Department of Health and Human Services

Public Health Service

National Cancer Institute

National Cancer Advisory Board

Summary of Meeting
December 8-10, 1986
Memorial Sloan-Kettering
Cancer Center
New York, New York

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

Minutes of Meeting
December 8-10, 1986

The National Cancer Advisory Board (NCAB) convened for its 60th regular meeting at 8:30 a.m., December 8, 1986, at the Memorial Sloan-Kettering Cancer Center, New York, New York. Dr. David Korn, Chairman, presided.

Board Members Present

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

President's Cancer Panel

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

Ex Officio Members

Dr. Dorothy A. Canter, NIEHS
Dr. James M. Melius, CDC/NIOSH
Captain Stephen R. Veach, DoD
Dr. Ralph E. Yodaiken, OSHA

Absent

Dr. Victor Braren
Dr. Tim Lee Carter
Dr. Armand Hammer

Liaison Representatives

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

Dr. Ann Belcher, Associate Clinical Professor of Nursing, School of Nursing, Columbia University, New York, New York, representing the Oncology Nursing Society.

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

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

Dr. John R. Nelson, Past President, Association of Community Cancer Centers.

Dr. Carl A. Olsson, Professor and Chairman, Department of Urology, Columbia University, New York, New York, representing the Society of Urologic Oncology.

Dr. Stanley Order, Director of Radiation Oncology, Johns Hopkins University, Baltimore, Maryland, representing the American Society of Therapeutic Radiologists.

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

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

Members, Executive Committee, National Cancer Institute

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

Chairmen, Boards of Scientific Counselors, National Cancer Institute

Division of Cancer Etiology--Dr. G. Barry Pierce, Professor of Pathology, University of Colorado

Division of Cancer Biology and Diagnosis--Dr. Matthew D. Scharff, Professor, Department of Cell Biology, Albert Einstein College of Medicine

Division of Cancer Treatment--Dr. Paul Calabresi, Professor and Chairman, Department of Medicine, Brown University, Roger Williams General Hospital

Division of Cancer Prevention and Control--Dr. Erwin P. Bettinghaus, Professor and Dean, College of Communications Arts and Sciences, Michigan State University

Frederick Cancer Research Facility--Dr. Werner H. Kirsten, Department of Pathology, University of Chicago

Cancer Center Directors

Mrs. Penny Ashwander--Assistant Director, Columbia University Comprehensive Cancer Center.

Dr. Vittorio Defendi--Cancer Center for New York University Medical Center.

Mr. Albert Dessureux--Deputy Director, Columbia University Comprehensive Cancer Center.

Dr. Peter N. Magee--Director, Fels Research Institute, Temple University School of Medicine.

Dr. I. Bernard Weinstein--Director, Columbia University Comprehensive Cancer Center.

Dr. Ernst L. Wynder--President and Medical Director, American Health Foundation.

In addition to NCI staff members, meeting participants, and guests, a total of 20 registered members of the public attended the meeting.

I. Call to Order, Opening Remarks, and Consideration of October 6-8, 1986, NCAB Meeting Minutes--Dr. David Korn

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

The minutes of the October 6-8, 1986, meeting were unanimously approved.

II. Future Board Meeting Dates

Future meeting dates were confirmed as follows: February 2-4, 1987; May 26-28, 1987; September 28-30, 1987; November 16-18, 1987; February 1-3, 1988; and December 5-7, 1988. Meeting dates were proposed as follows: May 16-18, 1988; and September 26-28, 1988.

III. Program Overview--Dr. Vincent DeVita

Dr. DeVita thanked the Memorial Sloan-Kettering Cancer Center (MSKCC) for hosting the meeting, the first NCAB meeting ever held off the National Institutes of Health (NIH) campus in Bethesda. He reviewed the annual NCAB schedule of meetings, stating that three meetings are held for conducting normal business, including a full day or more for reviewing grant submissions. The fourth meeting (in December) is the annual program review which includes 1) an overview of the work of the intramural Divisions and the Frederick Cancer Research Facility (FCRF) presented by the Divisional Directors and the Chairmen of the Boards of Scientific Counselors; 2) in-depth presentations on an area of scientific interest; 3) the annual report of cancer statistics by the Surveillance, Epidemiology and End Results Program; and 4) the Organ Systems Program annual report.

In keeping with the visit to MSKCC, Dr. DeVita said this meeting would focus on the Cancer Centers and how they relate to the National Cancer Program. An overview and history of Cancer Centers and their prospects for the future will be given, followed by scientific presentations by MSKCC.

Dr. DeVita described the organization of the NCI, noting two features that are unique to the Institute compared to the other Institutes: the President's Cancer Panel (PCP) created by the National Cancer Act to interface between the Director of NCI and the President and the Presidentially appointed National Cancer Advisory Board. NCI's four operating divisions have Boards of Scientific Counselors (BSC), comprised of scientists representing many disciplines, to perform advisory functions and review program plans and budgets of both the intramural and extramural programs, enabling them to balance allocation of resources. Committees of experts established by the Boards

also make site visits to review intramural programs. To link the Boards for purposes of planning and evaluation, the NCAB receives minutes of each BSC meeting, listings of contracts that have been awarded, and the annual reports of Division Directors and BSC Chairmen.

The NCI Executive Committee is responsible for day-to-day operation of the Institute. The Committee sets policy and allocates resources, making adjustments as required by scientific developments and exigencies. Directors' Retreats for long-range planning occur twice a year.

Referring to the budget, Dr. DeVita stated the estimated FY 1987 budget of $1.402 billion represents an increase of 14 percent over the the FY 1986 total budget of $1.228 billion. The Cancer Control line item in the Division of Cancer Prevention and Control's budget is lower than optimum because it is dependent on funds appropriated directly by Congress. FCRF's budget increase of 33 percent is due to the allocation of $7 million directly from the Office of the Director, NIH, for AIDS research. The Cancer Centers Program, with an FY 1987 budget of about $93 million, a 5.4 percent increase over FY 1986, received the lowest increase to any program in the NCI. Dr. DeVita noted that an additional $7 million would be needed in FY 1987 to fund competing grant applications in Cancer Centers at nearly recommended levels as was encouraged in the appropriation legislation. Despite the NCI interim funding plan, which calls for funding competing applications at 85 percent of their recommended level or at the FY 1986 level, whichever is higher, there will be a shortfall of $3.6 million in FY 1987 for funding of Cancer Centers, even though Cancer Center core grants have been getting excellent scores. Dr. DeVita stressed the importance of core grants in the support of basic research and the continuing problem of underfunding and indicated that the Board would probably be asked to review a request for reprogramming funds from other areas of the NCI at the next meeting.

IV. 1986 Annual Cancer Statistics--Dr. Edward Sondik

Dr. Sondik said the purpose of the annual review of cancer statistics is to continue to identify and interpret long-term trends and abrupt changes in cancer trends and evaluate progress and problems in the context of cancer control targets. Data on cancer incidence and survival are from NCI's Surveillance, Epidemiology and End Results (SEER) Program, and mortality data are from the National Center for Health Statistics. The SEER data presented are primarily from 1975 through 1984. Incidence is defined as the annual rate of new cases per 100,000 persons; mortality, the annual rate of cancer deaths per 100,000 persons; and survival, the percent of persons who survive for various points in time after having been diagnosed with cancer. Five-year relative survival is the percentage of persons who survive after diagnosis of cancer for at least 5 years divided by the percentage of persons matched from the general population who survive at least 5 years, or, in other words, the percentage of persons surviving at least 5 years if cancer were the only cause of death.

Dr. Sondik stated that from 1975 through 1984 cancer incidence for all sites, all ages, and all races increased 5.4 percent and mortality 4.2 percent.

If lung cancer is subtracted, incidence increased by 3.9 percent and mortality decreased by 0.2 percent. In looking at data by age, mortality has been decreasing in age groups under 55, which is all the more surprising in the lower age groups since incidence has increased 7.5 percent in the 35-44 age group. Again excluding lung cancer, an 8.4 percent decrease in mortality is seen in the 0-54 age group, as well as a decrease in cancer incidence. Therefore, Dr. Sondik said, the increase in cancer incidence and mortality is occurring primarily in persons over age 55, although the increase in mortality is less than the increase in incidence. The prognosis for younger persons seems better, perhaps owing in part to early detection and improved treatment.

Dr. Sondik noted the following statistics for specific cancer sites during the period of 1975 through 1984:

- Lung cancer incidence and mortality for males increased by about 11 percent; 5-year relative survival increased from about 10.8 to 11.4 percent

- Lung cancer incidence for females increased by 50 percent and mortality more than 50 percent

- Prostate cancer incidence increased 16 percent over the last decade but has fallen by 10 percent from the figure presented last year for a similar 10-year period; mortality continued to increase at about 7 percent for the 10-year period

- Colon and rectum cancer incidence continued to increase and mortality to decline

- Breast cancer incidence increased by 8 percent for the period; mortality continued to be relatively stable with 2.5 percent increase per 10-year period (in women under 50 there has been a decline in mortality)

- Uterine and ovarian cancer incidence and mortality decreased

- Melanoma incidence increased 30 percent over the last decade and mortality increased 17 percent

- Testicular cancer incidence increased but mortality decreased

- Hodgkin's disease incidence was unchanged but mortality decreased by 30.5 percent

- Non-Hodgkin's lymphoma incidence increased by 25 percent and mortality by 15 percent

- Leukemia incidence decreased 11 percent and mortality 1.5 percent

- Childhood cancer incidence increased by 8.4 percent but mortality decreased.

In further discussion, Dr. Sondik said that while the trend in lung cancer incidence in males remains downward and mortality continues to increase, the trend in mortality should begin to stabilize and decline, reflecting the decline in cigarette smoking in recent years. A stabilizing trend in lung cancer incidence and mortality for females is beginning to be seen before the time expected, based on smoking data.

Survival continues to increase except for blacks, which is largely attributable to lung cancer having a 60 percent higher incidence in black men than white men. Comparisons of relative survival rates among whites and blacks point to factors within the health care system, such as access and quality of care, as needing attention.

Dr. Sondik also pointed out that survival data vary with age at diagnosis, stage at diagnosis, and treatment. Data are also affected by changes in stage definition, early detection, and new treatments. Time lags between the application and impact of treatment and incentives and disincentives for their application also must be considered.

In conclusion, Dr. Sondik discussed costs of cancer, including direct costs of care, morbidity (the costs of factors such as time lost from work), and mortality (the costs of premature death). The total costs were estimated as $71.5 billion, about 10 percent of the total costs from all diseases.

Points raised in discussion included the following:

- Surgery has played a major role in the treatment of cancer and will have a future role in attaining the year 2000 goals
- Survival and improvements in treatment can also be interpreted in economic terms of potential years of life gained and dollars saved
- Other analyses might focus on the relationship between cancer and other diseases in terms of costs and benefits accrued outside NIH
- Detailed individual data are not available on socioeconomic factors and cancer survival; site-by-site analyses are necessary to draw conclusions about the influence of socioeconomic factors.

V. Division of Cancer Biology and Diagnosis--Dr. Alan Rabson

Dr. Rabson stated that the Division of Cancer Biology and Diagnosis (DCBD) has major programs in cancer cell biology and immunology and their applications to cancer diagnosis. He suggested that the tools of molecular genetics offer promise for the understanding of cancer. Dr. Rabson then reviewed the organization of the Division--an Extramural Program comprised of the Cancer Biology Branch directed, by Dr. Collette Freeman; the Cancer Immunology Branch, directed by Dr. Faye Austin; the Cancer Diagnosis Branch,

directed by Dr. Sheila Taube; and the Intramural Program composed of 12 laboratories. The intramural laboratories, their chiefs, and major research interests were summarized as follows:

- Molecular Biology (Dr. Ira Pastan)--use of immunotoxins in cancer treatment, and drug resistance in cancer cells
- Biochemistry (Dr. Maxine Singer)--nucleic acid biochemistry; study of repetitive DNA
- Mathematical Biology (Dr. Jacob Maizel)--supercomputer; application of computer technology to molecular genetics
- Genetics (Dr. Michael Potter)--mechanisms of plasma cell tumor formation
- Metabolism (Dr. Thomas Waldmann)--interleukin-2 (IL-2) receptors
- Cellular Oncology (Dr. Douglas Lowy)--ras-oncogenes, papilloma-viruses
- Dermatology (Dr. Steven Katz)--application of immunology to study of skin diseases
- Pathology (Dr. Lance Liotta)--tumor metastases; autocrine motility factor (AMF)
- Immunology (Dr. David Sachs)--organ and bone marrow transplantation
- Immunobiology (Dr. Tibor Borsos)--humoral immunity, antibodies, and complement
- Tumor Immunology and Biology (Dr. Jeffrey Schlom)--use of monoclonal antibodies in the diagnosis and treatment of cancer
- Cell Biology (Dr. Lloyd Law)--tumor specific antigens.

Dr. Rabson then described the membership of the DCBD Board of Scientific Counselors, noting their multidisciplinary expertise and active interest in the Division's programs. In 1986 site visits were made to the Laboratories of Pathology and Mathematical Biology, and in 1987, visits will be made to the Laboratories of Genetics, Molecular Biology, and Dermatology.

The intramural scientific highlights identified were 1) new approaches to immunotoxins, 2) understanding of the mechanisms of malignant transformation of plasma cells, 3) molecular analysis of ras-oncogenes, 4) genetic analysis of drug resistance in cancer cells, and 5) identification of the autocrine motility factor in cancer metastasis. Dr. Rabson provided additional details about the work on the autocrine motility factor in Dr. Liotta's laboratory and immunotoxins in Dr. Pastan's laboratory. The autocrine motility factor is made by malignant cells, and when it binds to a surface

receptor of the tumor cell, it increases the movement of that tumor cell by about 400 times. In Dr. Pastan's laboratory, the gene for pseudomonas toxin has been cloned and found to have portions for binding, entering, and killing the cell. The portion for killing has been removed to develop what appears to be a potent immunotoxin. Also, the P170 gene for the human multidrug resistance factor has been cloned and found to be an efflux pump, acting to remove drugs from the cells.

DCBD's estimated FY 1987 budget of $257 million represents a 14.9 percent increase over FY 1986, with a 17.4 percent increase in grants. An increase in RFA's from $1 to $2 million is for a new program in tissue procurement to make human tissue available to scientists conducting basic research.

Board of Scientific Counselors--Dr. Matthew Scharff

Dr. Scharff reviewed several BSC activities and pointed out that many of the initiatives and concepts were related to solid tumors. The Extramural Program was responsible for establishment of the human tissue network, which the Board considered an important initiative for studies of markers and biochemical changes in fresh tumor tissues. A Request for Applications was continued on the use of recombinant DNA technology in the diagnosis of cancer. The Board approved an RFA on cytogenetics and predisposition to cancer, which has implications both for diagnosis and predicting who will get cancer. Dr. Scharff said that discussions continue on how to stimulate collaboration between basic scientists and clinicians.

A second set of initiatives was brought to the DCBD BSC by the Organ Systems Program. Initiatives approved were a Program Announcement (PA) on the mechanism of metastases in prostate cancer, an RFA on markers for exfoliative bladder cancer, an RFA on molecular probes to identify markers for highly invasive colon cancer, and an RFA on the molecular biology of pancreatic cancer.

Dr. Scharff stated that the activities of the Division are contributing to significant advances in biology and medicine, such as the ability to predict the three dimensional structure of molecules from their linear sequence and the mapping of individual genes that are responsible for diseases. The two laboratories reviewed were found by site visit teams to be performing high quality work, although often within very confined space.

Dr. Scharff said the DCBD Board strongly believes that much scientific progress depends on investigator-initiated grants. Among the scientific highlights from the Division's Extramural Program, he noted, in particular, the development of transgenic mice containing oncogenes to study the effects of environmental and biochemical factors and the use of recombinant DNA technology to identify individual genes that either predispose to or cause diseases. In conclusion, Dr. Scharff emphasized the importance of the peer review system in assuring the high quality of research and the need to attract talented people into cancer and biomedical research.

In discussion, Dr. Rabson was asked to provide additional information, visual, if possible, on the autocrine motility factor.

VI. Division of Cancer Etiology Program Review--Dr. Richard Adamson

Dr. Adamson stated that the Division of Cancer Etiology (DCE) is responsible for planning and conducting the Institute's coordinated research program on cancer causation and its basic research program on cancer prevention. The Division supports intramural laboratories and extramural programs that seek to elucidate the mechanisms of cancer induction. In addition, epidemiologic studies of human populations are carried out to identify risk factors that predispose individuals to various cancers. Dr. Adamson outlined the organizational structure of DCE, which includes three major programs: Biological Carcinogenesis, Chemical and Physical Carcinogenesis, and Epidemiology and Biostatistics. Although no major organizational changes occurred in 1986, a new laboratory chief, Dr. Steven O'Brien, was appointed to the Laboratory of Viral Carcinogenesis, and the name of the extramural Low Level Radiation Effects Branch was changed to the Radiation Effects Branch.

The DCE section of the Board Book listed scientific highlights under the three programs. The following highlights were then discussed in detail:

- Studies on the chemopreventive ability of orange oil (from the Chemical and Physical Carcinogenesis Program)
- Studies of the genome structure in lentiviruses (from the Biological Carcinogenesis Program)
- Increased risk of non-Hodgkin's lymphoma among farmers exposed to 2,4-dichlorophenoxyacetic acid (2,4-D)

Dr. Adamson explained that orange oil, extracted from orange peel, inhibits carcinogenesis experimentally and that an alicyclic monoterpene, d-limonene, comprises 95 percent of orange oil. He described several studies in rats showing that d-limonene inhibits DMBA-induced mammary carcinogenesis and is effective both as an anti-initiator of the carcinogenic activity of DMBA, as well as an antipromoter in that experimental system. He noted that orange oil appears to be slightly more active than d-limonene alone, suggesting that other minor constituents of orange peel oil may contribute to its anti-carcinogenic effect.

To elucidate how the lentiviruses induce a variety of chronic diseases, researchers have cloned and characterized the genomes of the goat virus, the caprine arthritis encephalitis virus, and the equine infectious anemia virus (EIAV). Although the EIAV is not definitively classified as a lentivirus, it is morphologically similar. Studies have shown a closer relationship of the genomic organization of the caprine arthritis encephalitis virus and the EIAV to HTLV-III, the AIDS retrovirus, than to other retroviruses. Dr. Adamson stressed that the EIAV is an excellent model for determining the feasibility

of a vaccine against lentiviruses, and ultimately against the human retroviruses, particularly HTLV-III.

Dr. Adamson then described a collaborative case-control study by scientists at the NCI and the University of Kansas to evaluate the relationship between 2,4-D and the occurrence of soft tissue sarcomas, Hodgkin's disease, and non-Hodgkin's lymphomas. Although the risk for developing soft tissue sarcoma was about equal for the controls and those farmers exposed to 2,4-D, and the risk for Hodgkin's disease was slightly lower for farmers exposed to 2,4-D, the non-Hodgkin's lymphoma risk increased 600 percent among persons using the herbicide for 20 days or more per year. The level of risk was related to the total years of herbicide use. Farmers who did not use protective equipment (gloves, masks, etc.) while using herbicides had a 40 percent higher risk for non-Hodgkin's lymphoma than those who protected themselves.

The DCE budget was reviewed, showing a 12 percent increase from $248 million for FY 1986 to $278 million for FY 1987. The three major DCE Programs received approximately equal increases of about 11 percent. By organization, increases to the intramural program and contracts was about 7 percent, while the increase to grants is estimated to be about 14 percent.

Dr. Adamson concluded by thanking the Board and especially Dr. Pierce, who will be ending his term as Chairman of the DCE Board in June 1987, for their many contributions to the Division's operations.

DCE Board of Scientific Counselors--Dr. G. Barry Pierce

Dr. Pierce discussed the role of the DCE Board of Scientific Counselors (BSC) by first listing the members and noting that Dr. Peter Magee had accepted a second term on the Board. He explained that the DCE BSC organized each of their meetings to address a specific aspect of their responsibility (e.g., budgetary considerations), as well as the concepts analyzed at all meetings. Dr. Pierce noted that various Board members have been involved in workshops sponsored by the NCI Divisions and that some of the workshops had led to RFAs which provide the opportunity for interaction among intra- and extramural researchers and industry. He commented that site visits of three laboratories concluded that the overall quality of every aspect reviewed--science, personnel, cost-effectiveness--was extremely high.

Dr. Pierce mentioned the problems associated with personnel freezes and budgetary cuts, particularly the possibility of effects on laboratory structure and the ability to attract exceptional scientists. He noted that 1986 brought the first increase in intramural programs in eight years.

Dr. Pierce also illustrated the site visits projected for next year, as well as some of the highlights of workshops held over the past year. Some of these highlights were presented:

- A workshop on papillomaviruses, chaired by Dr. Renato Dulbecco, concluded that RFAs should be issued on the mechanisms of papillomaviruses in the etiology of human cancer.

- New Cooperative Agreement Awards were issued for National Collaborative Chemoprevention Projects in Texas, California, and Minnesota and would include aspects of experimental carcinogenesis, pharmacology, immunology, nutrition, and pathology.

- A subcommittee of the DCE BSC recommended that a small grants program be initiated for epidemiologic studies.

Dr. Pierce concluded by congratulating Dr. Adamson and Dr. DeVita for their effective administrative work and by urging the Board to focus on problems that are created by continual personnel freezes and budgetary cuts.

The following points were raised in discussion:

- National Toxicology Program results of oral carcinogenicity studies of d-limonene in rats and mice and studies of a resorcinol derivative will be shared with DCE scientists.

- It was clarified that although both DCE and DCPC support studies on chemoprevention, DCE concentrates on basic studies and DCPC focuses on interventional studies involving human populations. The development of this sequential process of research steps in cancer prevention was one of the main accomplishments of the past several years.

- It was stressed that individuals who follow listed precautions for 2,4-D (i.e., use protective masks and gloves) have a much lower increased risk of cancer than those who do not.

VII. Frederick Cancer Research Facility (FCRF) Program Review-- Dr. Peter J. Fischinger

Dr. Fischinger stressed that the FCRF was undergoing dynamic growth and change and pointed out that the Facility was perhaps the only area where the NCI could consider expansion. He noted that the FCRF differs in many ways from the other NCI Divisions, but does have a chartered Advisory Committee, headed by Dr. Werner H. Kirsten. Dr. Fischinger announced that Dr. Cedric W. Long had replaced Dr. Berge Hampar as General Manager/Project Officer of the Facility. The FCRF system of contracts was outlined as follows:

- The Basic Research Program, headed by Dr. George Vande Woude of Bionetics Research, Inc.

- Operations and Technical Support, the largest of all contract operations

- Animal Production, which serves most of the National Institutes of Health

- Computer Services, which provides support primarily for the systems of contracts

- Scientific Library Services, which are provided by Data Management Services, Inc.

Dr. Fischinger described some of the projects underway at the FCRF, and noted that:

- The FCRF has demonstrated the capacity of rapid response to various NCI initiatives.

- The supercomputer is now operating at 90 percent capacity.

- The new library/conference facility, which contains an auditorium that seats 250, has been completed and is being used extensively.

- Buildings 431 and 432 at the FCRF are being reconverted to house the in vitro drug screening project, which should be completed in the next one and a half years and will cost about $5 million.

- The FCRF generated space and personnel for the LAK cell project, which effectively doubled the size of the project.

- There was an increase in shared services at the FCRF.

- In the AIDs effort, the FCRF is maintaining large-scale virus production, vaccine development, and increased epidemiology support.

Dr. Fischinger then illustrated the rapid rate of the growth of the shared services at the FCRF and stressed that it would have to equilibrate soon. FCRF funding showed a significant increase between FY 1986 and FY 1987 (estimated), including increases in funding for basic research, operations and technical support, and animal production. Dr. Fischinger also outlined the FCRF funding by NCI Division, noting particularly that the significant increase for the Office of the Director reflected the potential costs of initiation of new contracts after the current recompetition. He concluded by stating that previous perturbations related to possible problems at the FCRF have been obviated.

Scientific Advisory Committee to the FCRF--Dr. Werner H. Kirsten

Dr. Kirsten explained that the role of the Scientific Advisory Committee is to determine whether the scientific efforts conducted at the FCRF meet the highest standards. About five years ago, Drs. DeVita and Fischinger appointed a Committee that included two current members of the NCAB, Drs. Korn and Mihich. At that time, the Committee had reviewed the FCRF and recommended

drastic changes, which Dr. Kirsten reassured the Board had been implemented. He noted that Dr. George Vande Woude, head of the basic research program, had been successful in attracting a group of first-rate scientists who work in the six different laboratories at the FCRF.

Dr. Kirsten mentioned that the results of three site visits conducted by the Committee were very favorable:

- The Laboratory of Molecular Virology and Carcinogenesis directed by Dr. Steven Oroszlan
- The Laboratory of Chemical and Physical Carcinogenesis directed by Dr. Lijinsky
- The Laboratory of Eukaryotic Gene Expression directed by Dr. Strathern.

Dr. Kirsten also noted that research on oncogenes directed by Dr. Vande Woude had yielded the discovery of the met-oncogene, the oncogene that is linked to, and provides a useful RFLP marker for, the gene for cystic fibrosis. Dr. Mariano Barbacid, Chief of the Laboratory of Developmental Oncology, was recognized as the Outstanding Young Scientist by the American Association for Cancer Research. Dr. Barbacid's research focuses on target cells expressing oncogenes in chemically induced tumors as a function of the developmental stage in animals.

Dr. Kirsten stated that the Committee would give particular consideration to support for the AIDS program, including research on murine, feline, and simian retroviruses, which forms the foundation for developmental work on the AIDS vaccine. Further review of the FCRF would also include consideration of establishment of a new crystallography laboratory. Dr. Kirsten concluded his presentation by assuring the Board that the Committee would continue to ensure that the research conducted at the FCRF is of the highest quality.

VIII. Division of Cancer Treatment--Dr. Bruce A. Chabner

Dr. Korn and Dr. DeVita noted the presence of Mrs. Mary Lasker and welcomed her interest and participation in the meeting.

Dr. Chabner stated that the Division of Cancer Treatment's (DCT) mission to develop therapeutic modalities is carried out through five divisional programs: Clinical Oncology (Dr. Samuel Broder, Associate Director); Radiation Research (Dr. John Antoine, Associate Director); Cancer Therapy Evaluation (Dr. Robert Wittes, Associate Director); Developmental Therapeutics (Dr. Michael Boyd, Associate Director); and Biological Response Modifiers (Dr. Dan Longo, Associate Director). Organizational changes, all within the Biological Response Modifiers Program (BRMP), included the establishment of the Laboratory of Biochemical Physiology, the Laboratory of Experimental Immunology, and the Clinical Research Branch and the abolition of the Biological Therapeutics Branch.

The estimated FY 1987 DCT budget represents an increase of approximately 16 percent over the FY 1986 budget, from $338.6 million to $391.8 million. The FY 1987 budget includes an increase of $10 million for AIDS research. In looking at the budget by programs, increases were 16 percent for Radiation Research, 17 percent for Biological Response Modifiers, 19 percent for Cancer Therapy Evaluation, 2 percent for Clinical Oncology, and 16 percent for Developmental Therapeutics. The lesser increase for Clinical Oncology in 1987 is the result of their receiving a significant increase in 1986; thus their requirements for 1987 are less. Dr. Chabner said the increase in the Cancer Therapy Evaluation Program (CTEP) is largely accounted for by the increase in Cooperative Group funding. The Developmental Therapeutics Program received a considerable increase in funds for AIDS because of the decision to undertake a full-scale AIDS drug development effort.

Of the management initiatives undertaken in FY 1986, Dr. Chabner noted the expansion of the interleukin-2/lymphokine activated killer (IL-2/LAK) cell trials to confirm Dr. Rosenberg's findings. This was accomplished through the Cooperative Group Program with clinical trials implemented at six centers. At the same time, CTEP reviewed the Cooperative Group Program and made recommendations for improved coordination in the setting of priorities for trials and undertaking larger intergroup studies. A CTEP-BRMP working group was established to coordinate the development of biologicals. A review committee was established to set guidelines for handling of animals. Third party recovery was instituted in neutron therapy clinical trials. NCI and the National Institute on Allergy and Infectious Diseases (NIAID) agreed to a collaborative AIDS effort in which DCT will be responsible for preclinical drug development and NIAID will be responsible for clinical trials.

Dr. Chabner then presented the scientific highlights, beginning with the developments in the use of LAK cells. In Dr. Steven Rosenberg's initial study, published in December 1985, 11 of 25 patients treated with LAK cells responded. Within three months, a series of trials was initiated around the country to confirm the findings. The protocol used involved administering IL-2, leukopheresis of lymphocytes in peripheral blood, and incubation of the lymphocytes with IL-2 in vitro. The activated lymphocytes, capable of lysing fresh tumor cells, were then reinfused into the patient. The CTEP was responsible for evaluation of the extramural trials. Dr. Rosenberg's results were somewhat better than the extramural results for renal cancer. Results for melanoma were roughly comparable and neither group observed activity against colon cancer. Dr. Chabner said that while LAK therapy does have antitumor activity, it may not be on the scale originally thought. He noted that Dr. Rosenberg's first patients had primarily lung involvement, while many of the later patients had bulky intra-abdominal tumors, which do not appear to respond as well. Plans to improve the therapy include Dr. Longo's trials of constant infusion of IL-2 and intraperitoneal administration to treat ovarian and colon cancer.

In the Clinical Oncology Program, Dr. Rosenberg is studying the activity of tumor infiltrating lymphocytes (TIL), a type of LAK cell found in the tumor itself. TIL appear to have more killing activity than lymphocytes in the peripheral blood. Trials are being initiated.

Another scientific highlight discussed by Dr. Chabner was AIDS drug development, in particular 3-azidothymidine (AZT). The clinical trial, conducted by Burroughs-Wellcome, was stopped because 16 deaths occurred among patients receiving the placebo and only 1 death occurred among those who received AZT. After about six to eight weeks, there was a markedly decreased incidence of opportunistic infections and Kaposi's sarcoma or lymphoma in the treated group. The drug has been released for general use, and a second generation of compounds blocked in the 3'-position has entered clinical trials.

The Developmental Therapeutics Program submitted investigational new drug applications in 1986 for five new anticancer drugs and one anti-AIDS drug. One of these drugs, anthrapyrazole, is active against some pleiotropically resistant cells, an area of particular interest. P170 glycoprotein, identified as a key protein in some forms of cellular drug resistance, has been found to have a drug binding function and can carry drugs out of cells and thus decrease intracellular concentration. This is thought to be a protective mechanism against natural product toxins.

Dr. Chabner then described a major change in the drug screening system, from the in vivo model, particularly the P388, to an in vitro system that involves the use of solid tumor cells, primarily human tumors. Panels of cell types are established to look at organ-specific tumors. Drug-resistant cells are also used in the screen. Drug companies are also moving away from mouse leukemia cells as the primary screen.

Dr. Chabner described Dr. Gallo's work on the isolation of a new virus, human B-lymphotropic virus (HBLV), from white blood cells of patients with lymphomas, some AIDS-related. The virus can infect and kill human B cells in culture, but it is not known whether HBLV is a human pathogen. Dr. Chabner suggested that this research would be important to understanding the etiology of B-cell lymphomas, which are more common than T-cell lymphomas in the United States.

The major activity in Radiation Research has been the establishment of neutron therapy facilities. Four facilities have been funded by NCI and are participating in several Phase II and III trials. The value of this treatment for recurrent salivary gland tumors is considered to be proven. New studies will cover upper aerodigestive carcinomas, prostatic cancer, non-small cell lung cancer, and cervical carcinoma.

In conclusion, Dr. Chabner described the institution of the National Collaborative Diagnostic Imaging Trials Project, established to compare different new imaging modalities. Awards are expected to be made in FY 1987.

Board of Scientific Counselors--Dr. Paul Calabresi

Dr. Calabresi reviewed the membership of the BSC and described some of the BSC's activities during 1986. In addition to its overall review function, the DCT BSC has established subcommittees to advise on new research initiatives

in surgical oncology, diagnostic imaging, radiotherapy and protocol review processes. The site visit team to the Medicine Branch suggested greater emphasis on Phase I and II clinical trials. The team also recognized the critical need for more nurses and sent a letter to Dr. Wyngaarden about this problem. Dr. Wyngaarden answered by outlining changes implemented and contemplated. The site visit team to the Radiation Oncology Branch found the Phase I and II clinical trials to be well executed and unique, with the only deficiency again being the shortage of nurses. Reviewers found the quality of protocol review conducted by the Cancer Therapy Evaluation Program to be excellent. It was suggested that the appeals process be better publicized to increase extramural awareness and that more use be made of reviews for Phase I trials. In FY 1987 site visits will be made to the Laboratory of Tumor Cell Biology, the Surgery Branch, and the NCI-Navy Medical Oncology Branch.

Dr. Calabresi said the Board was in near complete agreement with the DCT's staff recommendations on concept approvals. New RFA awards were approved for study of differentiating agents in human malignancies and NMR relaxation times. Nearly $2 million was awarded to the AIDS National Cooperative Drug Discovery Groups. The BSC recommendation to retain the AIDS drug development activity within DCT has been approved. Dr. Calabresi noted some of the BSC scientific highlights, including updates on AIDS drug development, adoptive immunotherapy, LAK cell therapy, and diagnostic imaging and presentations on advances in the molecular biology of breast cancer, photodynamic therapy, dose intensity and response to cancer treatment, and the molecular biology of childhood malignancy.

Dr. Calabresi stated that the BSC finds the scientific quality of DCT's programs to be excellent and looks forward to an exciting new year. Points raised in discussion included the following:

- In the intramural and extramural IL-2/LAK cell trials, differences in responses were probably not statistically significant. The differences may be due to the differences in patients: those in intramural trials had primary tumors resected with small pulmonary recurrences and those on extramural trials had bulky intra-abdominal disease.

- The effect of stopping AZT treatment is not known because no one has voluntarily gone off treatment, and treatment has only been stopped when serious side effects, primarily anemia, occurred.

- It is not known whether chloroquinoxaline sulfonamide is a protein kinase C inhibitor.

- Direct injection of IL-2/LAK cells into tumors is not being done, except for a small study in California on brain tumors.

- Approximately 70 percent of locally recurrent mixed cell salivary gland tumors respond to neutron therapy.

- Cytoreduction of tumor cells may be important for increasing the effectiveness of biological and chemotherapeutic treatments.

IX. Division of Career Prevention and Control--Dr. Peter Greenwald

Dr. Greenwald said that the Division of Cancer Prevention and Control (DCPC) is responsible for programs aimed at bridging basic and applied research to bring about a decrease in cancer incidence and mortality. He described a major accomplishment of the Division as clarification of the definition of cancer prevention and control to include research, particularly research on interventions that can have a broad population impact. A sequential process has been developed for following through from basic studies to clinical trials in prevention and on to widescale applications.

In describing DCPC's organization, Dr. Greenwald noted that the Deputy Director, Dr. Joseph Cullen, also leads the Smoking, Tobacco, and Cancer effort for NCI and during the past year, chaired the Surgeon General's Committee on Smokeless Tobacco. The Surveillance and Operations Branch, which includes the SEER program, is headed by Dr. Sondik. The Biometry Branch focuses largely on design and analysis of clinical trials. The three major program efforts are Cancer Prevention Research (a new Associate Director to be announced in the near future), Centers and Community Oncology, headed by Dr. Jerome Yates, and Cancer Control Science, headed by Dr. Lillian Gigliotti. The branches within these Programs, with new chiefs indicated, are as follows:

- Cancer Prevention Research
  - Diet and Cancer (Dr. Ritva Butrum)
  - Chemoprevention
  - Cancer Prevention
- Centers and Community Oncology
  - Cancer Centers Branch (includes the Organ Systems Program)
  - Community Oncology and Rehabilitation (includes the Community Clinical Oncology Program (CCOP))
  - Research Facilities
  - Early Detection (Dr. Charles Smart)
- Cancer Control of Science
  - Cancer Control Applications
  - Health Promotion Sciences
  - Special Population Studies
  - Cancer Training

DCPC's estimated FY 1987 budget is $277 million, representing about a 10 percent increase over the FY 1986 budget. Prevention and control accounts for about 25 percent, the Centers about 34 percent, and training about 15 percent. Dr. Greenwald said that during 1986 several new RFA awards were made based on concepts approved by the Board the previous year. These included studies on smoking prevention among women, 14 awards in the Small Grant Research Program, 8 awards to state health agencies, and a follow-up RFA to help states improve their technical data base capabilities.

The Board reviewed 15 concepts, including the recompetition and evaluation of CCOP, and concepts related to home care, quality of survival, childhood cancer, the Organ Systems Program, prevention, and avoidable mortality. The Board also conducted a site visit to the Biometry Branch.

Dr. Greenwald then discussed selected program highlights, referring Board members to their notebooks for full discussion. The Surveillance and Biometry Programs have developed an analytic model for projecting cancer control impact at state and local levels to assist health planners in allocating cancer control resources. The Centers and Community Oncology Program has funded a planning grant for the first minority consortium cancer center and awarded new cancer center grants in Utah and Kentucky. New initiatives include clinical studies in cancer prevention and control and studies on the influence of age on cancer detection and treatment. Within the Prevention Program, 24 chemoprevention trials are in progress and new ones are being planned. Also a BSC subcommittee has been formed to study the establishment of an intramural nutrition and cancer laboratory. Such a laboratory could contribute to large-scale prevention trials and small controlled metabolic studies. The BSC subcommittee has supported the concept, but it must still be approved by the NCI Executive Committee and the full DCPC BSC.

Board of Scientific Counselors--Dr. Erwin P. Bettinghaus

Dr. Bettinghaus reviewed the membership of the Board, noting the wide range of their expertise. The Board has divided itself into standing committees on Cancer Control Science, Budget and Evaluation, Centers and Community Oncology, and Prevention. These committees review RFAs before they are presented to the full Board for approval. One ad hoc group is the Cancer Detection Committee, which is considering the possibility of formulating recommendations to NCI on large-scale screening efforts. Another ad hoc committee is providing policy guidance to the Women's Health Trial, which is aimed at studying the effect of reducing dietary fat to 20 percent of total calories in women at high risk for breast cancer. During the time up to October 1987, questions need to be answered about dietary compliance and the feasibility of accruing 30,000 women for the full-scale trial. Progress then will be evaluated and results presented to the NCAB before a decision is made on proceeding with the trial. The effort to date has included holding workshops on statistical design, the ratio of polyunsaturated to saturated fats in the diet, biochemical markers and diet compliance, and problems of recruitment and participation in such a trial.

Indicating that he has completed his term on the Board, Dr. Bettinghaus reviewed changes that have occurred over the last four years. Comparing FY 1983 with FY 1986 figures, Dr. Bettinghaus noted an increase in spending on smoking programs from $955,000 to $17+ million, an increase in diet programs from $1 million to $9 million, and a $10 million increase in chemoprevention. Overall spending for cancer prevention and control has increased by 15 percent.

Dr. Bettinghaus then described some program highlights, beginning with the Cancer Control Science Program and noting that almost none of these efforts existed four years ago. Four contracts have been awarded to study

avoidable mortality in black populations and six contracts to study smoking behavior and prevention among blacks. A "Network for Cancer Control Research in Black Populations" has been established to facilitate the cohesion of a core of researchers with experience in and sensitivity to the needs of the black community. Public health initiatives have encouraged collaboration and coordination of cancer control efforts within states. The Cancer Control Associates Program is a new training effort, and two Cancer Control Research Units have been funded. New nutrition guidelines are being developed for school lunch programs and for the use of primary care physicians.

The Smoking, Tobacco, and Cancer Prevention Program has initiated large-scale smoking prevention interventions among adolescents, women, blacks, and Hispanics. Efforts are also underway on the prevention of smokeless tobacco use. These are the first efforts undertaken to use the mass media to help prevent smoking. Other activities are aimed at reaching the three-pack a day smoker and involving primary care physicians in the anti-smoking effort. A nationwide Smoking Intervention Network is being put into operation, and a tobacco advertising data base established. The Cancer Communication System continues to provide information on smoking and tobacco use and cessation.

Dr. Bettinghaus stated in conclusion that while much has been initiated and accomplished in the prevention area, the scientific data base is still being built. Much more effort is needed, particularly in the areas of smoking and diet, to achieve the year 2000 goals.

Points raised in discussion included the following:

- The slight decrease in the FY 1987 budget for the Organ Systems Program, when two new programs have been added, was questioned. Continuing commitment is needed to both treatment and prevention if the year 2000 goals are to be attained.

- Preliminary thoughts are that the proposed nutrition laboratory would include basic biochemistry and clinical metabolic components.

- The first phase of the Women's Low Fat Trial is expected to be completed in October 1987 and results reported to the NCAB in January 1988.

- The tobacco advertising data base is aimed at assessing the impact of advertising and how to deal with it. Anti-smoking advertising needs to be covered as well.

- NCI is cooperating with the World Health Organization on a study of the economic impact of tobacco.

X. Organ Systems Coordinating Center Annual Report--Dr. James P. Karr

Dr. Karr called the Board's attention to printed copies before them of the Organ Systems Coordinating Center (OSCC) Annual Report. He stated his belief that during the past year the Organ Systems Program (OSP) achieved

progress, owing to a number of factors, including the close interactions with NCI Divisions and NCI's expression of commitment by extending the OSCC through July 1989. The two new programs on tumors of the upper aerodigestive system and the central nervous system, approved by the NCAB in February 1986, have been initiated.

Dr. Karr reviewed OSP objectives: the multi-disciplinary definition of relevant problems; the development of concepts; and the stimulation of interdisciplinary research and multi-institutional collaboration in an attempt to link laboratory expertise and new technology to clinical applications. The OSP is administered through the Organ Systems section of the Cancer Centers Branch of DCPC. The OSCC is guided by an advisory board chaired by Dr. William Shingleton. The OSCC recruits chairpersons and members of the Working Groups, which are charged with the responsibility of identifying research opportunities relevant to the specific organ system and disease. To accomplish their objectives, the Working Groups sponsor workshops, develop concepts, and document the need for the transfer of basic research to clinical settings. The OSCC plans, coordinates, and integrates the activities of the seven Working Groups and prepares detailed documentation for concept development and presentation to a BSC. The OSCC also fosters the interaction of the Working Groups, NCI, and the biomedical community and disseminates information through the Organ Systems Newsletter.

The NCI Divisional BSCs have approved 13 of 15 OSP concepts. The following program announcements have been issued:

- Breast
  - Interaction among micronutrients in the prevention of experimental mammary cancer
  - Breast cancer in DES-treated mothers and DES-exposed offspring
- Large bowel
  - Mechanisms of drug resistance in colon carcinoma
- Prostate
  - Mechanisms of site-specific metastasis in prostate cancer.

Dr. Karr said the Working Groups are generally satisfied that the announcements are drawing the attention of investigators to these research areas. NCI plans to issue the announcements through three cycles of grant submissions.

RFAs that have been approved and are in various stages of implementation are as follows:

- Large bowel
  - Inheritance and markers of colorectal cancer and polyps
  - Characterization and relevance of specific molecular probes in unique subsets of colorectal cancer patients
- Pancreas
  - Prospective study to correlate pain reduction with treatment procedures employed in pancreatic cancer patients
  - Studies in the molecular biology of pancreatic cancer
- Bladder
  - Pharmacokinetics of agents for bladder cancer intravesical chemotherapy
  - Markers of exfoliated bladder cancer cells correlated with tumor progression and recurrence
- Breast
  - Assessment of breast cancer risk among women with proliferative benign breast disease
- Prostate
  - Early diagnosis of prostate adenocarcinoma.

Dr. Karr then summarized research areas that Working Groups will develop for future presentation of concepts:

- Bladder
  - Studies on carcinogens, proto-oncogene activation, and cytogenetic changes associated with neoplastic transformation
  - Role of radiation therapy when used with other modalities
  - Maintenance and use of data bases and specimens from the former Bladder Collaborative Clinical Trials Group
- Breast
  - Systems and markers for <u>in vitro</u> studies of transformation of human mammary cells

- Relationship between oncogene expression and the malignant phenotypes of mammary cancer cells

- Hormonal priming as a means of enhancing the effectiveness of chemotherapy

- Central nervous system

  - Neuropathology and the development of probes for diagnosis and prognosis

  - New initiatives in radiobiology

  - In vitro drug sensitivity testing

- Large bowel

  - Evaluation of conservative treatment of adenocarcinoma of the distal rectum and anus

  - Diet, polyps, and cancer

  - Cellular biology of stem cells in colorectal cancer

- Pancreas

  - Development of a transgenic mouse model for ductal cell adenocarcinoma

- Prostate

  - Growth regulatory factors

  - Models for carcinogenesis and transformation studies

  - Need for nomenclature and procedural uniformities (as a result of a workshop sponsored by the Working Group, Committees were formed to recommend to the NCI and the American Urological Association ways of standardization)

- Upper aerodigestive system

  - In vitro and in vivo models for alcohol- and tobacco-related cancers

  - Steroid hormone action and receptor characterization

  - Assessment of functional outcome following treatment.

Joint efforts that are being developed by the OSP include concepts on stromal epithelial interactions developed by four Working Groups and concepts

on hormonal synchronization developed by the Prostate and Breast Working Groups. Dr. Karr said there is interest in holding a joint workshop on solid tumors, and he encouraged NCAB members to propose topics for other joint Working Group workshops.

In conclusion, Dr. Karr raised the question of whether it would be possible to decrease the amount of time between BSC approval of a concept and its publication. The point was raised in discussion that the OSP may be a positive factor in promoting communication between the NCI and the clinical community.

XI. Centers Program Overview--Dr. Jerome Yates

Dr. Yates said that NCI-designated cancer centers are located mainly in the most populous areas of the country and noted multiple centers and community hospitals in the New York metropolitan area. Although cancer centers have a long history, beginning with Memorial Sloan-Kettering in 1884, it was not until the passage of the National Cancer Act in 1971 that guidelines outlining the essential characteristics of a cancer center were consolidated. The Act authorized the Director of NCI "to provide for the establishment of 15 new centers for clinical research, training, and demonstration of advanced diagnostic and treatment methods relating to cancer." In the mid-1970s, the essential characteristics of a cancer center seeking core grant support were delineated: high quality research, interdisciplinary coordination, organizational capability, center director with authority, institutional commitment, and adequate facilities. Dr. Yates emphasized the success of the Core Grant Program.

The role of the centers in cancer control in the 1970s was based on demonstration projects, established as an extension of productive clinical investigation in cancer treatment. Except for rehabilitation, the first cancer control support for research was in the Cooperative Group Outreach Program, a program that continues to be successful today. When Dr. Peter Greenwald joined NCI in 1981, there was a shift away from demonstration projects to an increase in the rigor of research in cancer control. The conceptualization of cancer control as a series of defined sequential steps from hypothesis development to national programs and strategies has fostered a new era of applied research, which should be reflected in increased emphasis on cancer control by the centers.

In 1971, the Report of the National Panel of Consultants on the Conquest of Cancer, chaired by Mr. Benno Schmidt, suggested the need for equitable geographic distribution of centers and an integrated organizational structure. Dr. Yates said that factors obstructing the implementation of cancer control at centers included concern about the science in cancer control research and the fact that medical schools often tended to be introverted, relying on their trainees to influence the community. Changes in the medical environment in the past five years have opened new opportunities for research in cancer control.

Cancer centers are diverse in their institutional affiliations, sources of support, regional interactions and scope of activity. They may be free-standing, university-based, or represent government institutions. Funding may come from Federal or state grants, universities, philanthropy, and patient care income. Cancer control activities may involve community outreach or extensive regional interactions including consortia. Dr. Yates said the components of a cancer center grant--administrative leadership, program leadership, shared resources, and developmental funding--provide a matrix cutting across the usual departmental lines found in most medical schools. This stimulates the diffusion of information and increases opportunities for both laboratory and clinical research. Dr. Yates emphasized that core grants are only awarded to institutions that have a foundation of peer-reviewed RO1/PO1 support.

Community cancer centers have resulted from the support of clinical research in the community by NCI programs and the efforts of local hospitals to consolidate services, improve efficiency, and facilitate patient access. Others call themselves centers to market care in regionally competitive areas. Medical schools are recognizing the need to make communities aware of differences between nominal and actual centers.

Currently there are 15 laboratory centers, 22 clinical centers, and 20 comprehensive centers with NCI-funded core grants. The comprehensive centers are expected to have both laboratory and clinical research and a commitment to providing regional leadership in cancer efforts. Centers are reviewed separately for comprehensive status, and receive no funding for that designation. A fourth type of center is the consortium center involving multiple institutions including state health departments. The distribution of the types of core grants is about equal, and funding is similar in terms of allocation of shared resources and professional personnel. The ratio of core grant support to support from NCI and other sources is about 20 percent.

Dr. Yates said the number of centers with core grants peaked in the mid-1970s, but the centers' budgets have been increasing, bringing the FY 1987 total to about $93 million. In anticipation of tighter funding, future issues that must be considered by the centers program relate to the number, type, and location of centers, the role of centers in cancer control research, interactions of centers with the community, and participation of centers in clinical trials networks. Dr. Yates said while the centers have demonstrated their leadership in laboratory and clinical research, the challenge for the centers over the next 10 years is in cancer control.

Points raised in discussion included the following:

- The nuclear magnetic resonance imaging (MRI) network was not funded because of the Gramm-Rudman-imposed need to reduce contracts and the existence of ongoing MRI activities within DCT. There are six contracts, primarily to cancer centers, to evaluate the clinical use of MRI in the treatment of specific cancers, and another effort is planned to involve multiple institutions in comparing MRI diagnostic capabilities to other modalities.

- Guidelines exist for comprehensive status center core grants, and consortium centers. NCI staff will examine whether changes in the present set of guidelines are needed.

- The intent of the cancer center core grant program has been to assure that the center director has authority comparable to departmental chairmen in the allocation of space, making appointments, and use of research dollars.

- It is not anticipated at this time that there is a need to change center guidelines to emphasize cancer control activities.

- The DCPC BSC will be asked to consider whether guidelines should be changed to provide for the review of the science of clinical research at the cancer centers. Little P01/R01 and U10 support is available as the foundation for a clinical research program at centers.

- Use of the word "comprehensive" cannot be restricted. NCI-designated centers that hold core grants may use the term NCI-designated cancer centers.

XII. Overview of Memorial Sloan-Kettering Cancer Center--Dr. Paul A. Marks

Dr. Marks welcomed Board members and provided a historical overview of Memorial Sloan-Kettering's (MSK) 103 years of existence. The hospital was established in 1884 as the New York Cancer Hospital and was designed to have circular wards and an innovative ventilation system thought to minimize or prevent infection. In 1889 the name was changed to General Memorial Hospital for the Treatment of Cancer and Allied Diseases. Dr. William Coley, an attending surgeon at that time, developed "toxins," which were believed to contribute to the remission of certain cancers. About 70 years later, Dr. Lloyd Old demonstrated that the active factors in Coley's toxins were the so-called tumor necrosis factors. Dr. Coley was the recipient of what was perhaps the first philanthropic gift in support of cancer research, donated by John D. Rockefeller, Sr. Mr. Rockefeller subsequently arranged for the move of the hospital to its present site and its collaboration with Cornell Medical School and Rockefeller University.

The research arm of the hospital came into being in 1945 as the Sloan-Kettering Institute (SKI), with Dr. Cornelius Rhoads, who initiated and developed the discipline of cancer chemotherapy, as the first Director. This marked the initiation of the close interaction between basic laboratory and clinical research programs and patient care.

In the current organization of the Center, Dr. Marks, as President, reports to the Board of Managers, chaired by Mr. Benno C. Schmidt with Laurance Rockefeller as Honorary Chairman. Dr. Samuel Hellman serves as Physician-in-Chief of Memorial Hospital and Dr. Richard Rifkind as Chairman of the Sloan-Kettering Institute. Dr. Marks summarized patient care commitments as follows: approximately 16,000 admissions per year with more than 1,000 of those to the Pediatric Unit; 89 to 90 percent occupancy rate; and 140,000

outpatient visits. Approximately 40 to 50 percent of patients participate in some approved clinical research protocol at some time during their illness. Memorial Sloan-Kettering Cancer Center's (MSKCC) 1986 budget is about $322 million, of which $63 million supports laboratory research, $11.5 million educational programs, and $248 million patient care. The staff comprises 428 physicians and researchers (356 on the hospital attending staff and 123 members of the Research Institute) and about 800 nurses.

Dr. Marks then described the long-range strategic planning process initiated by the Center in 1981. The effort was undertaken to examine all programs and identify their strengths and weaknesses in the context of resource requirements. A new and expanded radiation oncology center, an adult day hospital, renovation and expansion of ambulatory care facilities, upgrading clinical support laboratories, and a new research laboratory facility were among the high priority needs identified. Approximately 70 percent of the projected capital needs have been raised, and projects completed or underway include housing for staff, a medical library and information center, a magnetic resonance imaging center, and the future Rockefeller Research Laboratories.

In conclusion, Dr. Marks noted the importance to MSKCC of support from the National Cancer Institute. He stated that research is yielding very important information that should lead to promising approaches for earlier diagnosis, more effective treatment, and better strategies for cancer prevention.

XIII. Memorial Sloan-Kettering Cancer Center in the Context of the National Cancer Act--Mr. Benno C. Schmidt

Mr. Schmidt expressed his pleasure at being able to welcome members of the National Cancer Advisory Board to Memorial Sloan-Kettering on the 15th anniversary of the National Cancer Act. He then presented an historical account of the events preceding passage of the Act and the years following. Mr. Schmidt's involvement began in early 1970 when Senator Ralph Yarborough invited him to chair a panel to review and make recommendations about Federal support of biomedical research and, in particular, cancer. The Panel drafted the National Cancer Act by the end of 1970.

Mr. Schmidt described the scientific and political opposition to the Act. Passage of the Act and signing by President Nixon were accomplished through the Panel's efforts to convince opponents that the primary thrust was to expand and enhance the basic biomedical research already being supported by the Government. The President asked Mr. Schmidt to chair the President's Cancer Panel, established by the National Cancer Act.

As a result of the Act, NCI's budget increased from $180 million in 1971 to over $1.3 billion in 1986, and NIH's budget increased from $1 billion in 1971 to $5.3 billion in 1986. Over half of the money has been spent on basic biomedical research, which Mr. Schmidt suggested, has brought us to the early stages of a biomedical revolution. This revolution, initiated with the elucidation of the structure of DNA, should provide the knowledge to enable the conquest of the chronic diseases, including cancer, that are today's major killers.

Mr. Schmidt also mentioned the importance of the greatly improved capacity for moving basic research findings to clinical use. The National Cancer Act of 1971 included the provision that the Government, through grants, would stimulate the creation of comprehensive cancer centers throughout the Nation to 1) bring the best possible level of cancer care to as many citizens as possible and 2) improve both cancer care and research by bringing these programs together in the same institutions. Mr. Schmidt stated that in 1971 Memorial Sloan-Kettering was the model for the comprehensive cancer centers mandated by the National Cancer Act. Mr. Schmidt concluded by expressing the hope that in the next 15 years progress made in the clinic will be commensurate with that made in the laboratory during the last 15 years.

In discussion of Dr. Marks' and Mr. Schmidt's remarks, the following points were raised:

- MSKCC has extensive relationships with Cornell Medical School, including a joint M.D./Ph.D. program, clinical and didactic training of medical students, and a molecular biology Ph.D. program. In addition all MSKCC staff physicians have appointments at Cornell University and some also at Rockefeller University.

- MSKCC's operating deficit of $30 million is budgeted and covered by philanthropic contributions. Twelve million dollars of the deficit is attributed to free care provided by MSKCC, primarily to outpatients. Approximately half of the deficit is to support research and educational programs not funded by grants.

Dr. DeVita requested and received Mr. Schmidt's permission to publish his remarks in the special 50th anniversary issue of the Journal of the National Cancer Institute. (Copies of Mr. Schmidt's remarks were provided to the Board.)

XIV. Laboratory Research Programs--Dr. Richard A. Rifkind

Dr. Rifkind, Chairman of the Sloan-Kettering Institute, stated that the principal goal of the laboratory research programs is to assure a broad base of biological research relevant to cancer and cancer cell biology. In addition, the laboratory programs serve to assure the scientific quality of activities and help establish priorities for use of resources, facilities, and support. SKI's four research programs, which Dr. Rifkind described as faculty affinity groups rather than traditional faculty departments, are Molecular Biology and Virology, Cell Biology and Genetics, Immunology, and Developmental Therapy and Clinical Investigation. Interdisciplinary collaboration is a very important characteristic of all the programs, and embraces interlaboratory and laboratory-clinician collaboration, as well as the efficient transfer of research into clinical progress.

Dr. Rifkind said that both institutional and external resources are used to accomplish the goals of the research programs. He noted the support of the NCI through 11 P01 grants covering a broad spectrum of research strategies

and involving more than 60 center scientists. Institutional resources include space, core facilities, and funds, in particular, seed monies for the first phases of a project.

Finally, Dr. Rifkind noted the very important role of educational programs, at all levels from undergraduate to postdoctoral, in promoting interdisciplinary collaboration. At MSKCC, these include collaborative programs with Cornell University, Rockefeller University, and institutions throughout the country for medical, dental, and nursing students, residents, post-residents, doctoral and postdoctoral students, social work students, and others.

XV. Clinical Research Programs--Dr. Samuel Hellman

Dr. Hellman, Physician-in-Chief of Memorial Hospital, identified the strategies of the clinical research programs: develop new treatments; improve current treatments; and improve the complementary use of the three treatment modalities, surgery, chemotherapy, and radiation. Strategies for the future include the provision of facilities for the anticipated increased emphasis on interdisciplinary and outpatient and ambulatory care. In addition, attention is needed on the quality of life for cancer patients who survive and those who are not cured or have significant morbidity associated with their treatment. This area includes psychosocial aspects of cancer care and helping cured patients become functioning and active members of society.

Dr. Hellman then reviewed the clinical departments and noted some characteristics of each:

- Medicine--includes medical oncology, concerned with the use of agents to treat patients with cancer, and general medicine, concerned with other aspects relevant to the patients or to the cancer problem in general. The gastroenterology service is the WHO Center for colorectal disease and concerned with the early diagnosis of disease and identification of high-risk groups.

- Surgery--includes all major subspecialties with interdisciplinary aspects as well as research programs, for example, on the metabolism of the cancer patients.

- Radiation oncology--to be doubled in size to include 10 supervoltage units.

- Pediatrics--includes active research programs on solid tumors and leukemia, as well as an active bone marrow transplant program. MSKCC is a member of the National Cooperative Group on pediatric solid tumors.

- Neurology--includes brain cancer research, programs on the psychologic aspects of cancer, an active pain service, the neurologic aspects of the AIDS program, and PET scanning.

- Anesthesiology and Critical Care--emphasizes understanding the problems of the critically ill cancer patient and the patient treated with therapies that require active critical care monitoring.

- Pathology--includes surgical pathology and other aspects of pathology, such as flow cytometry, cytology, genetics, and immunology.

- Medical imaging--includes a new program in magnetic resonance imaging.

- Medical physics--embraces the long tradition of radiation treatment.

- Clinical chemistry--conducts research on tests to detect cancer.

- Epidemiology and biostatistics--includes a new program in genetic epidemiology.

The clinical research programs are managed through an Institutional Review Board (IRB) and Research Council. The Clinical Research Support Program (CRSP) provides a clinical research management information system that includes information on every protocol, e.g., the number of patients, the investigators, the departments, etc. CRSP also encompasses programs on biostatistics, the Committees on Investigational Drugs and Investigational Devices, the Committee on Radiation, the Animal Care Committee, the Psychosocial Task Force, and the AIDS Task Force.

There are a total of 469 open research protocols and about 41 percent of in-patients are on research protocols at any given time. Fifty percent of the clinical staff are listed as principal investigators on research protocols. The research protocols cover a wide range of activities including chemotherapy (40 percent), surgery (20 percent), radiation therapy (20 percent), and immunotherapy (10 percent).

Dr. Hellman pointed out AIDS, bone marrow transplantation, and the use of biologicals as different from other research activities because they are extraordinarily resource-consuming. These areas of research and patient care have implications for the entire institution.

The following points were raised in discussion:

- MSKCC's AIDS Task Force is a multidisciplinary group to coordinate institution-wide activities related to research programs and care of AIDS patients and bring issues to the attention of the Research Council.

- Because the largest number of admissions to MSKCC are surgical and for diagnosis, these patients would not be on research protocols. For cancers where there is active research, e.g., brain cancer, urological cancer, pediatric

cancers, nearly everyone with a definitive diagnosis is on a research protocol. Some of the protocols are Phase I trials or non-therapeutic trials.

- MSKCC has 86 agreements with 55 private companies for collaborative research efforts.

- While Memorial Hospital is organized by department, Sloan-Kettering Institute is non-departmental with funds allocated to research areas which may inter-relate with one or several clinical departments.

XVI. Molecular Biology Overview--Dr. Erwin J. Fleissner

Dr. Fleissner stated that the primary focus of the Sloan-Kettering Institute's Molecular Biology Program is on the mechanisms by which the tumor cell arises and the differences between tumor and normal cells. As introduction, he noted that specific genes, some of which are oncogenes, are expressed in a way that departs from normal development. The oncogenes must also have roles in normal development which may be related to the process of growth regulation. This convergence of research on oncogenes and growth factors is generating considerable interest among cancer researchers.

Dr. Fleissner identified the four research areas of the Molecular Biology Program: 1) DNA replication and RNA synthesis and processing; 2) programming of the transcription of certain genes in the normal development of various kinds of cells; 3) oncogenes; and 4) growth factors and other extracellular ligands and their biological effects. He then reviewed the laboratories and scientists working on these areas and mentioned the importance of frequent interactions among the Program's staff. Dr. Fleissner stated the underlying questions being addressed and identified certain aspects of the research addressing the question as deserving special note:

(1) What are the mechanisms of replication and transcription?

-- Nucleic acid biosynthesis; viral nucleic acid synthesis and control of transcription and translation; prokaryotic DNA synthesis

(2) How does cancer interfere with normal developmental processes?

-- Developmental genetics in drosophila; transgenic mice and developmental mutations; tyrosine protein kinases in yeast; *in vitro* control of hemoglobin or globulin synthesis, attachment proteins

(3) How do oncogenes control cell growth and how are normal growth mechanisms perturbed in cancer cells?

-- Retroviruses; oncogenes associated with retroviral neoplasias; human c-*myc* oncogene and Burkitt's lymphoma; n-*myc* oncogene

and childhood neuroblastomas; kit-oncogene in feline neoplasms; genetic engineering of retroviral vectors to develop cures of lethal genetic effects; mutation of ras-oncogenes in human leukemias

(4) Can the normal pathways of cell growth regulation be used to understand and control cancer?

-- Relation of oncogenes and growth factor receptors; genes induced by interferon and interferon receptors

Dr. Fleissner concluded by stating that scientists are now approaching an understanding of the molecular basis of cancer.

Points raised in discussion included the following:

- The focus of MSKCC's Molecular Biology Program is on the mechanisms of development of tumor cells, but there are research opportunities related to intervention.

- Collaborative research efforts are being conducted at MSKCC on oncogene expression as markers for tumors and tumor responsiveness to cytotoxic and cytodifferentiation agents. In addition, the potential for using these markers to diagnose specific cancers is being studied.

Growth Factor and Hormone Signalling--Dr. Ora Rosen

Dr. Rosen described the mechanism by which molecules that interact with cell surfaces but do not enter the cell persuade the cell to follow specific pathways of either growth, differentiation, or metabolism. Within the past 20 years one whole pathway has been elucidated: cyclic AMP by interacting with and activating the enzyme cyclic AMP-dependent protein kinase leads to the modification of certain proteins that either turn on or off specific pathways in the cells. This explained how a certain class of hormones, such as epinephrine and some neurotransmitters work. On the other hand, it became evident that some factors, including growth factors, peptides, and protein hormones, did not act like cyclic-AMP.

Insulin was chosen for study because of its importance and because quite a lot is known about its biochemistry and physiology. Dr. Rosen stated that insulin is a polypeptide hormone that interacts with cell surfaces and stimulates glucose uptake and disposes of carbohydrate. In addition, insulin has been found to be a growth factor that is related to other chemically similar molecules that are clearly growth factors. While knowledge about how insulin stimulates growth is incomplete, it is known that insulin causes proteins to be phosphorylated and that these changes occur on serine and tyrosine residues. All the effects of insulin are activated by the interaction of insulin with a specific macromolecule on the cell surface, known as the insulin receptor.

The insulin receptor is a large glycoprotein, made up of four subunits of two different kinds. Two of the subunits are outside of the cell and bind insulin. They are linked, however, to two other sets of subunits that actually traverse the cell membrane and anchor the insulin binding components to the cell surface. The insulin receptor is synthesized as one protein which has two domains encompassed within a single chain. Therefore, to clone the molecule, it was necessary to look for only one gene for the insulin receptor. The strategy used was to sequence part of the protein from the two different kinds of subunits and construct oligonucleotide polymers based on the amino acid sequences; these could then be used probe a human library to find homologous sequences, which was accomplished. Through biochemical study of the insulin receptor, the receptor itself was found to be an enzyme, a protein kinase that phosphorylates tyrosine rather than serine residues.

Dr. Rosen said these findings should lead to understanding the relationship between insulin's ability to phosphorylate proteins and the action of insulin. In the perspective of other research, Dr. Rosen noted that the protein encoded by viral oncogenes is in many cases an enzyme exactly like the enzyme that is a portion of the insulin receptor. Other growth factors are being found to have receptors, like the insulin receptor, that have tyrosine protein kinase activity. Additional studies further demonstrated that insulin action requires an active tyrosine protein kinase.

Dr. Rosen then outlined the next research challenges in this area of study:

-- Identify the proteins that are phosphorylated on tyrosine residues and involved in modulating insulin's actions.

-- Elucidate the biochemical pathways from phosphoprotein to physiologic response.

-- Determine how much of the information about insulin will be generally applicable to other growth factors.

-- Determine how complicated the action is, i.e., one protein phosphorylated giving a range of effects or 100 proteins phosphorylated leading independently to 100 effects.

-- Devise ways of modifying the reaction for possible use in treating diseases, including cancer and diabetes.

The following points were raised in discussion:

- Protease is probably not a component of the insulin receptor itself but is used for processing a group of growth factor receptors.

- Responses of cells to hormones depend on several factors, including what is on the cell surface, what the hormone interacts with, and what proteins are modified.

- Regions of the insulin protein, other than those that are already mapped, are likely also to be determinants of insulin's action.

- The insulin receptor down-regulates, meaning that the occupied receptor internalizes at a more rapid rate than the unoccupied receptor. The internalized receptor may go back to the cell surface, it may be degraded, or it may be active within the cell targeting kinase to substrates that are not accessible to the cell surface.

- The insulin receptor, tyrosine kinase, is one of a family of proteins that are related but not identical.

XVII. Delivery of Patient Care and Outreach--Dr. Samuel Hellman

Dr. Hellman described several examples of MSKCC's community outreach service and research activities operating within the tri-state area of New York, New Jersey, and Connecticut. The Cancer Information Service, supported in part by an NCI contract, received nearly 48,000 telephone calls from January 1983 through June 1986. These resulted in 7,801 referrals (16.3 percent) to NCI Cooperative Groups, to a comprehensive cancer center, or to NCI directly.

MSKCC is affiliated with seven New York and New Jersey CCOP (NCI's Community Clinical Oncology Program) hospitals. These hospitals submit patients for active participation in Memorial's protocols, which cover a large range of diseases. The CCOP program is governed by a steering committee which reports to MSKCC's Research Council. CCOP subcommittees on solid tumors, leukemia/lymphoma, pediatrics, surgery, and cancer control are all based at MSKCC. Other organizational components are from the specific areas that make up the CCOP research base.

MSKCC has a cooperative agreement with the New York City Health and Hospitals Corporation (HHC) to help the City meet the needs of patients with unusual cancers. Most pediatric tumor patients who go into other hospitals (except Bellevue, which has a relationship with New York University Hospital) would be referred to MSKCC. The cooperative agreement also provides for the development of a centralized quality assurance program for cancer care in HHC facilities. In addition, MSKCC is developing and testing cancer screening program models in HHC hospitals and clinics.

MSKCC recently began developing a cooperative program to set regional objectives for cancer screening with the New York State Department of Health. This program includes methodological research on small area variation in cancer incidence and mortality. Very high incidences of breast cancer have been identified in certain areas of New York City, and in these areas, efforts are being made to intensify screening efforts and provide early diagnosis. A statewide plan is to be developed for educating physicians, specifically on screening objectives. The agreement with the state also provides for the development and testing of models to refer high-risk populations into cancer

screening and the development of a quality assurance program to be used in the state's cancer screening services.

Another outreach effort is the Breast Examination Center of Harlem, where 9,600 women have been examined since June 1980. Dr. Hellman noted that a major problem of this program and any screening program is that patients referred for subsequent tests, i.e., mammography, do not show up. Therefore, MSKCC will install an on-site mammography unit in the Breast Cancer Center in Harlem in January 1987.

MSKCC's Social Work Department offers regular training for community health professionals. Activities include the New York City AIDS Training Program, which involved 900 participants from 95 hospitals and social agencies in 1986; the Student with Cancer Program for teachers, nurses, and guidance counselors; and a postgraduate course in psychosocial oncology for social workers and other mental health professionals.

Points raised in discussion included the following:

- Some of MSKCC's protocols are Phase I trials and some have proved too complicated for use by the CCOPs. MSKCC has done a study to show that CCOP's data are as good as their own in hopes of encouraging more participation in protocols.

- Approximately 85 percent of the callers to the Cancer Information Service are white, 10 percent black, and 5 percent Hispanic.

- At the Breast Cancer Center of Harlem, the cost of mammography is about $60 but is free to those without insurance.

- In microdistribution analyses, mortality and incidence should be looked at together. In areas with a high mortality rate and high incidence of early stage disease, there may be a problem in getting treatment. In areas with a high mortality rate and a high incidence of late stage disease, screening may be indicated.

An Alternative to Inpatient Care--Dr. Richard J. Gralla

Dr. Gralla described the medical day hospital unit established at MSKCC as an alternative to inpatient care. The effort was planned and evaluated in terms of psychosocial effects for the patients and their families, cost containment, and medical outcome. The two-year program was supported by grants from the Robert Wood Johnson Foundation, the Pugh Foundation, the Kaiser Family Foundation, and the United Hospital Fund.

Eligible patients were randomly assigned to either the day hospital or inpatient care (444 patients in each group). The patient's care plan must require more than four hours but less than eight hours of treatment. All patients assigned to the day hospital must have a care partner, usually a family member. In addition, the patients must have stable cardiovascular

status and be able to arrange transportation to and from the hospital. Patients come in for one day, consecutive days, or alternate days, depending on their specific treatment requirements.

The physical environment was designed to be more open and less hospital-like than the traditional hospital setting. Education of the patient and the family is a very important component in trying to shift the emphasis of care from the hospital staff to the patient and the family. Teaching is done by the primary care nurse, who also treats the patient. Many of the patients are on one or more research protocols, as well as the day hospital protocol.

Dr. Gralla said the final analysis of the program is not yet complete, but he provided interim findings. Patients were evaluated by telephone and home visits 20 and 60 days after entering the study. About 70 percent of the patients in the day hospital were male, which Dr. Gralla said probably reflected the fact that most treatments for breast cancer are done on an outpatient basis. More than half of the patients were employed, and the majority had a good performance status. Eighty-four percent of the patients were treated for 14 different malignancies, most of these the very common malignancies--lung, bladder, and prostate cancers, sarcomas--and there were a few AIDS patients. Most of the patients came in for chemotherapy, with many receiving cis-platin in high or moderate doses or in combination with other drugs. Phase I and II studies were conducted. In addition, the patients received supportive treatment, such as pain control, intravenous antibiotics, and antiemetics. Nearly all the patients were able to return home after their treatment.

Dr. Gralla said there is a high degree of patient and family satisfaction with the program. About 95 percent of the patients indicated that they would recommend the adult day hospital to others. Family members have experienced no increased burden in taking care of the patient, and in fact, miss fewer hours of work than family members of inpatients. Symptom control, response rates, and survival were identical for the patients in the day hospital program and those admitted as inpatients for treatments. The day hospital group had fewer treatment days and, costs were about one-third less than for inpatients.

In discussion it was noted that the typical length of stay for the in-patient group was three days. Approximately 15 percent of the patients eligible for the study refused randomization.

The Board then recessed for a tour of Memorial Sloan-Kettering Cancer Center.

Pain Research Program--Dr. Kathleen M. Foley

Dr. Foley introduced her presentation with discussion of the epidemiology of cancer pain: about half of cancer patients undergoing active therapy have significant pain; more than two-thirds of patients with advanced disease have significant pain; and about 25 million patients, worldwide, have died with inadequate pain control. As pain is clearly a significant problem for the cancer patient, Dr. Foley stated that good and adequate pain control should be integral to any approach to patient management.

MSKCC's Pain Research Program focuses on both basic mechanistic studies and clinical issues, using the concept that the cancer patient is really the experimental model of pain. Animal studies provide information on sensory physiology and pharmacology but cannot provide information on the emotional suffering components of pain. Dr. Foley said that in cancer, where pain is a component of the disease, intervention therapies must take into account the relationship between pain and suffering.

One area of pain research is elucidation of the mechanisms of analgesia, in particular differentiating the mu-1 and mu-2 receptors, which mediate different pharmacological effects of analgesic drugs. The finding that the mu-1 receptor mediates analgesia and the mu-2 receptor mediates respiratory depression is important for developing drugs targeted to the appropriate receptor and thus providing better pain control.

The clinical pharmacology research is based on the concept that drug therapy is the mainstay therapy for the cancer patient and that adjuvant analgesics play a major role. Dr. Foley said the opiate analgesics have been a major interest with emphasis on novel methods of drug administration. The rationale for the approach is that patients receiving drugs orally or intravenously become sedated before they experience pain relief. Intrathecal administration and administration of drugs into the lumbar area are methods being used to provide selective analgesia with minimal doses of drugs.

Dr. Foley identified the study of heroin as another important issue. In vitro studies have shown that heroin does not bind to the opiate receptor but is a pro-drug which produces its analgesic effect through its function as a carrier molecule. In the central nervous system, heroin is degraded to two active metabolites, 6-acetylmorphine and morphine, which appear to provide significant pain relief to cancer patients. When two groups of cancer patients were given equal analgesic doses of morphine and heroin, there were no differences in pain relief, mood effects, or side effects. Studies are now in progress on repetitive dosing of heroin and comparing heroin to hydromorphine, which is legal and available in the United States.

Dr. Foley stated that MSKCC has been a leader in the study of measurement of pain and developed the analgesic assay methodology that is used in clinical pharmacology to test new analgesic agents. Patients are given visual analog cards to indicate their pain intensity on a pain scale. Then patients are given a mood scale to define relative pain, which is used to ascertain the relative potency of analgesics and the relative effects of specific approaches used in pain management. The method developed for children includes a series of faces varying in expression from happy to sad, and children mark the one that represents how they feel. Dr. Foley said these pain assay methodologies have been validated in numerous studies and should be integrated into a variety of cancer treatments to assess the pain components. In addition, these methodological approaches, combined with pharmacologic and pharmacodynamic information, can be used to predict the drug and dose that would be best for a patient.

Another aspect of MSKCC's Pain Research Program centers on the psychosocial correlates of pain. Using pain scales and various behavioral approaches,

attempts are made to differentiate pain from suffering. MSKCC's clinical service consists of inpatient consultation and an outpatient clinic and provides patients with a wide variety of practical approaches to managing pain. MSKCC also offers training in pain control to physicians and nurses from other institutions.

The Pain Research Program includes a Supportive Care Program, which was developed for patients with very sophisticated cancer pain-related problems who leave MSKCC and go into community hospitals. The program provides education to physicians and health professionals and serves as a resource for the communities. Nurses are on call on a 24-hour basis and a hotline is available to give information to patients and their families.

In conclusion, Dr. Foley stated that because the problem of cancer pain is a global one, MSKCC has been working closely with the World Health Organization to develop a cancer pain relief program. The goal of the program is freedom from cancer pain, made available through drug therapy to all patients throughout the world.

Psychosocial Aspects of Cancer--Dr. Jimmie C. Holland

Dr. Holland reviewed the changes in the types of psychological issues associated with the cancer patient. In the 1940s, when survival rates were low, the main concern was helping the patient and the family deal with dying and death. In the 1950s and 60s patients had to cope with radical surgeries. As survival began to improve in the 1960s and 70s, a new set of issues related to the quality of life after cure has come to the fore. MSKCC's psychiatry program is within the Neurology Department and includes inpatient and outpatient consultations and care and a training program for clinical education and research.

The research program focuses on two psychological dimensions: what cancer does to the patient and the family and what people can do alter their risk and, having gotten cancer, their length of survival. To study the first question, a study was carried out across three cancer centers to randomly access patients with all stages of diseases to find out their common problems. Half of the patients in the hospital were found to be reacting normally to the stress of having cancer. About 30 percent of the patients had reactive depression or anxiety. A few were more severely depressed, a few were in confusional states, and a very few had pre-existing psychological problems. The conclusion was that most patients are psychologically normal and healthy people dealing with the stress of cancer.

Dr. Holland said that using that information, researchers are assessing the quality of life at different stages of illness. During the active treatment stage, behavioral interventions, counseling, and drugs may be used. Behavioral interventions have been particularly helpful in controlling nausea and vomiting experienced in anticipation of chemotherapy. Control of anxiety and pain also respond to behavioral interventions. Patients develop conditioned symptoms so that years after treatment, smells and tastes related to the clinic elicit deepseated immediate responses of nausea and anxiety.

MSKCC is also concerned about reducing stress among the staff who are involved in patient treatment. If health care providers are too stressed, they experience emotional fatigue and diminished empathy. A program is in place to reduce stress experienced in the hospital and at home and improve communication among staff. Patients are asked about the sensitivity of staff members, as well as about the medical care they receive.

Dr. Holland stated that, happily, attention must now be focused on a new group--those who have been cured or the long-term survivors. In one study, individuals cured of breast cancer, Hodgkin's disease, testicular cancer, and leukemia, were found to have continuing concerns about illness, they feel more vulnerable to death, and many are worried about fertility. Psychologically, these individuals have a sense of vulnerability about the future, a diminished sense of control, and increased anxiety. Some of these problems are directly related to social issues, such as discrimination in the workplace and problems in getting health care and insurance.

Psychological issues are also closely related to prevention, especially in regard to trying to change people's behaviors. Dr. Holland suggested that psychological issues are very important to prevention because people are concerned about health issues. In a study of women with breast cancer, 41 percent felt they have contributed to getting cancer because of stress in their lives. MSKCC is conducting a chemoprevention trial with thyroxin and omega-fatty acids in women at high risk of breast cancer. The psychological issues relate to consent and compliance.

Dr. Holland said a major part of the psychosocial research program has been diverted to AIDS, which has many psychological ramifications. Initially, the problems were related to the lack of information about the disease and how the staff should handle patients. The fact that most victims were from socially stigmatized groups increased the prejudicial attitudes and patient care problems. The problems of the patient--what the diagnosis means, the stigmatization, the response of others--are also being addressed. Increasingly, prevention efforts are aimed at substance abuse and changing patterns of behavior in the gay community.

Points raised in discussion included the following:

- The passage of the National Cancer Act in 1971 afforded the first opportunity to undertake demonstration projects and rehabilitation.

- Testing of psychological interventions would require a large-scale clinical trial of patients all treated the same way in several centers.

- Information is just beginning to be acquired on the problems of long-term survivors at different points in time. There is a need to advise people about where to get information and help if they experience work discrimination. For example, MSKCC is trying to obtain funding for a project to deal with non-medical consequences of survivorship.

XVIII. Cell Biology Overview--Dr. June L. Biedler

Dr. Biedler described the Cell Biology Program, its recent accomplishments, some current strategies for research, and some new directions for future research. She focused on the research areas of regulation of growth and differentiation of normal and transformed cells, hormonal regulation, and genetic mechanisms in phenotypic expression. Current strategies to identify the mechanisms of growth regulation and normal and abnormal growth include the following:

- Study of chemical agents that can induce terminal differentiation of erythroleukemia cells, indicating that extrinsic as well as intrinsic agents may regulate cell growth

- Flow cytometry to study oncogene expression as related to the cell cycle in leukemia cells

- Identification of the mechanisms of action and interaction of growth and differentiation factors that regulate normal and leukemic hematopoiesis

- Characterization of human neuroblastoma cells for tumorigenic potential and expression of the n-myc oncogene

- Purification and study of a growth factor produced by melanoma cells that supports the growth of normal melanocytes.

Current strategies to address questions about the regulation of peptide hormone-receptor interactions and glycoprotein hormone genes include the following:

- Testing the biological activities, which favor either growth or differentiation, of proteolytically cleaved fragments of growth hormone

- Large-scale purification and characterization of the subunit structure of the growth hormone receptor

- Identification and characterization of the receptor for tumor necrosis factor

- Gene transfer experiments using cloned and sequenced thyroid hormone stimulating (TSH) genes (the thyroid hormone has been found to regulate both TSH-beta and nerve growth factor genes which are closely linked on chromosome 1).

Current strategies to address questions about the genetic mechanisms involved in cancer etiology and altered gene expression include the following:

- Use of genetic epidemiologic approaches to delineate the genetic risk for large bowel and breast cancers

- Study of chromosome fragility, with potentially important implications for aging and malignancy

- Finding that in non-Hodgkin's lymphoma, non-random chromosomal translocations signal the transposition of certain cellular oncogenes into the immunoglobulin heavy chain region, probably resulting in their deregulation.

Also included in this research area is the study of the cellular genetic basis of acquired drug resistance. In studies of antifolate-resistant cells, one type of resistance found was overproduction of the target enzyme, dihydrofolate reductase. It was also discovered in the MSKCC laboratory that there was cytogenetic and molecular evidence of the dihydrofolate reductase gene amplification. Other research is studying the possibility that the folate transporter gene is altered in these resistant cells.

Studies of multidrug-resistant cells with gene amplification-associated cytogenetic aberrations have led to the identification of two proteins encoded by amplified genes and to the development of molecular probes and antibodies for clinical studies. Dr. Biedler said the question to be answered is what is the function of each of these proteins. She suggested that the answer should provide part of the bridge between basic science and the clinic.

Hematopoietic Growth Factors--Dr. Malcolm A.S. Moore

Dr. Moore defined hematopoietic growth factors as the factors involved in proliferation and differentiation of bone marrow stem cells, which result in the generation of peripheral blood cells of various types. His research has focused on the granulocytes and monocytes. At least six different hematopoietic growth factors have been identified.

An important aspect of growth factors has been found to be their impact on leukemia. The normal differentiation pathway from a bone marrow stem cell involves a programmed and orderly sequence of proliferation and differentiation resulting in mature blood cells. In leukemia, differentiation is blocked and immature cells accumulate. The cytotoxic chemotherapy approach to treating leukemia is to prevent proliferation of the immature cells. A complementary approach is to try to induce the leukemic cells to mature, to behave normally and differentiate. Over the past 10 years, studies have been conducted at MSKCC on the growth factors affecting differentiation of normal bone marrow cells and growth factors affecting leukemia.

Dr. Moore said in 1976 the only known human active growth factor for granulocytes and macrophages was purified from peripheral blood leukocytes. By developing specific assay systems, a factor was identified that was produced by a variety of sources and caused leukemic cells to proliferate. It was subsequently found that the same cells could produce the factor stimulating normal bone marrow differentiation and leukemic cell differentiation. This

factor, was termed pluripoietin or pluripotent granulocyte colony stimulating factor (G-CSF), reflecting its ability to cause normal and leukemic cells to turn into neutrophil granulocytes. The molecule was cloned, and pre-clinical in vivo studies were initiated in early 1986, prior to obtaining FDA clearance for the initiation of a clinical trial of G-CSF, which began in December 1986.

Dr. Moore then outlined potential uses for G-CSF. First, G-CSF will be used to cause differentiation of leukemic cells into granulocytes and macrophages that exhibit their normal physiological function of fighting infection. Receptors for this growth factor have been identified so that patients likely to respond therapeutically to the G-CSF can be preselected. Also, it is proposed that G-CSF is a physiological regulator of the production of neutrophils. The absence of these neutrophil granulocytes is a serious complication of chemotherapy, bone marrow transplantation, radiotherapy, and other procedures. In animals treated with G-CSF, there has been a dose-dependent increase in the neutrophils. The factor also activates the neutrophils, stimulating them to enhance their chemotaxis, their ability to kill bacteria, and their ability to mediate antibody-dependent, cell-mediated killing of tumor cells. There is also an expansion of early stem cells, as well as differentiation. Dr. Moore said that no obvious toxicity was observed over four months of continuous treatment with G-CSF.

G-CSF is also radioprotective in mice irradiated with doses up to levels that are normally lethal. In bone marrow transplantation, there is accelerated regeneration of neutrophils and the number of cells required for transplantation can be reduced by at least one log. In chemotherapy, studies in mice and primates have shown that G-CSF treatment prevents the neutropenia associated with high doses of cyclophosphamide. It accelerates myeloid regeneration and reduces mortality, allowing for higher drug dosage and more frequent and prolonged chemotherapy.

Dr. Moore said that a Phase I clinical trial has been initiated in patients with advanced cancer. The G-CSF is given in conjunction with a protocol involving intensive chemotherapy, where myelosuppression and impaired recovery of neutrophils are dose-limiting features of the therapy.

Points raised in discussion included the following:

- Situations have been encountered where there are no receptors for this factor, including receptor-negative leukemias that would not respond. Also, there may be impaired production of the factor, there may be other factors involved, and chemotherapy may cause sensitizing to this factor.

- Granulocyte-monocyte colony stimulating factor (GM-CSF) increases the eosinophils and the monocyte macrophage population as much as the neutrophils. There may be more toxicity associated with GM-CSF than G-CSF because GM-CSF has the ability to activate macrophages to release substances such as tumor necrosis factor, which in some situations

will enhance toxicity. GM-CSF is contraindicated in treating leukemia.

- G-CSF is administered before chemotherapy, with treatment stopped 48 to 72 hours before initiation of chemotherapy.
- G-CSF causes expansion of the early stem cell compartment, which more than compensates for the increased differentiation demand.
- G-CSF expression seems to be restricted to cells of lineages that would ultimately give rise to cells of the neutrophil granulocyte or monocyte type.
- G-CSF may prove to be useful in other clinical situations where enhancing neutrophil production and activating them would be important.

Induced Differentiation of Cancer Cells--Dr. Richard A. Rifkind

As discussed by Dr. Moore, some cancer cells are transformed precursors of organs or tissues arrested in their development at an immature stage where they continue to divide. Dr. Rifkind described an alternative strategy for control of some cancers as involving removal of the blockade to normal development, thus permitting cells to resume their normal differentiation and express their mature characteristics, including the cessation of cell division and growth. Among the agents found to induce differentiation are some cytocidal chemotherapeutic agents and x-irradiation. Dr. Rifkind suggested that some effects of traditional therapeutic approaches might include at least a component of induced differentiation when they achieve therapeutic success.

The original prototype agent for this approach was dimethylsulfoxide, a polar-planar compound. In synthesizing inducers, the attempt has been to identify the essential chemical features of a universally effective and relatively non-toxic agent. The synthesized inducer now being tested in Phase I trials, is hexamethylene bisacetamide (HMBA). The cellular target of the inducers is the expression of a series of genes, some turned on and some turned off, with the net effect being the onset of normal development and the curtailment of cell division.

Dr. Rifkind described some molecular changes observed to occur in a leukemic cell model: the onset of globin gene expression required for the synthesis of the red oxygen and carbon dioxide carrying protein hemoglobin; the turning off of the genes for ribosome synthesis; and the modulated expression of a number of genes thought to be important for cell division, i.e., the nuclear oncogenes. Current evidence indicates that the permanent suppression of expression of c-myb oncogene is pivotal to the initiation of differentiation. While the triggering event or signal is not known, Dr. Rifkind suggested that protein kinase C may be implicated in this pathway of induced differentiation. It is possible to determine the molecular signature of a cell arrested in development at a particular moment in its natural history and predict what tumors may be susceptible to agents that induce differentiation.

In cooperation with NCI and other cancer centers, Phase I trials of HMBA are being conducted to establish safe dosages. Laboratory studies are also being done with human tumor cells to define the opportunities available for Phase II trials.

Points raised in discussion included the following:

- The laboratory model being used is bladder tumor.
- While the inducing agents are less specific in their cell targeting ability than the unique hormones, the tumors have to be in some particularly receptive biological state, which is not yet defined.
- There are specificities in how cells respond to stimulatory interactions, but cells may not respond identically to the same stimuli.
- It appears that HMBA is directly stimulating differentiation at the molecular level.

XIX. Immunology Overview--Dr. Osias Stutman

Dr. Stutman described immunology as both a basic biological science and one that generates a variety of technologies and procedures that are essential to virtually all other sciences. The Immunology Program at MSKCC comprises 18 laboratories and a staff of 80. In the context of cancer, the immune system is studied so as to correct immunologic deficiencies that may be present, understand malignancies of the immune system, and develop immunologic approaches to diagnosis and treatments. MSKCC's research is focused on cellular immunology, immunogenetics, and tumor immunology.

Cellular immunology is a blend of biology, genetics, biochemistry, and molecular biology for the study of the lymphocyte, its accessory cells, and its products. Special areas covered are the development and maintenance of T-cell populations, development of the immunological repertoire, and signals involved in T-cell activation.

Cell surface immunogenetics is the study of the unique molecular constitution of the outer membrane of mammalians cells according to their developmental lineage and stage of differentiation. Dr. Stutman said the general strategy of immunogenetics progresses as follows: 1) initial serological identification of surface antigens, especially selective expression in normal and malignant cells; 2) determination of the number of genes (in mice), mapping of genes, and definition of chromosomal location by linkage; 3) immunochemical study of the gene product (surface antigen), leading to protein sequencing; 4) study of biological function; and 5) gene cloning and definition of gene structure and its relationship with other linked or unlinked genes. Research is in progress to determine why certain genes are expressed in some cells and not in others. Differences in expression--spontaneous or induced--of HLA class II are being studied in melanoma cells. Some single

genes have been found to have isoforms, meaning that the antigenic determinant has a variant form depending on the cell lineage.

Dr. Stutman described the changes in immunology paradigms over the years. The traditional view was that the immune system only responds to external "non-self," which was the theory behind the production of vaccines. Later, it was learned that the immune system detects "non-self" only in the context of "self." The new thinking is that the main preoccupation of the immune system is the internal "self" environment. Dr. Stutman said that while quite a lot is known about single cells at the molecular level, more information is needed on cell sociology and how cells interact with each other.

Monoclonal Antibodies for Diagnosis and Treatment--Dr. Lloyd Old

Dr. Old said that tumor immunology is based on the belief that immunity plays an important role in the development of cancer, which is evident with certain tumors such as Kaposi's sarcoma and probably melanoma. While less is known about the role of immunity in other more common cancers, Dr. Old said there are indirect indications that immune mechanisms are important and can be manipulated for therapeutic benefit. These indications include spontaneous regressions of cancer in patients with pyrogenic infections and increased incidence of certain types of cancer in immunodeficient individuals. Pathologically, lymphoid infiltrates are frequently seen in many types of solid tumors.

Dr. Old identified five approaches to the immunologic treatment of human cancer: 1) passive immunization with antibodies, 2) adoptive immunization with cloned cytotoxic cells, 3) active immunization with antigens characteristic of tumors or tumor targets, 4) use of microbial products, and 5) use of mediators of immunologic reactivity, such as lymphokines and monokines.

Dr. Old then focused the discussion on MSKCC's Monoclonal Antibody Program, which began about seven years ago with the revolutionary technique of developing hybridomas and producing a single species of antibody from hybridoma cells. Mice are immunized with human cancer cells, and hybrids are derived and cloned to see whether the antigen is expressed on human cell types. Genetic analysis, antigen detection in body fluids, imaging in vivo, and antitumor activity in vitro and in vivo are among the applied uses of the research in cancer diagnosis and treatment.

Antibodies can now be characterized in terms of their molecular weight, whether they are glycoproteins or glycolipids, and the chromosome genes that code for the antigens. Through immunopathologic studies, antigens have been found that are present only on the basal layer of the skin; others are present on the normal colon mucosa but absent in cancer; and others are present in colon cancer but not on the normal colon mucosa. MSKCC has a program to detect cancer cells in bone marrow and other tissues by immunocytological techniques. Another major program, involving imaging with monoclonal antibodies, is focusing on antibody specificity and the amount of antibody that can get to the tumor.

Dr. Old next discussed therapeutic applications of monoclonal antibodies. Agents considered include the alpha chain toxins, various chemotherapeutics, radionuclides, antitumor enzymes, and complement activators, which attach to antibodies but do not have a biological effector function. Dr. Old said the first study done at MSKCC used an antibody called R24, which detects the G3 ganglioside. The R24 antibody is found in a variety of normal tissues and in a high percentage of melanomas, astrocytomas, germ cell tumors, sarcomas, and some lung cancers. The antibody has a biological effector function in that it induces certain reactions, such as mediating complement-mediated cytotoxicity and producing antibody-dependent cellular cytotoxicity. Addition of the antibody to melanoma cells in vitro causes the cells to aggregate, which Dr. Old suggested may be related to its in vivo effects.

The clinical trial involved injecting R24 at four different dose levels over 14 to 16 days into melanoma patients. At doses above 1 mg/m^2, urticaria and erythema occurred shortly after injection; other toxic effects at high doses were wheezing, nausea, and vomiting. In the Phase I trial of 21 patients, five showed a partial response, defined as a 50 percent reduction in the maximum diameter of all measurable lesions, and two showed mixed responses. Dr. Old said the regression is a slow process and is probably due to both mediators of immediate hypersensitivity and specific immunological reactivity of the host. It has recently been found that R24 can cause proliferation of a certain subset of T cells, so that T-cell mediated immunity may be involved in the tumor regressions.

In addressing the question of why all lesions do not undergo regression, Dr. Old stated that a major challenge of cancer research is the heterogeneity of the cancer lesion. Within the same lesion, some cells may have G3 ganglioside and others do not. When two antibodies are added where there are two gangliosides, the effect is synergistic. Trials using R24 and an antibody to the G2 ganglioside are to be initiated in the near future.

To determine whether humans can form immune reactions against cancer, study is now underway on the repertoire of antibodies that can be captured by the human monoclonal antibody technique. More than 100 human monoclonal antibodies have been characterized, many to intracellular antigens and very few to the cell surface. One such antibody is to the G3 ganglioside, so that there is now a human counterpart to the R24 mouse monoclonal antibody.

MSKCC's melanoma vaccine program draws on past work to define antigenic targets in tumor cells and use of autoimmunogenic melanoma antigens as targets. One vaccine that is being tested uses the GM2 ganglioside, which is found in the brain and other normal tissues, either alone or with an adjuvant. Only one normal patient had any anti-GM2 responses. In stage II melanoma patients without vaccinations, none had high titers; whereas in stage II melanoma patients vaccinated with GM2 alone or with adjuvants or with pretreatment with cytotoxin, a very high percentage had anti-GM2 antibody. The antibody induced in the vaccinated patients is cytotoxic in the presence of human complement, which Dr. Old said means that it should be able to cause lysis of melanoma cells, leaving the antigen on their surface. Patients with high anti-GM2 titer have had delayed recurrence of melanoma, compared to those with low or no titer. In conclusion, Dr. Old stated that immunological approaches and principles offer very promising applications to the challenge of human cancer.

In discussion, it was noted that a randomized trial is planned using the BCG-GM2 vaccine. The immune system may have much greater potential to recognize appropriate targets than is currently recognized.

Bone Marrow Transplantation: Molecular Biology and Immunologic Aspects--Dr. Richard J. O'Reilly

Dr. O'Reilly briefly described the marrow transplant procedure and stated that the problems are not surgical complications, but rather that the host, with a well developed immune system, can reject the marrow cells. Marrow transplants normally require genetic similarity (in the HLA region) between the donor and the host. Without this similarity, transfused immune cells will grow within the foreign host, recognize the person as foreign, and attempt to reject the patient. This is known as graft versus host disease (gvh).

Marrow transplants were first done around 1968 and used initially to treat children with lethal immune deficiencies. In early studies of leukemia, bone marrow transplant was considered to be a treatment of last resort, however, marrow transplants were subsequently found to be effective early treatments for acute myelogenous leukemia. In the first 75 patients treated in 1978, 45 percent achieved a long-term, disease-free survival without leukemic therapy after the transplant. These results were replicated in other studies. With marrow transplant, a patient can be treated with doses of drugs and radiation well above what can normally be tolerated because these individuals are then reinfused with marrow from a normal donor.

The program at MSKCC is designed to 1) develop more effective transplant procedures for patients with hematologic malignancies; 2) develop transplant approaches for patients lacking a genetically matched donor; 3) extend applications of marrow transplants to other human diseases, such as genetic diseases; 4) develop systems to examine the biology of marrow grafts and the basis for allogeneic resistance; and 5) develop approaches to transplant genetically manipulated marrow cells into the patient.

Dr. O'Reilly said that early use of transplants in the treatment of acute myelogenous leukemia and chronic myelogenous leukemia has resulted in a high proportion of long-term, disease-free survivors. For children with high risk forms of acute leukemia, MSKCC is using transplants with novel approaches --the administration of radiation and altering the timing of chemotherapy. Sixty-three percent and 40 percent of patients transplanted in second and third remissions, respectively, are enjoying long-term, disease-free survival. Dr. O'Reilly said efforts are now underway to develop new approaches that would allow use of immunotoxins (monoclonal antibodies cross-coupled to agents such as ricin-A) in the post-grafting period.

While the effectiveness of marrow transplants has been quite good in children, the results in adults (those over age 20) have not been as good because of the early morbidity and mortality associated with transplants, primarily caused by acute graft versus host disease. In the mouse, elimination of T cells from the marrow permits transplants across genetic barriers without lethal gvh disease. Separation techniques have been developed to produce

1,000 to 10,000-fold reductions in the number of T cells in human marrow. In comparing patients transplanted with separated and unseparated marrow, 54 percent of those transplanted with unseparated marrow developed grade I to IV gvh disease and 31 percent developed chronic gvh. Of those who received the separated (T-cell depleted) marrow, 6 percent developed grade II gvh, and none developed grade III or IV or chronic gvh disease. The problem of graft rejection in adults, however, remains a major issue.

Separated marrow transplants have been used successfully to treat severe combined immune deficiency in cases of genetic disparity between the donor and patient. The technique is also being used in leukemia patients, and Dr. O'Reilly suggested that T-cell depleted marrow grafting may be broadly applicable to the treatment of leukemia and other diseases.

Studies are concurrently being conducted on autografts, especially for use in treatment of solid tumors. The principle is to take the marrow out of the patient, remove residual tumor cells either by drugs or antibodies, then reinfuse the marrow after agressive chemotherapy or radiotherapy. Dr. O'Reilly said use of marrow purging agents in patients with high risk lymphomas has produced promising early results with 11 of 14 patients in first remission.

The progress in marrow grafting opens up the possibility of conferring genetic resistance. This research includes defining factors that may contribute to an anti-leukemic effect and transferring genetic features of a normal individual into genetically diseased cells. Scientists are attempting to transfer a human gene (the deficiency of which causes combined immune deficiency) through the use of viruses into the hematopoietic cells of primates.

Points raised in discussion included the following:

- Phase I clinical trials of tumor necrosis factor (TNF) have been started at many institutions around the world. The major toxic effects are hypotension, in some patients hypertension, and inflammation. Only modest anti-tumor effects have been seen in relatively few patients. TNF has synergistic effects with other lymphokines, particularly with interferons, and Phase I TNF gamma-interferon trials are being initiated. Regressions of certain tumors have occurred with intratumor injections of TNF.

- Research on growth factors should contribute to the efforts to achieve long-term, sustained growth of human stem cells in culture.

- It is possible to cyropreserve marrow from an individual, and this is being considered for persons working at high-risk jobs, such as around nuclear installations.

- While LAK cells or non-specific cytotoxic populations of cells are active against tumor cells, they are not targeted and they are quite active in suppressing hematopoietic growth.

- Hepatic toxicity has not been observed in preclinical studies of ricin conjugated with monoclonal antibodies. At the doses being used in the Phase I trial (.05-2 mg/kg), no adverse effects have been observed, except for unexplained hypoalbluminemia.

- The question of whether T-cell depletion decreases therapeutic effectiveness remains unresolved. MSKCC gives no therapy in the post marrow transplant period and few relapses are occurring, while other groups are giving drugs, such as cyclosporin A, and relapses are occurring.

XX. Developmental Therapy Overview--Dr. Joseph R. Bertino

Dr. Bertino described MSKCC's program in Developmental Therapeutics and Clinical Investigation as unique in its capacity to follow an agent through all stages of study--medicinal chemistry, pharmacology, clinical pharmacology--to use in the clinical setting. For example, trimetrexate, a new antifolate thought to be useful in some methotrexate-resistant tumors, has completed Phase I trials and has shown some Phase II activity in patients with breast, head and neck, and lung cancer. Another antifolate, 10-EdAM, with an enhanced ability to be taken up by tumor cells compared to methotrexate, has also gone to Phase I and II trials for treatment of patients with head and neck and lung cancer. FMAU, a synthetic antifolate, has antiviral activity and is being tested in the treatment of chronic active hepatitis.

Dr. Bertino noted the collaboration brought to bear by the regional therapy program on specific problems. The two major activities are hepatic artery infusion in collaboration with surgeons and intraperitoneal drug administration in collaboration with gynecologists. The work in hepatic artery infusion is based on the finding that FUDR is effective in treating local disease. A dose escalation study is planned to attempt to find the maximum dose of leucovorin that will potentiate the local effects of FUDR in the liver. Organoid assays are also planned using tumor tissue to try to predict which patients will benefit from the therapy and what doses are required. Biochemical and in vivo NMR assays will be done as well.

Among new areas of research, Dr. Bertino said clinical multi-drug resistance and resistance to antifolates, and topoisomerase inhibitors are high priorities. MSKCC also has an active program on transfer of drug-resistant genes into marrow cells, so that larger doses of drugs could be used safely, hopefully increasing the prospects for cure. Methods to effect gene transfer use retroviruses and electroporation. Molecular modeling is another important research area for both drug development and developing drug-resistant genes. Molecular modeling enables predictions about drug binding. Using the new techniques of site-directed mutagenesis, predictions can also be made about what amino acid changes in a molecule will affect the binding of substrates and inhibitors to the enzyme. Drug targeting is another new direction for research.

Points raised in discussion included the following:

- An important consideration in drug development is decreasing the toxicity of the drugs. Analogs of methotrexate and platinum have been developed that are not more effective but are less toxic.

- Understanding of drug resistance is likely to be important to future drug development.

Gallium for Disorders of Bone Resorption--Dr. Raymond P. Warrell, Jr.

Dr. Warrell stated that gallium nitrate is a metal-based compound that came through NCI's Developmental Therapeutics Program several years ago. In clinical trials at MSKCC, many patients who received gallium experienced a decrease in their serum calcium levels and a sharp reduction in the loss of urinary calcium. This suggested that gallium exerts a major effect on body stores of calcium, 99 percent of which are contained in bone. Several agents, including parathyroid hormone, lymphokines, and tumor necrosis factors, cause dramatic loss of calcium. Gallium nitrate markedly decreases the calcium resorptive activity of these agents.

In attempting to elucidate gallium's mechanism of action, Dr. Warrell said it appears that the principal changes occur in bone mineral, with the formation of larger, more perfect bone crystals. In addition, gallium has been found to promote the formation of new bone. Dr. Warrell said these results indicate that gallium can increase the synthesis of collagen by bone tissue and suggest that this drug promotes new bone formation in vivo.

It is therefore expected that gallium should be useful for treatment of diseases characterized by increased loss of bone mineral. These include hypercalcemia in cancer, bone metastases, and renal osteodystrophy. In clinical evaluation of gallium, serum calcium was lowered to normal or near-normal levels in patients with cancer-related hypercalcemia. Gallium is currently being studied in a Phase III randomized, double-blind trial against standard therapy for patients with hypercalcemia.

Short-term gallium treatment of patients with bone metastases caused a highly significant decrease in urinary calcium excretion in 21 of 22 patients. Gallium also decreased urinary excretion of hydroxyproline, one of the major breakdown products of bone collagen. Dr. Warrell said a randomized controlled study of gallium administered chronically to patients with advanced bone loss due to multiple myeloma will begin in 1987. The study, conducted in collaboration with Brookhaven National Laboratory, will assess fractures and pain relief, as well as changes in whole body calcium. Dr. Warrell stated that gallium is expected to find clinical use for the remineralization and strengthening of bone eroded by cancer invasion or metastases.

Points raised in discussion included the following:

- Measurement of whole body calcium, by putting the patient's entire body in a counter, provides a sensitive measure of bone density and calcium.
- The hypercalcemic effect of TNF was observed in vitro.
- Much more study is needed to determine whether gallium would have an effect on osteoporosis.

XXI. Clinical Investigations Overview--Dr. John Mendelsohn

Dr. Mendelsohn began by emphasizing the importance of opportunities available at MSKCC for interdisciplinary clinical trials involving surgeons, radiotherapists, and chemotherapists. He then reviewed several interdisciplinary clinical trials involving localized disease. In esophageal cancer, investigators are exploring the possibility that aggressive chemotherapy before surgery may allow the lesion to shrink enough to be resectable. Radiotherapy and surgery are being compared with chemotherapy and surgery. The approach to treating bladder cancer uses aggressive chemotherapy before surgery in an attempt to avoid removal of the bladder. In laryngeal cancer also, the goal is preservation of normal organ function by use of chemotherapy before surgical exploration. For treatment of testicular cancer, efforts are focused on reducing toxicity of chemotherapy. In early stages, the primary tumor is removed without chemotherapy and if the tumor recurs, chemotherapy can be given later as a salvage with less toxicity. A three-drug combination has produced short-term improvement in patients with advanced lung cancer. The goal is to convert patients from inoperable to operable.

Interdisciplinary trials involving metastatic disease are also in progress. With testicular cancer, the approach involves agressive chemotherapy, exploration for residual disease, and additional chemotherapy if active tumors are found. For colon cancer metastatic to the liver, randomized trials are comparing intra-arterial and intravenous administration of FUDR. Preliminary results have shown a higher remission rate in the liver and a trend toward increased longevity with intra-arterial administration. Monoclonal antibody infusions are being used to treat melanoma and renal cancer.

Dr. Mendelsohn then described the Division of Medical Oncology which has four services--hematology/lymphoma, solid tumor, developmental chemotherapy, and clinical immunology--and two modalities--chemotherapy and cytokines. MSKCC has a number of ongoing and planned trials using growth factors and cytokines, including IL-2, LAK cells, G-CSF, GM-CSF, and anti-epidermal growth factor (EGF) receptor antibodies.

The hypothesis pertaining to anti-EGF receptor antibodies is that antibodies to the receptor block the binding of epidermal growth factor. The function of the cell dependent upon activation of tyrosine kinase, also a component of the expression of a number of oncogenes, would be blocked. Ten different tumors have been studied in vivo with three showing inhibitory

responses to intraperitoneal injections of two anti-EGF receptor antibodies. Increased numbers of receptors for this epidermal growth factor have been found on lung cancer, and the cancer binds large amounts of antibody. Dr. Mendelsohn said the antibody blocks a physiological function of the growth factor, and the antigen to which the antibody is reacting is amplified in expression on cancer cells. The antibody is now being tested in monkeys and is expected to be used in clinical trials in the near future.

Points raised in discussion included the following:

- The anti-EGF receptor antibody has a half-life of about 2.5 days in a murine system; human pharmacological data are not yet available.

- The EGF receptor is present on normal cells but many tumor cells express one or two log increased amounts of antigen.

- In laryngeal cancer, better microscopic laser surgery should allow more salvage of the larynx. For advanced tumors, the precision-site resection approach is used to get rid of most cancer cells, followed by chemotherapy and radiation therapy.

Neuro-AIDS--Dr. Richard W. Price

Dr. Price stated that while he would focus on the neurological aspects of AIDS, this program is carried out within the context of a number of programs dealing with AIDS at MSKCC. Since 1981 when AIDS was first described, it was recognized that the nervous system was commonly involved. Initial attention was focused on opportunistic infections and neoplasms, but now, Dr. Price said, certain conditions involving the nervous system are known to be unique to AIDS. Several terms--subacute encephalitis, AIDS dementia complex, vacuolar myelopathy, and aseptic meningitis--have been used to describe these conditions.

To approach the problem of the AIDS dementia complex, the first step has been to try to define the disease in terms of neurological symptoms and signs, diagnostic profile, neuropsychological characteristics, and neuropathology. Secondly, study is focused on the epidemiology and natural history of the condition. Pathobiology is being studied from the perspectives of viral pathogenesis and the pathopsychology of brain dysfunction.

An autopsy-based study was carried out to define the disease. Neurological findings were analyzed for those patients having good clinical-pathological correlations. Early in the disease, patients exhibit cognitive, behavioral, and motor deficits, including poor concentration, slowness of thought, loss of spontaneity, social withdrawal, clumsiness, etc. As the disease progresses, the patients become globally demented and at the end are almost vegetative with very little capacity for social or intellectual interaction. Many become mute, paraplegic, and incontinent.

Dr. Price said the epidemiology of the condition is imprecisely defined and biased by the type of patients who come into the hospital. In most of 46 moderately to severely demented patients, AIDS manifestations--Kaposi's sarcoma, pneumocystis--occurred first. However, in about one-third of the patients, dementia came first or at the same time as the AIDS symptoms. In about one-quarter of the patients, dementia is their first and only symptom. Dr. Price estimated that early in systemic AIDS about two-thirds of the patients develop either moderate to severe subclinical dementia. Late in the disease over 90 percent suffer from dementia.

The major abnormalities observed through brain imaging are loss of brain substance or brain atrophy and white matter abnormalities. Pathological studies show the central white matter to be pale and in patients with severe dementia, multinucleated cells, sometimes forming giant cells, are found in macrophage infiltrates. Vacuolar myelopathy of the spinal cord, similar to that seen in vitamin B12 deficiency, has also been found. Dr. Price said that 100 percent of the demented patients and 75 percent of the non-demented patients had white matter pallor.

Evidence is increasing that the disease is due to direct infection of the brain with AIDS virus. HIV antigen has been detected in the brain. The predominant cells that are infected in the brain are macrophages, multinucleated cells, and process-bearing cells, which may be astrocytes. In terms of the pathophysiology of brain dysfunction, the disease is defined as subcortical dementia.

The treatment phase of the study is being conducted within the AIDS Treatment Evaluation Unit contract. The Subcommittee on Neurological Evaluations, chaired by Dr. Price, is attempting to develop simple but accurate quantitative instruments to evaluate neurological deterioration and hopefully, with drug therapy, improvement. Protocols are also being designed and initiated for treatment of neurological disease with antiviral drugs, the first being AZT.

Points raised in discussion included the following:

- The vacuolar pattern seen in AIDS is similar to that seen with lentivirus, but AIDS is a non-inflammatory disease and antigens have not been found in association with vacuolar changes.

- Assessment of the neurotropic properties of the AIDS virus is a high research priority.

- Folic acid and B12 levels have been found to be normal in AIDS patients; B12 therapy has been tried in a few AIDS patients with no success.

- Information is lacking on how virus infection leads to damage to the nervous system. Virus infection can be demonstrated in only about one-third of the patients who

In studying fat metabolism in cancer patients, fat turnover was found to increase. When glucose was given, very little was oxidized and most was stored. Dr. Brennan said that while the intent is to get patients to utilize simple substrate, they are actually laying down fat, which is inappropriate for survival. This can be reversed by giving exogenous insulin to increase oxidation and decrease storage.

Dr. Brennan said this metabolic research has been applied to patients receiving monokine therapy. Monokines are thought to be involved in the metabolic response to injury. Fat has been found to be elevated in patients receiving above a certain amount of tumor necrosis factor. There is also a decrease in serum levels of zinc and other elements. Dr. Brennan concluded with the statement that this type of metabolic research addresses patient issues rather than issues related to the malignancy.

Points raised in discussion included the following:

- The turning on of this "metabolic cascade" in cancer patients is likely to have multiple etiologies. Tumor necrosis factor and other monokines alter amino acid transport in patients. There may be an independent factor produced by the tumor.

- In animal models, tumors may make up 5 to 10 percent of body weight, making them inappropriate for comparison to humans. However, with increasing tumor burden in animals, protein synthesis in the liver increases.

XXII. Summary--Dr. Paul Marks

With the conclusion of MSKCC's presentations, Dr. Marks expressed appreciation for the opportunity to host this meeting of the National Cancer Advisory Board. He also reiterated the importance of NCI support to cancer research at MSKCC and other institutions throughout the country.

Members of the Board joined Dr. DeVita and Dr. Korn in commending MSKCC's programs and thanking Dr. Marks, Mr. Schmidt, and their colleagues for their most enlightening presentations.

XXIII. National Cancer Advisory Board Public Participation Hearings--Mrs. Nancy Brinker

Mrs. Brinker outlined a plan to involve lay members of the Board, in conducting Public Participation Hearings in up to six cities. These hearings would increase public information and involvement in the National Cancer Program and increase the accessibility of NCAB members to the community. The audience is the concerned cancer community--consumers, health care professionals, educators, the media, and government, business, and civic leaders. Written and optional video reports could be prepared on the hearings findings, and the written report could be incorporated into the 1988 NCAB Biennial Report to the President and Congress.

are demented. There are patients who are moderately demented in whom the virus cannot be demonstrated, suggesting a less direct mechanism of pathology.

- T4 is known to be the receptor for the AIDS virus and has been demonstrated in the brain, although it is not known where.

Surgical Nutrition and Metabolism--Dr. Murray F. Brennan

Dr. Brennan said that surgeons are involved in both basic and clinical research at MSKCC. In some studies, surgery is the primary modality but the adjuvant modalities of radiation, chemotherapy, and immunotherapy are also included.

Dr. Brennan discussed the importance of considering body composition in treating cancer by surgery. The body is made up of a large amount of water, a smaller component of fat, a similar component of protein, and a small carbohydrate reserve. Most of the caloric reserve is fat. The surgeon has a limited amount of time before the reserves are used up and the patient dies by starvation. The cancer patient is usually already in a situation of prior starvation or at least semi-starvation before surgery or other treatment. If the patients do not receive supplementation, they will die of starvation. The problem is confounded by the fact that a majority of cancer patients do not eat. Intravenous feeding has been found to be less effective in the cancer patient than in other patients also suffering from starvation. Dr. Brennan described a tracer kinetic technique used to study the mechanism of that finding.

A radioactive label is put on the amino acid alanine, which is injected into the patient. After an overnight fast, the appearance of the label on glucose is measured in the plasma. This gives an indication of the amount of protein being broken down to make glucose, which can then be manipulated through parenteral nutrition. While there is a benefit to suppressing the amino acid, there is at the same time an energy wasteful cost occurring through a recycling of glucose.

An animal model was used to study what was happening in the liver. Increased consumption of oxygen occurred in the tumor-influenced hepatocytes. A relative disproportionate increase in oxygen consumption has been observed in many cancer patients, meaning that there is an increased demand for energy when the individual can least afford it.

Dr. Brennan said that alanine transport also was increased in tumor-influenced hepatocytes compared to controls. With markedly increased amounts of alanine, which might occur with starvation, there is marked increase in the production of glucose. The amount of glucose being synthesized from a lactate precursor (which is thought to be involved in the recycling phenomenon) in tumor-influenced hepatocytes also is increased.