishment of transgenic mouse and DNA-sequencing capabilities. He recalled that the recent Phase IV subcontracts for a number of AIDS-related activities were let through PRI with the approval of the FCRF Advisory Committee, as were the previous three Phases.

Dr. Fischinger pointed out that the FCRF's estimated FY 1988 budget of $92.9 million includes $1.3 million for the acquisition of the X-ray Crystallography Laboratory. The Office of the Director supports the basic research programs and all indirect costs, and NCI divisions and other Institutes also contribute funds to the operation of FCRF. Dr. Fischinger said that with several key exceptions, AIDS funds will go directly from the Office of the Director to the appropriate division rather than to FCRF. In conclusion, Dr. Fischinger said that although the amounts cited for contractors' operation appears quite high, it is a negotiated price for seven years and indicates FCRF's potential for growth.

FCRF Advisory Committee--Dr. Dante Scarpelli (for Dr. Werner Kirsten)

Dr. Scarpelli stated that the Advisory Committee, which includes experts in molecular biology, genetics, virology, and chemical carcinogenesis, reviews both basic research program laboratories and management of NCI/FCRF systems contracts, provides advice on new support efforts and shared services, and reviews concepts for recompetition. He said that the FCRF basic research program consists of 23 independent research units in seven major laboratories organized according to research interests. Of the 170 people working in the basic research programs, 110 are scientist professionals and half of these are postdoctoral fellows.

Dr. Scarpelli noted that the Crystallography Laboratory was established during 1987 under the direction of Dr. Alexander Wlodawer. The Laboratory will prepare crystals from many of the proteins of viral and cellular origin that have been overexpressed in novel prokaryotic and eukaryotic vector systems. A Developmental Genetics section has been added to the Laboratory of Eukaryotic Gene Expression headed by Dr. Jeffrey Strathern, and a new group to develop mice with chimeric cell types has been added to the Mammalian Genetics Laboratory headed by Dr. Neal Copeland.

Dr. Scarpelli stated that the basic research program had contributed significantly to the study of the AIDS virus. Dr. Stephen Oroszlan and his Laboratory of Molecular Virology and Carcinogenesis achieved the complete chemical synthesis of HIV protease, a protein essential for the synthesis of an infectious virus and responsible for the cleavage of the virion protein during virus assembly. Dr. Stephen Hughes and members of his section in the Molecular Mechanisms of Carcinogenesis Laboratory have expressed several HIV proteins in prokaryotes, most notably a very active viral reverse transcriptase. Dr. George Pavlakis in the same laboratory has developed a very rapid qualitative and quantitative assay for detecting infectious HIV and monitoring the ability of HIV to replicate.

Dr. Scarpelli also noted Dr. Hughes' efforts, in collaboration with the Department of Agriculture, to develop procedures for introducing genes into the germ line of chickens. By infecting early embryos with a genetically engineered recombinant retrovirus, they have produced a chicken that is resistant to a field strain of avian pathogenic virus. The Mammalian Genetics Laboratory has developed transgenic mice for evaluating gene structure and function. In the study of oncogenes, several have been identified that are the ultimate targets of chemical carcinogenesis. Dr. Scarpelli recalled Dr. Vande Woude's successful effort to isolate the met-oncogene, which is tightly linked to the genetic locus responsible for cystic fibrosis in humans. Several other new oncogenes have been identified, and their characterization should lead to the development of probes for use in human diagnosis. Other research has involved the substitution of individual carcinogen-modified bases into proto-oncogenes to study how carcinogens activate oncogenes. Among the new areas of scientific research highlighted by Dr. Scarpelli were 1) fusion of concepts in biological and chemical carcinogenesis at the level of the oncogene; 2) fusion of concepts

in molecular biology and crystallography for structure prediction; 3) probes for new oncogenes and for diagnosis of disease; and 4) development of transgenic and chimeric capabilities for studying genetic functions.

In conclusion, Dr. Scarpelli described the review of the laboratories of the basic research program as analogous to that of the intramural NCI laboratories. Each laboratory is reviewed every 3 years, and each review requires the preparation of a report detailing the accomplishments of the laboratory and proposed new research. The review is conducted by a site-visit team appointed by the Chairman of the FCRF Advisory Committee. In 1986, the Laboratory of Chromosome Biology was reviewed; in 1987, the Molecular Mechanisms of Carcinogenesis Laboratory; and in 1988, the Laboratories of Eukaryotic Gene Expression and Chemical and Physical Carcinogenesis will be reviewed.

In discussion, it was clarified that the NCI buildings at FCRF are NIH property. The renovation of FCRF buildings is paid for out of NCI's intramural construction budget.

Dr. DeVita and the Board members expressed their appreciation to Dr. Fischinger for his work in developing FCRF into a high-quality research facility.

XI. <u>Organ Systems Program Annual Report--Dr. James P. Karr</u>

Dr. Karr described the organ systems approach as focusing basic research in applied areas and suggested that it complements the existing disciplinary or categorical approaches to planning. He said that the organ systems approach is multidisciplinary, focusing on the differences in the causes and the biology of specific cancers and the need for early detection, treatment, and control of different cancers in the organ systems. The Organ Systems working groups assess the full spectrum of basic subjects that are relevant to a given cancer site and how these subjects can be integrated into the etiology, prevention, and control of the particular site. Dr. Karr emphasized that the research initiatives that are generated by the Organ Systems Program (OSP) feed into the regular NCI implementation procedures.

Dr. Karr said the program is administered through the Organ Systems Section of the Cancer Centers Branch in DCPC. The program includes an external coordinating center, the OSCC; the Organ Systems staff within NCI; and an OSCC Advisory Board which provides recommendations and advice on how the OSCC can better serve the needs and goals of the Program. The working groups comprise a chairman, 14 members, an OSCC scientific administrator, an NCI program director, NCI divisional representatives, and frequently ad hoc consultants. Dr. Karr said that there are currently seven working groups representing the organ sites that collectively account for 50 percent of the new cancer cases and 40 percent of the cancer mortality annually. The approaches used by the working groups include workshops, involvement of consultants, development of concepts, development of position papers, and formulation of recommendations for NCI, medical associations, and scientific societies. In addition, Dr. Karr said that the working groups document the need for recommended research efforts.

Dr. Karr explained that once a concept has been developed by a working group, it is presented to the appropriate Board of Scientific Counselors. If the concept is approved by the BSC, then it continues to be processed through the NCI system and eventually is published in the NIH Guide to Grants and Contracts. The applications received in response to the announcements are reviewed by regular NIH study sections or ad hoc review committees that are established by the Division of Extramural Activities. Dr. Karr said that the NCI evaluates organ systems grants and funds them on the basis of the payline that applies to all other NCI grants.

As the communication center, the OSCC provides overall programmatic and administrative support and services for all components of the OSP. Dr. Karr said that the OSCC also supports the working groups in documentation of ongoing research and literature publications, as well as supporting their meetings and coordinating all of the groups' activities. He suggested that the OSCC is essential to the program because of its administrative flexibility, undiluted focus, and commitment to ensuring that planning activities and recommendations of the working groups are implemented with speed and proficiency. The OSCC publishes a newsletter, distributed free to over 8,000 subscribers, to keep the scientific public informed of ongoing activities and future plans. The newsletter includes contents of organ systems and other concepts, once they have been approved by a Board of Scientific Counselors, thus giving investigators advance notice of announcements.

In referring Board members to the Annual Report, Dr. Karr noted that a total of 23 concepts have been reviewed--12 were approved as RFAs and 8 as Program Announcements, and 3 disapproved. He stated that there still is some disappointment over the amount of time it takes for some concepts to get published in the NIH Guide after BSC approval. Dr. Karr then summarized the RFAs that were published during 1987:

- Bladder
  - Identification of genetic alterations involved in bladder carcinogenesis (13 applications received)
- Large bowel
  - Molecular probes in unique subsets of colorectal cancer patients (15 applications received; 3 to 4 will be funded)
- Pancreas
  - Prospective randomized studies correlating current treatment procedures with pain reduction in pancreatic cancer patients (15 applications received and none funded; RFA was revised and will be reissued)
  - Molecular approaches to pancreatic cancer research (9 applications received; 3 are expected to be funded)

- Prostate

  - Early diagnosis and quantitative assessment of prostate adenocarcinoma by ultrasonography (under review).

He referred the Board members to Appendix I of the Annual Report for a full description of the seven concepts that were approved by BSCs during 1987 but are not yet published. Dr. Karr stated that most of the concepts would require multidisciplinary expertise and some would require the collaboration of basic and clinical investigators.

Dr. Karr next focused attention on the OSP workshops, which have served to stimulate ideas and disseminate new information and technology. He pointed out that the Workshop on the Management of Prostate Cancer had resulted in a unanimous recommendation that four committees be established to address the inadequacies in the current system of grading, staging, disease evaluation and treatment response criteria, and statistical analysis of clinical studies. These committees have developed recommendations for publication and for consideration by the American Urologic Association and NCI. In addition, Dr. Karr said that the committees' reports directly support and address needs and deficiencies that were identified at the June 1987 NIH Consensus Development Conference on Treatment of Localized Prostate Cancer. An OSP workshop scheduled for January 1988, which cuts across all seven working groups, will provide a state-of-the-art overview of the technology for developing new markers and probes for diagnosis and prognosis. Other OSP joint activities that are under consideration include the development of a monograph on epithelial cell growth and a workshop to explore new approaches and unique targets for the detection, localization, and treatment of solid tumors.

As to future activities, Dr. Karr said that the working groups each had developed specific ideas that they propose to assess and develop in the next year. Each working group has four to five subcommittees that are working on the development of concepts. Dr. Karr noted that the issue of immediate concern was the December 3, 1987, hearing before the NCAB subcommittee to discuss the following:

- Reissuance of an RFA for an external coordinating center
- Dispersal of the OSP grants portfolio across the four NCI divisions
- Procedures for initiating and phasing out working groups
- Addressing the goal for the year 2000 for the organ systems.

He expressed the view that the last issue could be addressed quite easily because the working groups are involving experts in cancer control and the OSCC had already prepared a draft document on adding and eliminating working groups. He noted that NCI had received inquiries about establishing working groups on lung cancer, melanoma, and mesothelioma. Dr. Karr said that he hoped the December 3 meeting would focus primarily on the first two issues,

which will affect both the immediate future and the survival of the OSP. He questioned whether the elimination of an external coordinating center would weaken the program and suggested that the dispersal of grant portfolios would make the continuation of a comprehensive overview more difficult.

In conclusion, Dr. Karr assured the Board that the working groups are unanimous in their intent to support a strong and even a strengthened Organ Systems Program. He said that the testimony at the December 3 meeting would be both in support of continuing the existing structure and recommending means to strengthen and improve the overall effectiveness of the OSP.

The following points were raised in discussion:

- When RFAs are presented for concept review, documentation also is included on other existing research. The OSP RFAs tend to bring together several research areas that may be functioning independently of each other.

- To ensure better coordination of activities, all OSP workshops and working group activities are now being held in Bethesda.

- It is hoped that the working groups will become involved in the year 2000 goals and in the Clinical Trials Program.

XII. Approval of Minutes--Dr. David Korn

The minutes of the September 28-30, 1987, meeting were unanimously approved.

XIII. AIDS Research at NCI

Introduction and Overview--Dr. Vincent DeVita

Dr. DeVita began by emphasizing the need for frequent updates on AIDS research because the field is changing so rapidly. In 1981, when AIDS was first described as a disease, NCI sponsored a national meeting to discuss all aspects of the AIDS problem. In addition, a special task force was appointed in 1982 to consider NCI's role in AIDS research. The task force was chaired by Dr. Peter Fischinger with Dr. Robert Gallo as the scientific director and Dr. Samuel Broder as the clinical director; other intramural and extramural scientists were involved on an ad hoc basis. Some NCI researchers were studying retroviruses that were known to cause cancer in rodents. Dr. Robert Gallo at NCI and Dr. Myron Essex in Boston thought that AIDS had some of the characteristics of retroviral illnesses. Therefore, the goals of the NCI Task Force on AIDS were to 1) investigate the etiologic agent or agents for AIDS, and 2) try and improve the treatment of AIDS-associated conditions. The task force was dissolved in 1984 when the AIDS virus was discovered.

Dr. DeVita pointed out that NCI was involved early in the work on opportunistic infections because almost all of the opportunistic infections

that occur in AIDS patients also occur in immune-suppressed cancer patients. For example, pneumocystis carinii pneumonia, which occurs in many AIDS patients, was first described in lymphoma and leukemia patients.

Dr. DeVita said that when Dr. Gallo reported his findings on 45 isolates of the virus in 1984, it was clear that a diagnostic test would be the next breakthrough. Secretary Margaret Heckler announced at a press conference that the virus that caused AIDS had been identified and that a diagnostic test would be available in 6 months. The latter announcement was intended to open competition for the transfer of the technology to the private sector. In fact, the test was available in 9 months. Secretary Heckler also said that there would be a vaccine available for early testing within 3 years. Although this goal has also been met, some people had interpreted this statement to mean that there would be an effective, generally applicable vaccine within 3 years. Dr. DeVita pointed out that vaccines are now available for testing, but it remains uncertain whether a vaccine can be developed that will be effective against AIDS.

Because a number of people in different places in NCI were working on AIDS, two subcommittees were formed, which later were combined to form an advisory committee. The subcommittee of the DCT Board of Scientific Counselors was chaired by Dr. Dani Bolognesi and the subcommittee of the DCE Board was chaired by Dr. Hilary Koprowski. In 1984, the two subcommittees were combined into the AVIS committee, which tried to map out appropriate areas of research for NCI. Dr. DeVita said the committee sought and received assurances from him that NCI would not withdraw from AIDS research. The committee established a series of programs, which because of the speed required, were issued as subcontracts from FCRF. These contracts, totaling about $6 million, were primarily for the identification of materials and animal systems for potential models to be used for drug and vaccine development.

In describing the NCI budget for AIDS, Dr. DeVita said that it had increased from about $2.4 million in 1982 to the projected FY 1988 level of $93.9 million, which is 6.9 percent of the total NCI budget. He expressed doubt that there would be any decrease in the AIDS budget. Initially, funds (about $9 to 10 million) were transferred from cancer programs into the AIDS research program, but since about 1985 all of the money for AIDS has been new money, including some supplemental appropriations from Congress. Dr. DeVita pointed out that NCI's share is a decreasing fraction of the total amount for AIDS research--approximately $93.9 million out of $442 million for NIH in FY 1988. He noted the preponderance of contracts, which is related to the requirements of the drug development program. In FY 1988, the major emphasis again will be on therapeutics ($40 million), with substantial amounts in vaccine development and basic biology. Dr. DeVita said NCI's role in AIDS epidemiology is decreasing as more epidemiologic studies are being undertaken in other Institutes or agencies.

Dr. DeVita described NCI's relationship with the National Institute of Allergy and Infectious Diseases (NIAID) as very strong and close, with scientists working together in an atmosphere of healthy scientific competition. He noted that NIAID's need to expand was accommodated through a

facility at FCRF. The drug development program is a joint effort that started with a single committee to oversee both the preclinical and clinical components of the program. Dr. DeVita stated that it had been agreed upon from the beginning that NIAID would have the responsibility for clinical development and NCI for preclinical development. There is now a committee to focus on clinical development through the AIDS Therapy Evaluation Units (ATEUs) and one to focus on preclinical development in the Cancer Institute's program. A memorandum of understanding was signed to provide that if the screening program for antiviral agents was still needed in 1992, it would be transferred from NCI to NIAID. Dr. DeVita suggested that part of NCAB's function is to monitor the program and its transfer, if that should occur. He emphasized that the AIDS drug development program is a separable program, and he also noted that the National Cooperative Drug Discovery Group (NCDDG) program, a grant program, was transferred to NIAID. In addition, NCI has sought to consolidate most of its AIDS program in one area, which was exemplified by the transfer of Dr. Gallo's laboratory to DCE.

In conclusion Dr. DeVita enumerated the following issues for the NCAB and its AIDS Subcommittee to consider:

- Scientific content and breadth of the AIDS research program
- Extent of NCI's collaborations with other agencies and the private sector
- Technology development
- Management and transfer of programs
- Benefit of AIDS research to cancer research
- Impact of AIDS research on cancer programs.

The following points were raised in the discussion:

- The Federal government has been generous in allocating money for AIDS research, and the field is moving extremely rapidly.
- Up to now, new money for AIDS research has not meant that less money has been provided for other NIH research.
- The Centers for Disease Control (CDC) has responsibility for AIDS education; NIAID and CDC are undertaking epidemiologic studies.

<u>Basic Biology--Dr. Robert Gallo</u>

Dr. Gallo began his overview by showing a slide of the known retroviruses and explained that a fifth retrovirus has been identified by Dr. Vittorio Manzari in Rome. HTLV-1 and 2 are associated with leukemia and HTLV-3 (HIV-1) and 4 (HIV-2) are associated with immunodeficiency. Dr. Gallo said that HTLV-2 appears to be limited to western Africa and pilot studies in

England, Italy, and the United States have not revealed a significant spread of the virus. Epidemiologic studies indicate that HTLV-2 is not a new virus, and the majority of those infected with the virus are healthy. Dr. Gallo emphasized that although HIV-1 and HIV-2 are 50 percent related, attention should be focused on HIV-1 as the etiologic agent in AIDS. He pointed out that any human retrovirus infecting T4 lymphocytes is capable of causing some immune deficiency. There does not appear to be evidence that there are individuals with genetic resistance either to infection with the virus or to progression to disease.

Dr. Gallo said it is known that the human retroviruses are very closely related to monkey retroviruses. The retroviruses infecting African green monkeys and other old-world monkeys and chimpanzees are about 95 percent identical to HTLV-1. Dr. Gallo suggested that all human retroviruses may have their counterparts in old-world subhuman primates. He said that he has identified another retrovirus in some people in Nigeria, which is immunologically distinct from other retroviruses but not as yet characterized. Although this retrovirus was first identified in healthy people, it also has been found in a few people with immune deficiencies.

Dr. Gallo said another new retrovirus, HTLV-5, was identified by Dr. Manzari (University of Rome) in a subset of classical cutaneous T-cell lymphoma, mycosis fungoides. Malignancies associated with HTLV-1 and 2 are usually tac positive, while HTLV-5 is associated with tumors that are tac antigen negative (interleukin-2 receptor negative).

Dr. Gallo next summarized the information on the other four known retroviruses. He said there are strong epidemiologic data linking HTLV-1 to neurologic disease, tropical spastic paraparesis (TSP) or HTLV-1-associated myelopathy. Recent data indicate that the disease is an encephalomyelopathy, and in some cases, it is clinically and pathologically impossible to distinguish this disease from multiple sclerosis. One suggested pathogenetic mechanism is a class II HLA DR pattern that is associated with neurologic disease and that results in much more virus replication, higher antibody responses, and leads to an autoimmune neurologic disease. Dr. Gallo suggested that HTLV-1 may turn out to be more important as a neurologic disease virus than a leukemia virus. HTLV-1 is also associated with T-cell chronic lymphocytic leukemia and may have an indirect role in enhancing the development of B-cell lymphoma.

Dr. Gallo said HTLV-2 was first reported from a T-cell variant of hairy cell leukemia. Approximately seven isolates of the virus have been identified from a chronic T4-cell lymphoma, a T-cell chronic lymphocytic leukemia, and a hairy cell leukemia in which the virus is found in the T cells but not in the B cells. Dr. Gallo said there is no immunologic assay to rapidly differentiate between HTLV-1 and 2, which is a limitation of epidemiologic studies.

The AIDS virus, HIV-1, causes central nervous system disease as well as immune deficiency. In addition, it causes enhancement or increased incidence of B-cell lymphomas, Kaposi's sarcoma, and some other malignancies. Dr. Gallo indicated that the data relating HIV-2 to immune deficiency may be

overstated. He noted the importance of knowledge about the life cycle of retroviruses in developing antiviral therapy and said that the AIDS virus appears to have a replication cycle like other retroviruses. The replication cycle involves entry of the virus into the cell, integration within the cell, and then expression of the virus. Dr. Gallo suggested that blocking the entry of the virus offered an interesting prospect for the future control of the virus. He reported that there is consensus among those who work with the virus that early treatment is important.

Dr. Gallo cited as a peculiar characteristic of the HIV-1 virus the envelope affinity for binding to the receptor, the CD4 component of the T4 molecule. The binding of the gp120 to the CD4 is much tighter than any known for other retroviruses, which may be one of the reasons for the immune deficiency. The unique characteristics of the AIDS virus appear to be that a great amount of virus is liberated in a short period of time when the T cell is immune-activated and the envelope of the virus binds tightly to the cell membrane receptor. Dr. Gallo said several researchers are investigating the use of the soluble T4 molecule to bind to the virus so that it does not find its receptor on the cell membrane, thus blocking entry.

After penetration, the viral RNA is transcribed by the enzyme reverse transcriptase, eventually producing a double-stranded DNA and an integrated form of virus. Dr. Gallo said that the reverse transcriptase and accompanying protease are natural targets for intervention. AZT acts at this level as an analog or antimetabolite for the normal nucleotide dTTP. Dr. Broder and others are working to develop other analogs that are likely to interfere at this step but are less toxic than AZT.

Dr. Gallo said that it is suspected that in the future greater advances will occur from interfering with expression of the virus. This is because the genome of the virus contains extra genes that appear to be essential for the virus life cycle. Dr. Gallo pointed out that animal retroviruses characteristically have three essential genes, but a new gene called tat was discovered with HTLV-1 and 2, and there is evidence that the product of this gene is probably necessary for the immortalizing activity of T cells by the retrovirus. Dr. Gallo said that it appears that the product of the tat gene acts to promote the activity of genes that promote T-cell proliferation, including interleukin-2 and its receptor. HIV-1 was found subsequently to have a gene functionally analogous to tat of HTLV-I, but mapped to the middle of the genome instead of near the 3' end. Dr. Gallo explained that although its sequence and mechanism of action are different, this gene has been found to be essential for the replication of the virus. He said the surprise was that many other genes were found in the genome of the AIDS virus. Although their exact functions are not all known, it is known that most of them are involved at the level of RNA transcription and processing. Dr. Gallo suggested that because the protein products of the trs and tat genes are absolutely essential for viral replication, and because there may not be exact analogs like them in normal cells, it may be possible to selectively block virus formation by interfering with the function of these genes. Toward that end, investigators are trying to make enough of the protein to crystallize and then develop a model to predict what kind of drugs

would interact with active sites of this protein. Dr. Gallo pointed out that HIV-2 has almost the same genomic organization as HIV-1.

Next Dr. Gallo summarized the epidemiology of human retroviruses and identified two conclusions that can be drawn from these data: humans can be infected with more than retrovirus, and patterns of infection vary with regard to time, place, and population. He noted that in some areas of the United States, testing for HTLV-1 infection may be more important than testing for HIV because it is a relatively common infection in certain groups. Some studies have indicated that 1 percent of the people infected with HTLV-1 will develop leukemia. Dr. Gallo identified another point derived from the epidemiology as the overwhelming importance of the AIDS virus in Africa and among intravenous drug users.

Dr. Gallo showed maps of Central Africa to demonstrate areas having the greatest concentration of viruses and the distribution of monkeys. The HTLV-1 retroviruses seem to be distributed in the greatest density in the regions that have the most monkeys, especially the African green monkey. Dr. Gallo said it is not known where the AIDS virus originated, but old sera were positive for the virus in Central Africa. He stated his views that the virus is not new in humans but is a variant of old virus and that the present day epidemic is probably occurring because of socioeconomic changes, which resulted in migrations to large cities with associated increases in prostitution. What is known with certainty is that the virus spread rather explosively in the 1970s and 1980s.

Dr. Gallo next described the modes of transmission of retroviruses. HTLV-1 can be transmitted from mother to child through milk. The AIDS virus is both heterosexually and homosexually transmitted and appears to be more readily transmitted from man to woman. The mode of transmission in laboratory workers who have become infected is not known. Dr. Gallo suggested the presence of dermatitis and infection of the macrophage Langerhans cells of the skin as possibilities. He stated that epidemiologic studies provide no evidence that the virus can be transmitted by insects or casual contact.

When the virus infects and replicates, there is viremia and Dr. Gallo said that most people have a prompt immune response, which includes both cellular and humoral immunity. However, even with relatively high titers, the neutralizing antibodies are not effective. Dr. Gallo pointed out that with time, there sometimes is a drop in both cellular and humoral immunity, and in the declining clinical stages of disease, this drop in immunity can be associated with a return of viremia, which is often found in the final stages of AIDS. He stated that in his view the P24 antigen assay is very good but may not be sensitive enough to detect virus in the blood without antibody. It has been found that macrophage and related cells can be infected, and minor changes in the envelope gene can affect the ability of a variant of the same strain of virus to infect the macrophage versus the T cell. Dr. Gallo noted that a laboratory worker was found to be infected with a macrophage virus, although the viruses that the person was working with were very poorly macrophage-tropic. Apparently a selection occurs of some minor variant in the population that is macrophage-tropic. Dr. Gallo said it

is suspected that the macrophage is one of the earliest cells infected and is an important reservoir for the virus because it is not as easily killed as the T4 cell and virus particles are contained within the cell vesicle. An important question to be answered is whether the spread of the virus is promoted if the macrophage is smashed, releasing virus particles. Dr. Gallo stated that it is also thought that it is the macrophage that brings the virus to the brain and is the virus's major target in the brain.

In describing the mechanism of cell killing, Dr. Gallo said that when a T4-infected lymphocyte is immunologically triggered, the virus is expressed and cell death follows soon thereafter. Whether cell death requires virus expression is not known for certain, although Dr. Gallo said there is a strong correlation. The virus also can lead to a decline in the population of T4 cells by other mechanisms such as cell fusion. A fusion peptide from the viral envelope expressed from the cell membrane allows one cell to fuse to another and form giant, multinucleated cells that have a short lifespan. Another possible mechanism for depletion of T cells is that virus-infected cells release protein or peptide that can inhibit T-cell proliferation, as well as the proliferation of granulocytes and macrophages. Dr. Bolognesi and his colleagues from Duke University have found antibody-dependent cell killing. Free envelope of the virus binds to the receptor on an uninfected cell that is attacked by antibodies. Dr. Gallo noted that this could be an important way of depleting the T4 population without all cells being infected.

In discussing cancers associated with AIDS, Dr. Gallo reiterated NCI's expertise in retrovirology and T-cell biology, and he also pointed out that information from AIDS research will be beneficial in the study of basic immunology, cell biology, and cell proliferation. However, an important point is that AIDS is an epidemic of malignancy--specifically B-cell lymphoma and Kaposi's sarcoma, which are both associated with HIV infection. Dr. Gallo stated that the pathogenesis of B-cell lymphoma in AIDS appears to be parallel to African Burkitt's lymphoma. About 60 to 70 percent of B-cell lymphomas in AIDS patients are Epstein-Barr virus (EBV) genome positive, and these same cases have the myc proto-oncogene translocation as in Burkitt's lymphoma.

Dr. Gallo remarked that about 2 years ago he had reported a new herpes virus, HBLV-6, which genomically is only slightly related to the other human herpes viruses and immunologically is weakly or not cross-reactive with human or monkey herpes viruses. In the laboratory, it is possible to infect cells other than B lymphocytes with the virus. These cells include megakaryocytes, certain subsets of immature T cells, and glial cells. This virus has been found in patients with B-cell lymphoma and Burkitt's lymphoma. Dr. Gallo said that the significance of findings of seroprevalence rates up to 82 percent of sera from some groups of patients suffering from "chronic fatigue syndrome" is still unclear.

In turning to discussion of Kaposi's sarcoma, Dr. Gallo stated his view that it may not be a full-fledged malignancy, at least in many of its stages. Kaposi's sarcoma occurs as 1) the classical type in older Mediterranean males; 2) the endemic type in Africa; 3) the iatrogenic type in

people who have been made immune deficient; and 4) the type associated with the HIV epidemic. Dr. Gallo said that like Hodgkin's disease, Kaposi's sarcoma includes many different kinds of cells, including endothelial cells, fibroblasts, spindle-shaped cells of unknown origin, and new blood vessel formation. He also pointed out that Kaposi's sarcoma is more prevalent in homosexuals than in other HIV-positive groups, according to the Centers for Disease Control. A new growth factor has been found that when it is added to Kaposi tumor cells causes the cells to grow rapidly. The mixed population of Kaposi's cells produces this growth factor, interleukin-1, endothelial cell growth factor, fibroblast growth factor, and other biologically active substances that together explain all the clinical features of Kaposi's sarcoma. Dr. Gallo stated that a virus has not been found, which points to the conclusion that Kaposi's is a growth factor-driven phenomenon and at least in its early stages is probably not a true malignancy. He suggested that Kaposi's sarcoma involves a multicentric growth factor-dependent proliferation of nonimmortalized cells and that theoretically it may be controllable by interfering at the early stage of the disease.

As his final topic of discussion, Dr. Gallo addressed AIDS vaccine development. The source material is not expected to be the whole virus; rather, investigators are working with envelope or envelope fragments and core proteins. He identified the limited availability of animal models as an important problem, which has adversely affected testing of materials. Although there is a simian immunodeficiency virus (SIV), Dr. Gallo said it is 50 percent or less related to HIV and may not work in exactly the same way. The testing of candidate materials is initiated in small animals with the purpose of trying to develop neutralizing antibody in a T-cell immune response. When a positive response is obtained, the material is tested in a chimpanzee. If there is a positive response in the chimp, then the animal is challenged with virus to determine whether there is protection. Dr. Gallo stated that to his knowledge, no one has been able to achieve protection of a chimp from a single strain of the virus.

Another important problem in vaccine development is the variation in the virus that occurs among patients and even within patients. Dr. Gallo showed a restriction endonuclease map of viral isolates from a single patient over 3 years and pointed out several minor changes in the virus. He said that these minor variations appear to be very important because they can lead to an inability to neutralize the virus. However, there are constant regions on the viral envelope that may be useful in developing a vaccine that works against all strains of the virus. Dr. Gallo noted, for example, a region that is believed to be necessary for the virus to bind, a region or epitope where cellular immune response occurs, and a region that induces type-specific neutralizing antibody. In conclusion, Dr. Gallo expressed the hope that continued progress in fundamental research on the nature of the viral proteins and the immune response will lead to the development of a vaccine.

In discussion, the following points were raised:

- Macrophage-activating agents may have some activity in tissue culture systems on HIV infection.

- After inoculation of chimps, viremia occurs, even with very small doses, within 4 weeks.

- More than one strain of virus has not been found to occur in humans, which may indicate some immunity against additional infections.

- An antibody present before the virus gets into the genome may confer some immunity to the virus.

- Studies are in progress to try and relate the quantity of the dose to infectivity in vivo.

- The AIDS and leukemia viruses imitate in vitro the diseases they cause in vivo.

- It is now thought that about 30 percent of the individuals infected with the HIV-1 virus eventually get the disease.

- Considering every cancer in every age group, the amount of cancer that may be the result of HIV and HTLV-1 infection is probably about 1 percent but may increase in the future. In certain areas such as New York City or San Francisco and among the 20- to 40-year-old age group, particularly among males, perhaps 20 to 40 percent of cancers are related to the AIDS virus.

- Data are insufficient on whether a person who was antibody positive can become antibody negative.

- Genetic studies in Japan have suggested that some individuals respond to HTLV-1 infection with much more virus replication and much greater immune response, which is associated with the development of a neurologic disease that is similar to multiple sclerosis.

- Domestic animals do not become infected with the HIV virus.

- It may be useful, from an intervention standpoint, to study the possibilities of selective T-cell killing or of selected blockage of the receptor with fragments of the antibody.

- Many persons with AIDS also are infected with EBV, which may add to the AIDS immune deficiency.

- Other laboratories have isolated thymidine kinase from HTLV.

Epidemiology--Dr. William Blattner

Dr. Blattner illustrated the distribution of AIDS cases through various subsets of the U.S. population and within various geographic locations. In addition to the homosexual male population and the

heterosexual drug abusers in certain urban areas, there are secondary epidemics of AIDS among hemophiliacs and blood transfusion recipients, and the subsequent emergence of the disease among the heterosexual population. Geographically, the mid-Atlantic area was the first to have experienced the epidemic, followed by the West Coast and then other parts of the country. He noted that, while this pattern is emerging in the United States, Europe, and Australia, a different pattern is evident in developing areas, such as in Central Africa, the Caribbean Basin, Trinidad, and South America. In these countries, the pattern suggests a major role for heterosexual spread of the disease.

Dr. Blattner conveyed the hopeful news that the incidence of transfusion-associated AIDS in the pediatric age group seems to have peaked, due to the progress made in screening and blood tests. Unfortunately, the incidence of pediatric cases is increasing, particularly in the AIDS epicenters such as New York and New Jersey, which have a larger representation of drug abusers, and in Florida with its large representation of immigrants from the Caribbean, especially Haiti.

It is often difficult to track the incidence, onset, and progression of the disease in these high-risk subpopulations. For most of them, it is not known when they became seropositive; thus, the latency time for the development of AIDS cannot be ascertained. Dr. Blattner stated that the hemophiliac population, many of whom were exposed to the AIDS virus in the early 1980s through infectious lots of Factor 8, is being studied. They have a relatively narrow window of time for seroconversion and allow for close monitoring and counseling with regard to the disease. He presented data that suggest that there may be host factors that are age-dependent in the development of the disease. Data from the hemophiliac population also suggest that the risk factor for the development of AIDS may be different--lower--for this population than for other infected populations. In response to questions and comments from the Board, Dr. Blattner agreed that this apparent risk factor difference may be tempered by other factors, such as the viability of the virus that was introduced into the hemophiliac population and the age differential between the hemophiliac and the homosexual cohorts in light of the age cofactor evidence.

Dr. Blattner stated that, by determining particular behavioral risk factors for seroconversion, the population at risk can be counseled to reduce the risk. Because of the geographical differences in the incidence of the disease, behaviors that have been shown to promote infection or seroconversion in an AIDS epicenter can be guarded against and perhaps modified before the disease can spread within other population areas. Regarding seroconversion of laboratory workers, Dr. Blattner said that considering the very few cases of seropositives, it would appear that the laboratory protocols for biosafety level 3, if carefully and consistently followed, provide an adequate margin of safety against infection. A study of persons who experienced a needle stick is being conducted by CDC to obtain more information with regard to the transmission of the virus among health care workers.

Dr. Blattner then described a phenomenon that has been observed in AIDS development: in the earlier stage of seropositivity, there is a loss of about one T4 cell per cubic millimeter per month. However, about one to one-and-one-half years before the clinical development of AIDS, the pattern abruptly shifts into an accelerated T4 cell loss, which is equal to about one cell per cubic millimeter per day. This ultimately manifests itself as clinical AIDS. The data also suggest that this shift may correlate with an increase in the infectivity of the infected person to another person. This theory is supported by a study of 34 wives of seroconverted hemophiliacs who continued to have unprotected sexual contact with their husbands; they remained immune to the virus for several years but four seroconverted within a 1-year span, which coincided with the decline in the immunological states of their husbands. This hypothesis offers hope that if the accelerated T4 cell loss can be delayed, the extent of the infection may be arrested.

Another area of epidemiologic research discussed by Dr. Blattner was the role of certain immunogenetic factors in the susceptibility of various populations to AIDS. A study by Dr. Mann and Dr. Goedert of NCI identifed that HLADR-1 is associated with accelerated progression to AIDS. The study was conducted in Trinidad where there are two populations--black and Asian-Indian. There is a significantly higher rate of AIDS in the black population; this may be correlated with the presence of the DR1 haplotype in blacks and its absence in the Asian population.

The last topic of discussion dealt with cancers associated with AIDS. Kaposi's sarcoma has been shown to be associated, although the rate of cases may be declining. Dr. Blattner stated that other tumors are emerging as possible AIDS-associated cancers, such as non-Hodgkin's lymphomas, hepatomas, ano-rectal cancers, and cancers of the pancreas and tongue. In closing, he commented that the study of these associated cancers in followup of treated HIV-infected persons, who are immunocompromised but long-term survivors, may provide an excellent opportunity to gain insights into the etiology of the cancers.

Other points raised in discussion included the following:

- There is a bimodal pattern in AIDS development that relates to age--there is an early peak in newborns and then a slower rate in older age groups.

- It is possible that the period of natural immunity may be due in part to changes in the virus, as well as critical events in the ablation of the immune system.

- The cause for the difference between heterosexual transmission in Africa and in the United States is not clear, but it may be related to the presence of cofactors such as venereal disease.

<u>AIDS Drug Development--Dr. Michael Boyd</u>

Dr. Boyd referred the Board to a packet of materials distributed, which outlined the preclinical drug development program for AIDS and included

background information such as a chapter from an upcoming book edited by Dr. DeVita, AIDS: Etiology, Diagnosis, Treatment, and Prevention; a verbatim transcript of the NCI/NIAID workshop on issues for implementation of the national anti-HIV drug development program; and handouts describing the operational aspects of the program. He acknowledged the dedication of DTP staff who were involved in implementing the program, particularly Drs. Owen Weislow and Robert Shoemaker.

Dr. Boyd explained that the components of the overall goal to implement a preclinical drug development program for AIDS had been "piggybacked" onto the NCI anticancer drug development program, with key NCI managers assuming parallel responsibilities in the AIDS program. He outlined the main program components, including acquisitions, biological testing, chemical synthesis and bulk drug production, preclinical pharmacology and toxicology, and clinical formulation, production, and quality control of the bulk materials used in clinical trials. He further explained that the program is divided into several phases: a discovery phase that encompasses the acquisitions of materials for biological testing; a preclinical development phase, Stage A, for feasibility evaluations; and a further preclinical development phase, Stage B, for full preclinical development and commitment to clinical trials. He stated that the program operation is accomplished predominantly through specific AIDS-designated contracts that parallel those for the anticancer drug development program.

Dr. Boyd described the four key DTP committees involved in managing the drug development system, as follows:

- Acquisitions Input Committee, which oversees the input and prioritization of materials for screening

- Biological Evaluations Committee, which evaluates the output of the screen and provides data on active compounds to the Decision Network Committee

- Decision Network Committee, which is chaired by Dr. Chabner and includes all DCT Associate Directors, chairpersons of the key DTP committees, key representatives from NIAID and invited ad hoc experts as members and is the key decision-making body of the program

- Operating Committee, which ensures the efficient flow of compounds through the drug development system.

Dr. Boyd stated that initial efforts for implementing the large-scale screening program have focused on primary AIDS antiviral agents and chemotherapeutic agents. Compounds that are currently undergoing Stage B preclinical development include dideoxyadenosine and dideoxyinosine. Castanospermine, a natural product from the Moreton Bay chestnut, is undergoing Stage A development. Dr. Boyd emphasized that although the mechanism of action (e.g., interference with reverse transcriptase) of the agents under development was largely unknown, the screening program identifies interesting compounds with the desired endpoint biological

activity and provides information that may eventually lead to an understanding of their biological mechanisms of action. He stressed that biological testing is an important support to the process of drug discovery through screening. He explained that the large-scale AIDS antiviral screen was needed to supplement the limited number of existing laboratories that perform tests for anti-HIV activity; provide uniformity of test systems, protocols, and criteria; and provide screening capacity under safe conditions.

Describing the screening effort in more detail, Dr. Boyd explained that the microculture tetrazolium assay technology was adapted for anti-AIDS screening from the anticancer drug screening program, which is undergoing further development. Anti-AIDS screening has been implemented at the Frederick Cancer Research Facility and under contract at the Southern Research Institute in Birmingham, Alabama. The screening strategy involves in vitro primary screening with one or more human host cells with or without infection with the AIDS virus and use of the endpoint assay as a determinant of the effect of the drug on the virus. Some new approaches to in vivo model systems (i.e., human host cells in an animal model) are also being developed for possible use in preclinical toxicology and pharmacology studies.

Dr. Boyd briefly reviewed the chronology of the development of the large-scale anti-AIDS screening system from concept approval by the DCT Board of Scientific Counselors through achievement of the current screening capacity of approximately 240 to 300 compounds per week. He stated that the development of the large-scale screen had involved evaluation of use of several potential host cells, including ATH8 and MT-2, the cell line upon which the current screen depends. He noted the hope that future screening would involve several host cell lines, as the evidence suggests that individual drugs produce different patterns of activity, depending on the host cell line that is used for evaluation.

Dr. Boyd then outlined the two screening protocols. One utilizes virus-infected carrier cells to infect the host cells, and the other uses the intact virus without the carrier cells to infect the host cells. The endpoint assay, which is the same for both protocols, is based on colorimetric quantitation of metabolism of a colorless tetrazolium derivative to a colored product. Illustrations of the assay plates, with examples of this quantitative measure, were shown. Dr. Boyd projected that once the facility for the screen is completed at the FCRF, screening capacity should be approximately 500 compounds per week or 24,000 compounds per year against one or more host cell lines.

Turning to the ongoing development of a novel in vivo model system, Dr. Boyd noted that a good model should employ those human host cells that are infected by human virus in an appropriate animal system. This approach would allow the evaluation of candidate agents that require in vivo metabolic activation. Outlining the current research on such models, Dr. Boyd described ongoing efforts at FCRF to adapt the microencapsulated human tumor assay methodology from the cancer program to the antiviral screen also at FCRF. He illustrated the process for encapsulation of tumor cells and noted

that because the microencapsulation process generates an aerosol, development with AIDS-infected cells requires considerable containment procedures. He also pointed out that these endpoint assays--for antitumor or antiviral effect--measure growth modulation.

Turning to the acquisitions program component, Dr. Boyd emphasized the very broad range of sources of materials, including the NCI chemical repository of an extensive variety of organic molecules acquired by the cancer program. He stressed the importance of assuring confidentiality to the original supplier on the structure of the materials as well as the biological data derived from testing. He stated that data transfer to suppliers is accomplished as quickly as possible after testing is complete, with the current turnaround time from the receipt of material for the AIDS antiviral screen to data transfer to suppliers being approximately 6 to 8 weeks.

Dr. Boyd then described the new Natural Products Program that was implemented for the anticancer drug development program and its application to the anti-AIDS program. He outlined the areas of emphasis for worldwide collection of plant specimens, marine organisms, unusual microbes, fungi, cyanobacteria, and algae under NCI-funded contracts. He emphasized the underlying importance of establishing a repository of materials at the FCRF to serve as a library of source materials for evaluation in the current and future anticancer, AIDS antiviral, and other screening systems. He also described several collection sites and the extraction and storage facilities that are under development at the FCRF. He noted that the voucher specimens will be housed, in part, at the Smithsonian Institution.

In discussion following Dr. Boyd's presentation, the following points arose:

- High-priority compounds for AIDS antiviral screening include products of the rational drug design program, crude natural products, and drugs that are active against other viruses.

- The importance of querying the suppliers of pure materials about whether the submitted compounds can be tested in both the anticancer and antiviral screens was stressed.

- While the current anti-AIDS screening system focuses on the evaluation of compounds for antiviral activity, other models may provide additional important information other than that on antiviral activity. To that end, there is considerable ongoing grant-supported research, as well as research within the Drug Discovery Groups and the intramural structural biology group.

- There was general agreement that the initial efforts to combat AIDS should focus on antiviral chemotherapy as opposed to stimulation of the immune system.

- The grants for the AIDS Drug Discovery Groups, awarded in 1985, were transferred to NIAID in 1986.

Clinical Trials--Dr. Samuel Broder

In addressing the question of why NCI should be involved in AIDS research, Dr. Broder pointed to the scope and urgency of the problem from a public health perspective, NCI's expertise in human retroviral research, the occurrence of cancer as a common feature of AIDS, and the probability that AIDS research will shed light on the relationship between immunodeficiency and cancer. He also suggested that some drugs emerging from AIDS research will find a specific role for the treatment of certain cancers per se, as well as for their activity as suppressors of retroviral replication. Dr. Broder then proceeded to describe some of the target stages of replication of the human AIDS virus that may be susceptible to therapeutic intervention, with examples of work being done in the intramural program.

The first stage discussed by Dr. Broder was the binding of the AIDS virus to the target cell. The virus has a special affinity for at least one receptor site defined by what is called the CD4 antigen. Dr. Broder said this determinant is expressed on a class of helper T cells, and while there may be other sites where the virus can attack a target cell, this appears to be a very important one. He stated that it is possible that antibodies to the virus or the cellular receptor and certain defined drugs could interfere with the binding process. The actual CD4 receptor itself, genetically engineered, may constitute a potential drug for intervention against the virus. Dr. Broder said that it is theoretically possible to make high-affinity mutations of the CD4 receptor to improve upon the natural affinity of the retrovirus to the binder receptor. In addition, it may be theoretically possible to create a chimera or pseudoimmunoglobulin which is a new molecule created from the CD4 receptor or a portion thereof.

Dr. Broder stated that the precise mechanism by which the virus enters a cell is still under study, but it appears that a fusion event is necessary in which part of the virus membrane fuses with the target cell, thus permitting the virus to enter a susceptible target. Citing the analogy of calmodulin, an antagonist for the Epstein-Barr virus in some systems, Dr. Broder said it is conceivable that a drug could be developed to interfere with the early entry events or perhaps the uncoating by which the viral RNA becomes free of its outer shell. The viral RNA contains the genetic information necessary for the virus to continue its assault on the cell. Dr. Broder suggested that the process of the transcription of RNA to DNA, first postulated by Dr. Howard Temin, offers an important opportunity for a direct attack on the virus. Reverse transcriptase is known to be necessary to convert the genetic information of RNA and DNA, and Dr. Broder pointed out, a number of reverse transcriptase inhibitors are now or soon will be available. He described the reverse transcriptase as a very tempting target for therapeutic intervention. AZT, for example, has been developed on the basis of its capacity to inhibit reverse transcription.

Dr. Broder cited the next stage in viral replication as the process of degrading the RNA. Once it is complexed as a DNA/RNA hybrid, the original genomic RNA of the virus is destroyed so that the virus can then effectively make a single and double strand of DNA of itself. Dr. Broder explained that this is an enzymatic activity, which is encoded by the same region (pol) that

encodes reverse transcriptase but in a slightly different domain. He said it was possible that an enzymatic inhibitor could be developed to inhibit this unique RNase activity responsible for the degradation of RNA.

Dr. Broder speculated that it is also theoretically possible to attack the integration of the proviral DNA, once it is formed, into the host genome. While it is unclear how clinically important this integration is, it is clear that the AIDS virus has the capacity to integrate into host cells. Dr. Broder said that in the future it may be possible to specifically block pol genes, the genetic region necessary for synthesizing the relevant enzymes, from becoming expressed. The pol encoded integrase function could be inhibited, thus interfering with retroviral replication. Dr. Broder pointed out once a virus is in a cell, its replication requires transcription back to RNA. Certain products may be able to inhibit the special regulatory genes that are essential for this process. The genes defined to date are tat-3 and art or trs. Dr. Broder noted that the tat-3 gene has a specific target site on RNA where it must bind, and it is conceivable that snythetic products could be made that would bind to the tat region. He suggested that such a product might be an anti-sense construct which anneals or binds to the RNA of the virus in such a way as to permanently or significantly inactivate the message encoded in the viral RNA.

In addition, Dr. Broder mentioned the process of ribosomal frame shifting, meaning that the virus shifts frames and produces the gag/pol polyprotein. This process does not appear to be associated with physiologic gene expression in mammalian cells and, therefore, Dr. Broder said it may be conceivable to develop frame shift inhibitors that are very specific for retroviral replication.

The process of viral component production and assembly also was identified by Dr. Broder as possibly amenable to inhibition. If the special proteases that allow large components of core proteins to be reduced to smaller components could be inhibited, it is possible that the virus would not be able to continue the orderly process of assembly.

The last process described by Dr. Broder as a possible target for intervention was viral budding. The virus must pinch off and be released from the infected target cell to continue the cycle of retroviral replication, thereby infecting new cells. Interferons may be effective at this stage, or perhaps Dr. Broder suggested, antibodies to a viral antigen could be constructed that would interfere with or actually kill cells as they expressed the virus.

Dr. Broder stated that many of the ideas he had presented had already been translated to the clinical level or were nearing a level where they could be tested in humans in the near future. He noted a screening test developed by Dr. Hiroaki Mitsuya in his group that made possible the rapid and effective development of AZT. On the basis of the screening test, it was established that AZT was able to protect highly sensitive T cells from infection with HTLV-3b. Dr. Broder pointed out that different results may be achieved with very low viral loads. He said he would not discuss screening

per se, but instead would focus the discussion on a few types of drugs likely to yield early practical gains.

Dr. Broder explained that thymidine is a normal starting building block of DNA, and an analog of thymidine with an azido group in the erythro configuration at the 3'-carbon, azidothymidine or AZT, has been shown to have clinical efficacy. AZT was first synthesized by Dr. Jerome Horowitz in 1964 when retroviruses were not known to exist. Dr. Broder said that the concept of using a structural functional correlation also can be used with other nucleoside analogs, such as cytidine. Dideoxycytidine alone or in combination regimens is being tested. He emphasized that an azido group cannot be assumed to be appropriate for all analogs, but it seems to be especially important in the thymidine series. All of these drugs in either the purine or pyrimidine series require anabolic phosphorylation for activation. Dr. Broder said testing of dideoxyadenosine would begin in the near future.

Dr. Broder next discussed the concept of chain termination within the context of drug development. The virus incorporates a false building block as it attempts to go from RNA to DNA and that false building block is incapable of forming a linkage in the newly growing chain of DNA at the 5'-position causing the virus to be unable to continue the process of elongation. He said that mechanism is still under investigation, but it appears from preliminary data that the virus cannot repair a mistake if it incorporates the wrong nucleotide into a growing chain of DNA.

Dr. Broder stressed that the drugs he was discussing are not uniquely active against the currently understood AIDS virus, but would be active against all retroviruses, provided that the target cell has the ability to activate the drugs. These drugs cannot be active without an appropriate set of cellular enzymes that need to be put on phosphate esters. Dr. Broder stated that if the correct target is chosen, these drugs can be shown to be active against a new strain of human immunodeficiency virus called HIV-2. In tests with other viruses--lentiviruses, eg., caprine arthritis and encephalitis viruses--both dideoxyadenosine and dideoxyinosine can suppress viral replication. He pointed out that unlike some purine analogs, dideoxyadenosine can be deaminated to an inosine product and still have activity. It appears that dideoxyadenosine can be deaminated inside a cell, become dideoxyinosine, and then become a prodrug of itself.

Dr. Broder noted that both the structural functional relationships and the pattern of activation are important considerations in drug development. AZT has a Km for thymidine kinase of approximately 3 micromolar and has good ability to suppress viral replication and destructive activity at one micromolar. Toxicity does not occur until about 5 micromolar. Dideoxythymidine has poor activity for the initial thymidine kinase, and although it has activity against the AIDS virus, it requires a higher dose than AZT. Dr. Broder emphasized that it is necessary to consider what are the relevant activating enzymes, and it cannot be assumed that they will be the same in different species. He cited the mouse as an example of a model that handles AZT fundamentally differently than humans.

Dr. Broder next discussed biologicals or natural products and noted the coordinated efforts of the Developmental Therapeutics Program, the Clinical Oncology Program, the Biological Response Modifiers Program, and the Cancer Therapy Evaluation Program. He suggested that the concept that certain natural products may contain agents that could be useful against AIDS and cancer is very important.

Other new drugs include dextran sulfate, which is being developed in collaboration with Dr. Gallo's laboratory. This drug can suppress viral replication and, when sulfated groups are present, appears to inhibit virion attachment to target cells. Another potential new drug is genetically engineered soluble CD4, a very effective inhibitor of viral replication, as already discussed.

In turning to discussion of clinical trials, Dr. Broder suggested that the trials and the speed at which they are instituted are as important as the initial research observations on the efficacy of a potential drug. He recalled the AZT experience and reminded the Board that he had presented to them the first clinical data on AZT in humans in 1985. The first patient who received AZT experienced an increase in T4 cells, and in another assay, the ability of a patient's cells to kill influenza-modified target lymphocytes was normal, a response that is usually weak or absent in patients with fulminant AIDS. Dr. Broder said reversals of dementias also have been observed in some AIDS patients. As seen on a positive emission tomogram scan of a patient, restoration of hypoactive areas of the brain correlated with improvement in intellectual function. Dr. Broder stated that there have been astonishing reversals of certain types of AIDS dementias in children who received AZT. Where dementia had improved but AZT administration had to be stopped because of excessive bone marrow toxicities, the patients generally reverted to a state of dementia.

Dr. Broder noted that the Wellcome Research Laboratory and NIH organized a double-blind placebo control trial involving patients with poor prognoses who had AIDS-related complex (ARC) and patients with fulminant AIDS. The trial began accruing patients in February 1986, shortly after the completion of NCI's Phase I study. In September 1986, an emergency session of the Data Safety Monitoring Board was called because there were 20 deaths and 19 of them were in the arm of the study that had received the placebo. Dr. Broder stated that in his view this was a clear demonstration that it was possible to treat advanced retroviral infections. The differences between the placebo and AZT groups were significant, both statistically and clinically.

The dominant toxicity from AZT is bone marrow suppression, mostly a megaloblastic suppression that often selectively affects red blood cells. Dr. Broder pointed out that the current discussion of long-term toxicity of AZT is an indirect message that its effects have been beneficial. A problem that may be encountered is that some patients may survive so long that they become at risk of malignancies that may be associated with abnormalities of immunosurveillance. In addition, those patients who require transfusion support, and some do in order to receive AZT, may be at risk of hemochromatic heart disease. Dr. Broder said that the Clinical Oncology Program is

considering the use of colony-stimulating factors and other treatments in those patients whose marrow is very fragile as a result of AZT treatment. However, he pointed out that when AZT is given early in the disease, it appears to have significantly less bone marrow suppression as a complication. One of the mechanisms of bone marrow suppression is thought to be depression of the critical normal substrate thymidine triphosphate and accumulation of thymidine monophosphate. AZT, as a first monophosphate, inhibits a critical enzyme, thymidylate kinase, and becomes a competitive inhibitor for that enzyme, which results in pyrimidine starvation. Dr. Broder said this effect can be monitored relatively easily in patients. He cited the example of an AIDS patient on AZT whose T4 count rose rapidly, plateaued, and then fell. He suggested that the reason for this common occurrence is that continued administration of AZT induces lymphotoxicity. The mean corpuscular volume (MCV) of the patient's red cells increases when the cells are thymidine triphosphate-starved, and the patient becomes megaloblastic, which is reflected in the peripheral blood. Dr. Broder said the increase in MCV is often dramatic in patients on AZT. He suggested that these manifestations of toxic effects should not discourage the use of AZT in patients who might benefit from it.

Dr. Broder said that Phase I clinical studies have indicated that dideoxycytidine may have certain clinical effects in AIDS patients. He described a patient who experienced a rise in the T4 count and weight gain, but no change in MCV with this drug. Dideoxycytidine does not appear to cause pyrimidine starvation and results in much less bone marrow suppression than AZT. Dr. Broder noted that P24 circulating antigenemia has been adopted as one new index of in vivo replication of the virus. It is thought that a drop in P24 antigenemia reflects inhibition of in vivo replication. Dr. Broder said that a drop in in vivo circulating antigen level and improved in vitro immunoreactivity of lymphocytes taken from patients is preliminary evidence that dideoxycytidine has a positive effect in some patients. The predominant toxicity of the drug, occurring at high doses, appears to be painful peripheral neuropathy. Dr. Broder stated that this toxicity seems to be dose-dependent, and if regimens can be developed that are effective but do not cause peripheral neuropathy, the drug may have a reasonable chance to make an impact on the disease. He pointed out that dideoxycytidine is much more powerful than anticipated and very low doses are now being studied. It appears that if rest periods are built in, the drug's neurotoxicity is greatly diminished.

Dr. Broder next described a pilot study in which the two drugs (AZT and dideoxycytidine) are combined in an alternating sequence. T4 counts increased in patients on the study for 22 weeks but in a pattern different from that seen with continuous AZT. The patients' P24 levels have fallen, and MCVs were rising slowly. Dr. Broder cautioned that this intramural study is very small, and the possibility that all of the effect is due to AZT cannot be ruled out. However, in the patients under evaluation, neuropathy is reduced to a significant degree and bone marrow suppression also seems to be reduced.

Dr. Broder stated that the possibility of inhibiting expression of the virus in already infected cells also is under investigation.

Dr. Jack Cohen has synthesized oligonucleotides that use a sulfur group instead of standard phosphodiester linkages. With the sulfur group, the body's enzymes cannot destroy the complex. These drugs can protect uninfected cells against the virus, and in preliminary experiments at certain doses and in certain ordered sequences, they can turn off the expression of viral genes in cells that are chronically infected. Dr. Broder said an anti-sense configuration has been made to bind to the RNA of the art gene, a critical regulatory gene. These substances block the expression of P24 gag protein in cells that are already infected. Dr. Broder suggested that, therefore, it is at least theoretically possible to develop drugs that inhibit viral expression in already infected cells.

Dr. Broder noted the study of Dr. Ruth Ruprecht at the Dana-Farber Cancer Institute in which some mice were given AZT in drinking water and other mice were given placebo. When the mice were given a lethal inoculum of Rauscher leukemia virus, there was a permanent suppression of the virus in those mice that received AZT. Dr. Broder suggested that may be a model for early intervention in AIDS or in people who are seropositive and described this as a high priority study; but we should not assume we know the answer in human beings until the studies are done.

In conclusion, Dr. Broder listed what he considered to be goals achievable within the next 2 years, including the following:

- Establish clinically predictive screening systems for antiretroviral agents
- Develop comparative antiviral efficacy profiles against both human and animal retroviruses
- Define structure-activity relationships for certain nucleoside analogs, such as AZT, dideoxycytidine, dideoxyadenosine, and the other didehydro analogs
- Develop, at least to the point of clinical trials, antiviral agents that can inhibit binding to cells
- Develop antiviral effects using defined oligonucleotides and chemically modified nucleotides, including anti-sense constructs
- Rapidly implement Phase I studies and initial clinical pharmacology studies of relevant drugs in adults and children
- Derive results from the early intervention study
- Develop therapy against retroviral neurological diseases
- Develop principles for combining or alternating antiretroviral therapies.

In discussion, Dr. Broder replied to the question of whether there are differentiated cells from the body that cannot activate AZT. He said

that researchers are learning that certain types of cells may lose their kinases following some differentiation steps. Elutriated monocytes, for example, as they come out of the body can be infected by HIV and then protected by a panel of antiretroviral nucleoside analogs. However, if cells are allowed to differentiate in culture, they retain their susceptibility to retroviral infection. However, they are differentiated macrophages, and their level of kinases drops significantly. At that point, Dr. Broder said, it appears that there is drug resistance, not due to an inherent change in the virus but to the cell. Therefore, there is interest in phosphorothioate analogs because they do not require anabolic phosphorylation and should not be sensitive to kinase fluctuations. Depending on the effects of kinases, a drug might act as a mitochondrial toxin. Dr. Chabner added that dideoxycytidine is lineage-dependent and that the proliferative state of a cell will determine how much deoxycytidine kinase it has, which may explain why it is easier to kill cells that are rapidly growing in culture. In addition, Dr. Broder pointed out that a virus cannot elect to mutate to become kinase negative, which a cancer cell can do. Also, the drug is resistant to cytidine deaminase, one factor that prevents Ara-C from being adapted as an oral drug.

XIV. Overview of AIDS Research--Dr. Anthony Fauci

Dr. Fauci began his broad overview of AIDS research efforts at NIH by noting that his focus would be on the efforts of NIH as a whole, how the NCI activities fit into the total effort, and how NCI's activities are complemented by efforts being undertaken by other Institutes of NIH. The NIH AIDS budget was approximately $3 million in 1982 and in 1988, the President's amended budget requests $422 million. An additional $50 million could be added by the Congress. NIH accounts for 53 percent of the entire Public Health Service AIDS budget for 1988, Centers for Disease Control (CDC) 30 percent, and Alcohol, Drug Abuse and Mental Health Administration (ADAMHA) is allotted 15 percent. The remainder of the effort is spread among the Food and Drug Administration (FDA), Health Resources and Services Administration (HRSA), and the Office of the Assistant Secretary.

NIAID accounts for the largest share of the NIH portion of PHS AIDS budget, with 53 percent, followed by NCI with 22 percent. Dr. Fauci noted that although the portion of NIH AIDS funds allotted to other Institutes is relatively small, there has been increased interest over the past year in involvement by these other Institutes. Still referring to the President's amended budget for 1988, Dr. Fauci commented that the portion of the total NIAID budget that is dedicated to AIDS is 38.9 percent; 6.8 percent of NCI's budget is AIDS-related, with percentages of 2 percent and less for the other Institutes. In actual dollars, these percentages translate into $223.3 million in AIDS research by NIAID, and $93.9 million by NCI.

Although the AIDS budgets for other Institutes are relatively small, Dr. Fauci noted that their efforts are important: NHLBI, $25 million for blood and blood products; NINCDS, just under $13 million for study of the neurological manifestations of HIV infection; and $10 million for the National Institute on Child Health and Human Development (NICHHD) to examine perinatal infection and treatment of AIDS in children.

Dr. Fauci shifted the focus of the discussion from Institute to functional categories. The primary areas of emphasis are on pathogenesis and clinical manifestations (including virology, molecular biology, viral etiology, viral pathogenesis, and immunological studies), and therapeutics (including vaccine development). Given the NIH mission, less emphasis is placed on public health control measures and patient care and health needs. In the 1988 President's budget, 84 percent of NIH AIDS research is extramural, 13 percent is intramural, and 3 percent is allocated to the Office of the Director. This contrasts markedly with the early AIDS funding, for which more than half of the resources were allocated for intramural activities. This emphasis on intramural research was necessary to enable the laboratories to change directions quickly in response to a rapidly evolving knowledge base about AIDS. Now, the trend is toward extramural research, and Dr. Fauci estimated that the proportion of activities undertaken in the extramural environment will plateau at about 90 percent.

Dr. Fauci noted that NIH activities on AIDS are coordinated by an NIH AIDS Executive Committee, whose purposes are to 1) develop policies, 2) facilitate faster program coordination and information exchange, 3) allocate resources where appropriate, and 4) maintain liaison with the PHS AIDS Executive Task Force. The Committee is comprised of representatives of all of the Bureaus, Institutes, or Divisions involved in AIDS research, and it is co-chaired by Drs. Wyngaarden and Fauci. This Committee will receive input from the newly formed NIH AIDS Program Advisory Committee.

Dr. Fauci then focused on details of AIDS research underway and planned for NIH. NIAID has two major programs: microbiology and infectious diseases and immunology, allergy, and immunological diseases. It became evident that because of the amount of research at NIAID on AIDS, an additional program focusing specifically on AIDS was needed. The NIAID AIDS Program was established in 1986 and consists of five major branches: treatment, prevention, pathogenesis, epidemiology, and developmental therapeutics.

Dr. Fauci continued by noting that the overall NIH AIDS research effort also breaks down into five areas, which are 1) epidemiology and natural history, 2) the etiologic agent, 3) pathogenesis, 4) antiretroviral therapy and immunological reconstitution, and 5) vaccine development and evaluation. Because of the depth of involvement by NIAID and NCI in AIDS efforts, Dr. Fauci noted that these five areas also represent the major thrusts of those two Institutes. He clarified that NIH is involved in natural history and epidemiology because insight is gained into pathogenesis, etiology, and diversity of etiological agents from surveillance and natural history studies.

Dr. Fauci described the "iceberg of HIV infection," to which the following numbers pertain: although there are approximately 44,000 cases of AIDS in the United States, there are 150,000 cases of AIDS-related complex (ARC), and about 1 to 1.5 million asymptomatic, HIV-infected individuals. Studies are confirming that, within 5 years of infection, between 20 and 30 percent of infected individuals will develop AIDS. Although Dr. Fauci noted that it is unknown at this time how many HIV-infected individuals will

develop AIDS, immunologic studies suggest that 80 to 90 percent of them will suffer some immunological deterioration. These projections give even greater impetus to early intervention studies prior to the onset of AIDS.

Dr. Fauci then discussed a number of studies underway at the NIH. He mentioned that NIAID and NCI had initiated a prospective AIDS cohort study of approximately 5,000 individuals in five American cities. This study has provided information on natural history, viral isolates, and immunological abnormalities. In addition, there have been international collaborations with the World Health Organization, the Pan American Health Organization, the Caribbean Epidemiology Center, universities with third world country liaisons, the Fogarty International Center, and an NIAID/CDC/Zaire government/University of Antwerp collaboration.

Dr. Fauci mentioned that NIAID and NCI are looking at the functions of the various HIV genes through their intramural programs and by grantees. He suggested that the amount of knowledge that has accrued in delineating the proviral DNA genomal function is extraordinary and unprecedented in the history of microbiology. NCI and NIAID also share the primary interest in pathogenesis, particularly immunopathogenesis. Although the immunopathogenic mechanisms of the HIV are not fully understood, much is known, such as the nature of the relationship between cell-free and cell-associated virus, the portal of entry, the infection of susceptible CD4-positive T4 cells and monocyte/macrophages, and, most importantly from the NIAID perspective, an understanding exists about the various activation signals which convert a latent monocyte/macrophage or T-cell infection into a productive infection. The productive infections lead either to immunosuppression and opportunistic infections, or brain infection with neuropsychiatric manifestations.

Dr. Fauci next discussed the most significant area of cooperation between NIAID and NCI, antiretroviral therapy and immunological reconstitution. The stages, briefly, are 1) AIDS drug development, 2) drug screening, 3) preclinical development and testing, and 4) clinical testing. A new area has been designated "targeted antiviral therapy." There are three major foci of this area, which are somewhat distinct from the four drug development phases:

- The Structural Biology Program, funded through the Office of the NIH Director, is designed to facilitate cooperation among intramural scientists in non-AIDS disciplines to synthesize specific antiviral drugs.

- The National Institute of General Medical Sciences is sponsoring a program project grant to study structural biology for targeted drug design.

- The National Cooperative Drug Discovery Groups (NCDDGs), were originally a joint effort of NIAID/NCI, for which NCI had taken the early lead and for which NIAID is now responsible. Approximately $13 million will be spent in 1987 on cooperative agreements whose goal is to foster collaboration between government, industry, and academia to encourage the discovery of

more effective targeted agents for the treatment of AIDS. Participants in the NCDDGs include academic institutions, pharmaceutical and bioengineering companies, international organizations, and intramural scientists from NIH.

Dr. Fauci next discussed the four major areas of clinical trials: NIAID AIDS Treatment Evaluation Units; NIAID Clinical Study Groups; NCI intramural trials; and NIAID intramural trials.

The ATEUs have an estimated 1987 budget of $31.2 million, for 19 specific contracts to make available facilities to test drugs in universities. These drugs are submitted by a variety of sources including industry, academia, and the Drug Development Programs of NCI and NIAID. These Units, which are located primarily on the east and west coasts, are now studying approximately 2,400 individuals.

The Clinical Study Groups have complemented the large-scale efforts of the AIDS Treatment Evaluation Units, but are more geographically distributed with outreach programs. In September 1987, 17 awards were made, totalling $18.6 million.

Approximately 25 protocols are in effect in the clinical trials program, including studies of ddC, foscarnet, AL721, and combinations such as alpha interferon with AZT, gamma interferon with tumor necrosis factor, and acyclovir with AZT. In one ATEU study involving 1,600 HIV-positive but completely asymptomatic individuals, early intervention with AZT is being conducted to see whether AZT can block the progression to AIDS.

The NCI intramural clinical trials program is examining drugs such as AZT. The NIAID intramural clinical trials program involves a slightly different, but complementary, focus to that of the NCI. For example, AZT is being studied in combination with bone marrow transplantation and peripheral lymphocyte transfers. Other studies include alpha interferon in Kaposi's sarcoma, liposome-encapsulated CGP 19835A in Kaposi's sarcoma, intravenous dihydroxyperpoxy methylguanine for cytomegalovirus colitis, alpha-interferon in asymptomatic HIV infection, and AZT in combination with alpha interferon for Kaposi's sarcoma.

Dr. Fauci briefly mentioned that there are several potential approaches for an AIDS vaccine, including the whole killed virus, natural products, synthetic peptides, recombinant products, vaccina vector, and anti-idiotype. He also discussed an intramural NIAID trial using the recombinant gp160 made by the MicroGenesys system and expressed in a baculovirus vector. This trial is a Phase I safety and immunogenicity trial, approved by the FDA in 1987, which involves the injection of a candidate vaccine into 81 healthy volunteers. The first dose has already been completed, and the 15 or 20 people who have received it are exhibiting no untoward side effects. Information on immunogenicity is not yet available. Dr. Fauci noted that the National Cooperative Vaccine Development Groups, planned for award early in 1988, are akin to the NCDDGs except that the focus is on vaccines. These cooperative agreements, for which between $5 and $7 million will be budgeted, will foster the collaborative efforts of government, industry, and academia.

Dr. Fauci concluded his discussion of vaccine efforts by stressing that Vaccine Evaluation Units, which have been in place for decades and which have studied the influenza, pneumococcal, and hepatitis B vaccines, will be expanded over the coming years. As candidate vaccines from the various collaborative efforts discussed above are produced, these will be channeled into the Vaccine Evaluation Units for Phase I, II, and III testing.

Dr. Fauci summarized his remarks by noting that the NIH AIDS effort covers epidemiology and natural history through vaccine development and testing. Although the primary leaders of the NIH effort are NCI and NIAID, other Institutes are also participating. He expressed gratitude for the cooperation between the Institutes, cooperation that has been responsible for the rapid accrual of knowledge, which will continue and eventually lead to the solution of the AIDS problem.

During the question and comment period after Dr. Fauci's presentation, the following points were raised:

- Although AIDS is an infectious disease, and NIAID is the NIH focal point for study of infectious diseases, NCI's role has and continues to be important because HIV is a retrovirus associated with a variety of opportunistic neoplasms. NCI has taken a lead role for years in both retroviruses and neoplasms.

- Although theoretically it is possible to determine whether there has been a reduction in the transmission of HIV among asymptomatic individuals among the male homosexual population, current transmission is so low that statistically significant measures might be difficult to obtain. Evidence of changes in sexual behavior, measured by the significant reduction of sexually transmitted diseases such as rectal gonorrhea and syphilis, strongly suggests that male homosexuals have responded to education efforts.

- There is no evidence to suggest that education is modifying the behavior of IV drug abusers and the heterosexual population.

- The strength of the AIDS effort of NIH is that multiple Institutes have common denominators in basic research, applied to a single disease--AIDS. To create an AIDS Institute would pull this basic research from other Institutes, and reduce scientific exchange.

- Although education is a very important component in fighting AIDS, the mandate for health education does not rest with NIH, but predominantly with CDC. Approximately $132 million was spent in 1987, primarily by CDC, on education. In 1988, the figure will be increased by nearly another $100 million.

XV. AIDS Vaccine Development--Dr. Peter Fischinger

Dr. Peter Fischinger began by emphasizing the need for basic scientific information and commending the collaborative efforts of the Frederick Group, including Dr. Larry Arthur of PRI, Dr. Peter Nara of NCI, and Dr. Robert Gallo's laboratory. He noted that NCI was involved early in virus production and identified two important roles for the Federal effort: the establishment of benchmarks for the isolated so-called native viral proteins and the definition of the virus titer in vivo to enable in vivo challenge testing.

Dr. Fischinger stated that it was necessary to think in terms of a potentially biphasic vaccine--one that will prevent the initial infection from occurring and interfere with the progression to clinical disease. He said his discussion would focus on the primary prevention of HIV infection.

Dr. Fischinger summarized the inherent problems in vaccine development. First, it does not appear likely that a vaccine can be modeled on a natural protected state because it has not been possible to identify protected individuals who had been infected at one time and had the virus adequately controlled or eliminated. The heterogeneity of HIV is another problem, and there is the additional problem of cellular association, i.e., the virus can exist in the cell without having antiviral RNA, and therefore, the cell does not express targets for the immune system. Dr. Fischinger also pointed out that because there is no perfect animal model for human AIDS, it is only possible to test a vaccine for primary prevention.

In discussing approaches to vaccine development, Dr. Fischinger first mentioned killed or inactivated HIV. He stated that there is no known way of "cleaning up" the virus when it is purified. In addition, when non-pathogenic infectious agents are constructed, they could potentially revert back to pathogenicity. Dr. Fischinger said the ISCOMS approach has been useful in some animal models and is a rapid and effective way of making a viral protein immunogenic. He defined ISCOMS as immunogenic structures that are assembled into small spheres that can carry viral proteins. He suggested that the highest priority is the benchmark study to consider genetic engineering of the virus. An equally important study is to put the gene of interest into an infectious recombinant vaccinia virus and let it replicate. Together with an immune response to the virus, there would also be an immune response against the viral protein of interest. The peptides approach involves scaling down to identify the dose-specific regions of protein subunits thought to be most important. Dr. Fischinger said he would not discuss the anti-idiotype approach because of its theoretical complexity.

The viral targets for the vaccine include the envelope gene, the major glycoproteins gp160, gp120, and gp41, and the internal viral proteins in the core. Dr. Fischinger said it may eventually be necessary to look at other non-structural genes to determine whether they may be targets for vaccine. With so many potential targets, it will be necessary to consider numbers of adjuvants and routes of inoculation and testing in various species, as well as safety, immunogenicity, and potency. There must also be definition of desired response, e.g., reactivity, neutralizing antibody,

cellular immunities, and the challenge matrix. Dr. Fischinger said there are literally thousands of possibilities in this multidimensional matrix, but the limitations of numbers of animals available for testing restrict the number of attempts that could be tested.

Dr. Fischinger next explained what makes a molecule antigenic in terms of response as a retroviral protein. If a viral glycoprotein can elicit an immune response, joining it with a transmembrane protein enhances that response. Rosettes produce a better response, and ISCOMS a markedly better response. Dr. Fischinger said ISCOMS have been made with HIV, but one of the problems is that although viral proteins are incorporated, many cellular proteins are also incorporated. In addition, it is particularly difficult to incorporate the gp120, although it has been done.

Antibodies that have been induced by HTLV-3b (HIV-1b) gp120 include precipitating antibodies, which precipitate all strains of HIV-1, neutralizing antibodies, and cytotoxic antibodies. Although gp120 induces a type-specific antibody, Dr. Fischinger said what will probably be needed, based on the different kinds of field isolates, is a group-specific antibody. He said that AIDS human sera precipitate gp120, and they are not cytotoxic but have a type-specific neutralizing antibody. Human sera will also neutralize other kinds of viruses, but that response is sometimes erratic.

Dr. Fischinger next summarized the research involving chimpanzees. Chimps are susceptible to HIV infection and develop antibodies to HIV, but they do not get AIDS. The virus persists in the animals for long periods of time and is cell-associated, but can be easily reisolated. The virus also changes slightly with reisolation. The chimps exhibit immune responses, including neutralizing antibody, ACC, cytotoxic and cellular responses. Over time, a very strong type-specific antibody develops. When the same animals were tested against a different strain of HIV-1, a strong neutralizing response against that virus also developed over time. Dr. Fischinger said injection of purified gp120 of HTLV-3b produced a moderate response in every animal, which improved after repeated immunizations. The use of engineered bacteria produced a moderate type-specific response. The use of the HIV envelope gene in vaccinia as a vector produced a low level of neutralizing antibody and cell-mediated immunity. Dr. Fischinger emphasized that the antibody responses were highly type-specific.

In summarizing the progress of vaccine development, Dr. Fischinger said a few candidates are in the challenge phase, but only one has reached the IND phase and Phase I testing in humans. As discussed by Dr. Fauci, the material in the IND phase is derived from the baculovirus insect vector system. The material is very difficult to purify and contains at least 10 to 30 percent insect material, which may cause hypersensitivity reactions in humans. Dr. Fischinger said that the testing of candidate vaccines requires developing an *in vitro* challenge pool, so that it is known how much virus is being put into the animal in order to relate that to any immune response observed. A series of assays was done *in vivo*, and six chimpanzees were inoculated with HTLV-3b. One challenge experiment used the vaccinia infectious recombinant with the French isolate, LAV. At first not much immunity could be detected, in terms of neutralizing antibody, but cell-

mediated immunity was present and virus was isolated. Dr. Fischinger said this experiment could not be described as successful in preventing primary infection. The other challenge experiment with native gp120 produced a moderate type-specific response. The challenge was with a minimal amount of HTLV-3b. There was an immediate response with a rise in neutralizing antibody, and virus was isolated. The immediate type-specific response changed over several weeks into a group-specific response that improved with time. Dr. Fischinger described the response as antibody-dependent, cell-mediated (ADCC) immunity; cytotoxic antibodies recognize virus-infected cells and kill them. The gp120 ends up in a cell membrane that is budding out and is one of the targets for killing.

Dr. Fischinger stated that viruses reisolated from the chimpanzees after the challenge are not the same as the original virus. Passage through the cells apparently affects the virus coming out of them, which also happens to some degree in vitro. Immune pressure may also change the virus. Dr. Fischinger said that for whatever reason, the virus becomes less susceptible to a type-specific neutralizing antiserum. Because the neutralizing antibody in the infected animals can neutralize not only the homologous virus but also a totally unrelated virus, the question is whether it will neutralize the virus that existed in the animal at that time. To answer that question, isolates of the virus were taken from the vaccinated animals after 6 weeks. Serum collected at the same time did not neutralize the virus, but at 30 weeks that serum was able to neutralize what is called the early virus. Dr. Fischinger concluded that the viruses are not susceptible to the immune responses the animal is generating. The virus may, by selection, change, or adaption, run ahead of the immune system and as the immune system catches up and makes antibodies, the virus is already evolving further ahead. Therefore, for primary prevention, it will be necessary to induce an extremely broad neutralizing antibody.

In conclusion, Dr. Fischinger said that humoral immunity has occurred and there is also evidence for cellular immunity in vaccinated chimps. The question remains of what is the appropriate time to go into Phase I trials in humans with the available preparations. The gp160, now in human trials, does give type-specific immunity and a reasonable titer. However, before Phase II trials, it may be important to know whether there is actual protective immunity occurring against the homologous virus and later the heterologous virus. Dr. Fischinger suggested that if there is failure of protection in one instance, an effort might be made to increase the titer and the cell-mediated immunity using the T-specific epitopes. He concluded that a sense of optimism is warranted, although the virus is very tricky.

The following points were raised in discussion:

- The isolate from the infected laboratory worker was tested against type-specific sera and found to be different.

- Research is in progress to develop endonuclease maps of isolates, and it is likely that they will need to be completely sequenced because the changes are so small.

- Phenotypic mixing and genomic masking make it difficult to recognize a field isolate or non-cloned virus.

XVI. NIH and DHHS AIDS Advisory Committees Update--Dr. Maryann Roper

Dr. Roper explained that on the NIH campus, the primary committee in the AIDS program structure is the NIH AIDS Executive Committee, which is responsible for liaison with the Public Health Service Task Force; coordination of the NIH research program; exchange of information among the various Institutes; policy development; generation and termination of studies; development of a surveillance program; allocation of resources; and identification of gaps in the research. Dr. Fauci is the NIH AIDS coordinator and is the chairman of the NIH AIDS Executive Committee. Dr. Wyngaarden, as the NIH AIDS co-coordinator, is co-chairman of this committee.

Dr. Roper noted that most of the Institutes on the NIH campus were currently involved in the AIDS program. For example, the National Institute of Child Health and Human Development is starting a Phase II study comparing AZT versus AZT with gamma globulin to see if gamma globulin confers added protection against opportunistic infections in children with AIDS.

Dr. Roper went on to list several other NIH committees involved in the AIDS program. The NIH AIDS Vaccine Committee is chaired by Dr. Bernard Moss and is primarily involved in the exchange of information among scientists doing vaccine-related research. The AIDS Clinical Drug Development Committee, chaired by Dr. Henry Masur, includes representatives from both NCI and NIAID and considers the readiness of drugs for human use. The Drug Decision Network Committee is chaired by Dr. Chabner and decides which drugs are ready to go from preclinical to clinical testing. Both NCI and NIAID are represented on this committee.

Dr. Roper next explained that the Public Health Service (PHS) Executive Task Force on AIDS has responsibility for coordinating AIDS work among the various PHS agencies, providing a forum for discussion of problems, developing operating strategies for PHS programs, and assuring exchange of information. This committee is chaired by the Assistant Secretary for Health, Dr. Robert Windom, and Dr. Peter Fischinger as the PHS AIDS Coordinator. The agencies involved are the National Institutes of Health, the Centers for Disease Control, the Food and Drug Administration, the Health Resources and Services Administration (HRSA), and the Alcohol, Drug Abuse and Mental Health Administration (ADAMHA).

Dr. Roper stated that several subcommittees representing different problem areas in AIDS research have grown out of PHS Executive Task Force on AIDS. The subcommittees deal with vaccine development, drug development, information and education, epidemiology and surveillance, neuroscience and behavior, blood and blood products, patient care, health service delivery, and addiction and behavior. NCI is represented on the Vaccine Committee (Roper), the Therapeutics Development Committee (Chabner), and on the Epidemiology and Surveillance Committee (Blattner). Dr. Fauci chairs the Therapeutic Intervention Committee, and Dr. Blattner with Dr. Curran from the

CDC, co-chairs the Epidemiology Committee. Dr. Roper explained that also at the PHS level, the Federal Coordinating Committee on AIDS disseminates information from the PHS Executive Task Force to other Government departments.

Next, Dr. Roper described the Department of Health and Human Services (DHHS) AIDS Task Force. It meets weekly and is chaired by Dr. Windom. Members represent various divisions within DHHS, including the Medicare/Medicaid Program, Social Security, the Family Services Program, and the Assistant Secretaries from the Office of the Secretary.

Dr. Roper stated that the primary committee at the Federal Government level is the Domestic Policy Council, composed of cabinet secretaries, which discusses a broad range of issues among which health and AIDS are a small subset. The Working Group on Health Policy, chaired by Mr. Gary Bauer at the Office of Policy Development, includes departmental representatives at the Assistant Secretary level. Working Group members discuss health matters, including AIDS issues, and provide detailed information to the Domestic Policy Council.

In summary, Dr. Roper stated that information flows from the NIH Executive Committee to the PHS Executive Task Force on AIDS. The Task Force advises the Domestic Policy Council through the Health Policy Working Group. Information generated from all of these committees is shared with the Presidential Commission on AIDS as requested.

Dr. Roper moved on to discuss the AIDS program budget. The NCI budget has grown along with the PHS budget for AIDS, but whereas NCI initially represented 44 percent of the total PHS AIDS expenditure, that figure has dropped to 9.7 percent. The amount projected for PHS for FY 1988 is $971 million, with NIH receiving the largest amount, followed by CDC, ADAMHA, FDA, and HRSA. In addition, a $5 million emergency fund is available to cover any major gaps identified in the research effort.

The total Federal Government AIDS budget projected for FY 1988 is $1.5 billion, with the major portion going to DHHS. Within DHHS, other major expenditures besides NIH are in the Health Care Financing Administration and Social Security. The lesser amounts are for the Veterans Administration, and the Departments of Labor, State, and Justice. Dr. Roper noted no money was allocated to the Education Department.

Dr. Roper then outlined NCI's position overall in the AIDS program. NCI represents 20 percent of the NIH budget, and 9.7 percent of the total PHS budget, 6.5 percent of the total Department budget, and roughly 6 percent of the total Federal Government expenditure for AIDS. DHHS accounts for 92 percent of the total Federal Government spending in AIDS. The Veterans Administration, Labor, State, and Justice Departments make up the remaining 8 percent.

Dr. Fischinger noted that the Deficit Reduction Act could affect the AIDS budget. Dr. DeVita added that Gramm-Rudman-Hollings legislation would

automatically reduce the AIDS budget unless a compromise was reached, as the program was not technically protected in the bill.

Dr. Temin suggested that overall, the Board seemed comfortable with NCI's degree of involvement in the AIDS program. Dr. DeVita noted that NCI involvement was decreasing proportionally as other Institutes took on responsibilities. A future consideration would be the shifting of drug development efforts to NIAID, but currently NCI is likely to remain quite active in drug development. Dr. DeVita noted that although most of the early work in clinical trials had fallen to NCI, this was shifting to NIAID and to the extramural community.

The concluding discussion focused on the possibility that as AIDS patients' survival is extended, more patients will develop cancer. Dr. DeVita noted that as AZT is mutagenic, the possibility of developing cancer was distinct. Dr. Chabner noted that increased incidence of lymphomas and Kaposi's syndrome had been seen in the AZT follow-up. In the future, many diseases now classified as cancers may be recognized as viral diseases, as in Hodgkin's disease.

In conclusion Dr. DeVita suggested that new areas of cancer research will open up as AIDS becomes understood, which will benefit both AIDS and cancer research and intensify NCI involvement.

XVII. **Adjournment**

The 64th meeting of the NCAB was adjourned at 4:40 p.m. on Tuesday, November 17, 1987.

JAN 28 1988

Date

David Korn, M.D.

National Cancer Advisory Board Meeting

November 16-17, 1987

Action Items

- The February 1988 meeting of the NCAB will include an expanded discussion of clinical trials and proposed efforts to increase accruals.

- The Board book for the February meeting will include review articles on mutagens in foods.