Department of Health and Human Services

Public Health Service

National Cancer Institute

National Cancer Advisory Board

Summary of Meeting
December 2-4, 1985
Building 31, Conference Room 6
National Institutes of Health
Bethesda, Maryland

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

Summary of Meeting*
December 2-4, 1985

The National Cancer Advisory Board (NCAB) convened for its 56th regular meeting at 8:30 a.m., December 2, 1985, in Building 31, National Institutes of Health (NIH), Bethesda, Maryland. Dr. David Korn, Chairman, presided.

Board Members Present

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

Absent

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

President's Cancer Panel

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

Ex Officio Members

Ms. Lois Ann Beaver, FDA
Dr. Hollis Boren, VA
Dr. Jean French, NIOSH
Dr. Lakshmi Mishra, CPSC
Dr. Robert Rabin, OSTP
Dr. David P. Rall, NIEHS
Vice Admiral Lewis H. Seaton, DOD
Dr. Ralph E. Yodaiken, OSHA

Liaison Representatives

Mr. Alan Davis, Vice-President for Governmental Relations, American Cancer Society, New York, New York, representing the American Cancer Society.

Ms. Cheryl Lane, Vice-President, Oncology Nursing Society, Rockledge, Florida, representing the Oncology Nursing Society.

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

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

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

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

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

Members, Executive Committee, National Cancer Institute

Dr. Vincent J. DeVita, Director, National Cancer Institute
Dr. 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. Samuel A. Wells, Jr., Chairman, Department of Surgery, Washington University School of Medicine

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

In addition to NCI staff members, meeting participants, and guests, a total of 27 registered members of the public attended the meeting.

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

Dr. Korn, Chairman, called the meeting to order and welcomed members of the Board, the President's Cancer Panel, liaison representatives, guests, staff of the National Cancer Institute (NCI), and members of the public. Members of the public who wished to express their 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 7-9, 1985, NCAB meeting were unanimously approved as presented.

In response to a question, Mrs. Brown stated that the mock-up of the poster about unproven methods in cancer treatment was not ready for presentation to the Board.

II. Future Board Meeting Dates

Future meeting dates were confirmed as follows: February 3-5, 1986; May 19-21, 1986; October 6-8, 1986; December 1-3, 1986. The following meeting dates are to be confirmed: February 2-4, 1987; May 25-27, 1987; October 5-7, 1987; November 30-December 2, 1987.

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

Dr. Hammer congratulated Dr. Fischinger on his appointment as Deputy Director of the National Cancer Institute on behalf of the Panel. He expressed satisfaction that H.R. 2409, the Health Research Extension Act of 1985, had been passed by Congress, thus reauthorizing the National Cancer Program, the main concern and responsibility of the Panel.

Dr. Hammer recognized awards and honors granted to colleagues as follows:

- Dr. John Montgomery received the Alfred Burger Award in Medical Chemistry, for his work on the chemical structure and activity of certain drugs.

- Ann Landers was chosen for a public service award at the recent Lasker Awards ceremony in New York, in recognition of her work in helping educate the public regarding cancer.

- Dr. Vincent DeVita received the Medal of Honor of the American Cancer Society and was designated to deliver the Stratton Lecture at the December meeting of the American Society of Hematology in New Orleans, the highest honor the Society can bestow. Dr. DeVita was also selected to deliver England's Annual Leukemia Research

Fund Lecture in London and received the Barbara Bohen Pfeifer Award for scientific achievement from the American-Italian Foundation for Cancer Research.

Dr. Hammer reported that the Panel has been considering a number of options for its agenda next year. He noted that the Panel had completed the agenda for this year and was pleased to observe from its meetings around the country that so many innovative and promising areas of basic research are being explored and pursued.

While AIDS receives much media and public attention, it should not be forgotten that cancer kills over 450,000 people each year, and the NCI's top priority must be finding the most effective methods of detection, treatment, and prevention of cancer. The Panel believes however, that NCI has much to contribute to finding a solution to the AIDS problem and has worked well with other agencies in this area.

In 1986, the Panel is considering investigating scientific issues that are of interest to the NCI to learn from the scientists what the problems are and what resources are needed to allow these fields to flourish. Another possible project is finding more effective ways of communicating to the public, the media, the Administration, etc., the true state of affairs of the cancer field, for instance by finding ways to involve members of the public and media in discussions at Panel meetings. Dr. Hammer welcomed any suggestions the Board members had in this regard.

Dr. Hammer closed his report with the announcement that the 1985 Hammer Cancer Prize of $100,000 would be awarded jointly to Dr. Tadatsuga Taniguchi of Japan and Dr. Steven Rosenberg of the NCI. Dr. Taniguchi, who is at the Institute for Molecular and Cellular Biology at Osaka, Japan, was the first to clone a gene for human interleukin-2, and Dr. Rosenberg was recognized for his work on treatment with lymphokine-activated killer cells and interleukin-2. The award ceremony is scheduled to take place in January in Los Angeles.

Finally, Dr. Hammer expressed regrets that Dr. George Keyworth is leaving his position as the President's science advisor and noted his support of and interest in the work of the National Cancer Institute.

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

Dr. DeVita thanked Dr. Hammer for his comments, and suggested that Ann Landers' acceptance speech for the Lasker Award be distributed to the Board. He said that some concerns about the newly reauthorized Cancer Act will be discussed at the next Board meeting.

In brief discussion of the budget, Dr. DeVita said that 99.9 percent of the 1985 budget had been obligated. For 1986, Congress has recommended that NCI receive $1,258.2 billion, an increase of 5.7 percent over last year's budget. The Congress provided $70 million in the budget of the Office of the Director, NIH, for AIDS research. The NCI budget would increase further over

the 1985 level when a portion of these funds is allocated to NCI. It was emphasized that these appropriations had not been voted by Congress or signed by the President.

Total receipts to the NCI Gift Fund for 1985 were $332,000. One large stipend is being used to set up a special fellowship program. The sum of $50,975 was used to support 53 summer trainees. Donations for the summer program were received from the following corporations: Boeringer Mannheim MnbH (Germany), Procter & Gamble, Monsanto Company, Mobil Oil Corporation, The Dow Chemical Company, McCormick & Company, Inc., Pfizer, The Standard Oil Company, Dupont, Coca-Cola, The Shell Companies Foundation, Abbott, Bristol-Meyers Company, Hercules Inc. (Medical Dept.), Union Carbide Corporation, and Allied Corporation.

Dr. DeVita welcomed Dr. Peter Fischinger as the new Deputy Director. Dr. Fischinger's outstanding background in viral oncology and molecular biology was noted. Dr. Fischinger will continue to direct the Frederick Cancer Research Facility.

An overview of the organization of the Office of the Director was then presented and the Institute's advisory structure described. Dr. DeVita noted that the agenda was too full for a presentation on the Office of Cancer Communications, which the Board had requested, but such a presentation will be given at a future meeting.

In considering the many sources of scientific advice--the National Cancer Advisory Board, the President's Cancer Panel, the Divisional Boards of Scientific Counselors, individual grantees, scientists who serve on peer review groups, the Organ Systems Coordinating Center and their Working Groups--it is evident that the number of scientists advising the Institute is considerable. The NCI Executive Committee uses the advice of all these groups to set priorities and distribute resources. The Executive Committee also has scientific seminars to keep abreast of emerging scientific issues. The Board members were invited to suggest topics for these seminars. All of this advice and information is integrated at two planning sessions in January and July to develop the budget and set priorities.

V. 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 program of research on cancer causation and its basic research programs 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. The DCE's three major programs are Biological Carcinogenesis, Chemical and Physical Carcinogenesis, and Epidemiology and Biostatistics. While no major organizational changes occurred in 1985, three new laboratory/branch chiefs were appointed: Dr. Takis Papas as Chief of the Laboratory of Molecular Oncology in the Biological Carcinogenesis Program and in the Epidemiology and Biostatistics

Program, Dr. John Cooper as Chief of the Extramural Programs Branch, and Dr. William Blot as Chief of the Biostatistics Branch.

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

- Establishment of lines of transgenic mice for viral oncogenesis studies (from the Biological Carcinogenesis Program)
- Identification of activated oncogenes in chemically induced tumors (from the Chemical and Physical Carcinogenesis Program)
- Association of passive smoking with lung cancer risk (from the Epidemiology and Biostatistics Program).

Dr. Adamson explained that transgenic mice have foreign DNA integrated into their germline through micro-injection of recombinant DNA molecules into the pronuclei of fertilized eggs or through infection of embryos with retroviruses or retroviral vectors. He said that transgenic mice provide an excellent system for examining the selective expression of genes in developing eukaryotic organisms and the tumor-specific tumorigenesis by SV40 large T antigen.

Various laboratories are studying oncogenes created by chemical carcinogens. Using nitrosoethylurea and methyl or methoxymethyl nitrosamine, transforming genes have been identified in renal mesenchymal tumors, nasal carcinomas, and tumors of the peripheral nervous system. Such studies further demonstrate the specific association between activated oncogenes and chemically induced tumors and suggest that further research may reveal steps in the carcinogenic process that may be amenable to prevention interventions.

Dr. Adamson then described two case-control studies, one in the United States and one in Japan, that have strengthened the evidence associating passive smoking with lung cancer risk. Both studies revealed that the risk of lung cancer increased with the amount of smoking by a spouse. In neither study, could confounding factors be found to account for this association. Dr. Adamson concluded that although the evidence is not definitive, results are suggestive enough to warrant further study.

The 1986 DCE budget was reviewed (based on the FY 86 planning budget for the NCI). A program summary of the budget showed a slight increase for nutrition in the DCE budget of $237 million. The other three programs were approximately level. Dr. Adamson expressed appreciation to Dr. Pierce and members of the Board for their many contributions to the Division's operations.

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

Dr. Pierce discussed the role of the Board of Scientific Counselors (BSC). During the last few years, several initiatives have come from workshops and subcommittees of the Board of Scientific Counselors. Dr. Pierce said the advantage of the workshops is that intramural and extramural

scientists can be brought together with people from industry to focus on specific conceptual problems. The information is then given to DCE staff and reviewed by Dr. Adamson at least twice before presentation to the Board of Scientific Counselors. Dr. Pierce stated that this mechanism has improved the quality of concepts presented to the BSC. It was noted that some initiatives developed by workshops have resulted in requests for applications and expanded research. These include studies of papillomavirus, feline leukemia viruses, and chemoprevention.

During the past year, the DCE BSC has conducted the following site visits of intramural laboratories. Some highlights of these site visits were presented:

- The Laboratory of Cellular Carcinogenesis and Tumor Promotion (Chief, Dr. Stuart Yuspa) is making significant contributions in the study of skin cancer on differentiation and the isolation and characterization of the genes for keratin proteins

- The Laboratory of Chemoprevention (Chief, Dr. Michael Sporn) has undergone a transition from research on retinoids to research on tumor growth factors and is the only laboratory that has been able to produce antibodies to some of the growth factors

- The Laboratory of Molecular Oncology (Chief, Dr. Takis Papas) is focusing study on oncogenes as well as the construction of expression vectors for expression of their products

- The Laboratory of Comparative Carcinogenesis (Chief, Dr. Jerry Rice) is unique in its study of transplacental carcinogenesis in nonhuman primates.

All laboratories were found to be of high quality, but freezes in personnel hiring are adversely affecting the smooth functioning of the scientific efforts.

Dr. Pierce said that a Working Group had been convened to consider how extramural researchers could receive more support for epidemiologic studies. The group recommended that research in cancer etiology be accorded equal standing with cancer prevention and control in the Preventive Oncology Academic Awards; a small grants research program be created to support small innovative studies in cancer etiology; and guidelines for core grants be flexible enough to allow for support in epidemiologic and biometric research. These recommendations have been approved and implemented.

Dr. Pierce concluded by saying that the DCE Board is very gratified to have an active role in providing advice to the Division of Cancer Etiology. The Board is very pleased with the quality of the Division.

The following points were raised in discussion:

- Animal models showing tissue specificity among various species for the same carcinogen are important in the development of potential therapies and screening techniques and for studying how the initiation of the carcinogenic process might be prevented.

- The Laboratory of Human Carcinogenesis uses human tissues and has found some of the same adduct formation that occurs in animals, although DNA repair mechanisms seem to be more efficient in human tissues than in animal systems.

- Studies in chick embryo cells have shown the same numbers of copies and levels of expression of c-myb in normal cell populations and tumor cell lines, and apparently the c-myb is responsible for controlling the differentiation of normal macrophages.

- A future Board meeting might include a presentation on mutagenesis, including mutagens formed as a result of cooking food.

- Immunologic probes have been useful in patients to indicate the extent and duration of response to chemotherapy but have not been used for other aspects of cancer therapy.

- Cervical cancer metastatic cells have been found to contain the human papillomavirus.

- Although DCE and the Division of Cancer Biology and Diagnosis both perform research on oncogenes, their focus is different (that of the former is chemical carcinogens and viruses and the latter, cellular oncogenes).

- It was suggested that Board members receive copies of the referral guidelines used to assign grants to Divisions.

- Exposure of the respiratory or digestive system to carcinogens results in gradual changes that can be documented by electron microscopy and biopsies. Such information could be used in studies of passive smoking; current efforts are to use non-invasive techniques, such as measurement of cotinine in urine, to measure exposure.

- DCE is supporting both intramural and extramural research on biochemical epidemiology.

- Adducts have been used to document exposure of coke oven workers to benz(a)pyrene and environmental exposure of populations at risk of hepatocellular carcinoma to aflatoxin.

- Substantial progress has been made in the study of genetics and virus-related cancers, e.g., the association between translocated chromosomes and familial renal cancer.

- The Executive Committee is evaluating the use of RFAs and will discuss the issue with the NCAB next year.

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

Dr. Rabson reviewed the organization of the Division of Cancer Biology and Diagnosis (DCBD), noting that it is divided into an Extramural and an Intramural Program. Organizational changes involved abolishing sections and establishing three branches--Cancer Diagnosis, Cancer Immunology, and Cancer Biology--in the Extramural Program, and, in the Intramural Program, abolishing two sections in the Laboratory of Pathology and abolishing the Laboratory of Pathophysiology and transferring sections to the Laboratory of Tumor Immunology and Biology and one section to the Laboratory of Mathematical Biology. He pointed out some specific areas of research being addressed by the 12 intramural laboratory chiefs:

- Molecular Biology (Chief, Dr. Ira Pastan)--drug resistance to chemotherapeutic drugs and immunotoxins
- Biochemistry (Chief, Dr. Maxine Singer)--repetitive DNA
- Mathematical Biology (Chief, Dr. Jake Maizel)--installation and operation of a high speed computer and application of computer technology to nucleic acid sequencing
- Genetics (Chief, Dr. Michael Potter)--formation of plasma cell tumors
- Cellular Oncology (Chief, Dr. Douglas Lowy)--papillomavirus and ras-oncogenes
- Dermatology Branch (Chief, Dr. Steve Katz)--immunodermatology
- Pathology (Chief, Dr. Lance Liotta)--metastasis
- Immunology Branch (Chief, Dr. David Sachs)--transplantation biology and genetics
- Immunobiology (Chief, Dr. Tibor Borsos)--complement and humoral killing of cells
- Tumor Immunology and Biology (Chief, Dr. Jeffrey Schlom)--applications of monoclonal antibodies to diagnosis and treatment of cancer
- Cell Biology (Chief, Dr. Lloyd Law)--transplantation antigens and chemically-induced tumors.

Dr. Rabson reviewed the membership of the DCBD Board of Scientific Counselors and the site visits conducted by members of the Board and other

scientists. Site visits were made to the Metabolism Branch, the Laboratory of Biochemistry, and the Laboratory of Tumor Immunology and Biology. Upcoming site visits will be to the Laboratories of Mathematical Biology, Cell Biology, and Cellular Oncology.

Of the scientific highlights, Dr. Rabson noted, in particular, the following:

- Application of basic advances in molecular genetics and cytogenetics to cancer diagnosis and risk assessment
- Immunoglobin gene rearrangements and T-cell receptor rearrangements applied to diagnosis and classification of human malignant lymphomas
- Gene amplification of the N-myc oncogene for the diagnosis of human neural tumors
- Demonstration that some kinds of cancer, such as retinoblastoma and Wilm's tumor, result because normal genes are missing
- Understanding of how T-lymphocytes recognize foreign proteins
- Identification of a suppressor (uromodulin) of the immune response found in the urine of pregnant women.

Slides were shown of some of the Division's laboratory scientists, and their backgrounds and areas of research were described.

In reviewing budget information, it was noted that there was about a 1 percent increase in the DCBD budget with the total estimated at $215 million.

DCBD Board of Scientific Counselors--Dr. Matthew Scharff

Dr. Scharff reported that the site visit teams have found the work being done of very high quality. He said that organizational changes have generally been positive and favorably influenced the quality and productivity of work. Dr. Scharff pointed out in particular the work of Dr. Jeffrey Schlom and his colleagues in systematically examining the diagnostic and therapeutic potential of a set of mouse monoclonal antibodies that recognize human colon cancer cells. He said these studies represent the first carefully controlled studies on the real diagnostic and therapeutic potential of these mouse monoclonal antibodies.

At the May meeting the Board was pleased to learn that a contract to distribute tissue culture cell lines was not going to be renewed because the contractor had become self-supporting. In addition, the Board discussed the need for cooperative networks to provide clinical investigators with fresh human cancer tissue. The Division plans to develop programs to provide such tissue to investigators throughout the country. The May Board

meeting also included a presentation by Dr. Brian Kimes on the need to ensure a more rapid transfer of new basic discoveries to new diagnostic tests for cancer, and mechanisms for accomplishing this purpose. This discussion was continued at the October Board meeting, when Dr. Kimes presented a proposal to use supplemental grant applications to existing basic science grants to promote clinical collaboration and explore new diagnostic ideas which was enthusiastically approved by the Board.

The October Board meeting also included a discussion on prostatic cancer metastases, the DCBD BSC's first interaction with the Organ Systems Program. Dr. Donald Coffey's recommendation for a Program Area Announcement (PAA) was approved.

The DCBD Board recommended renewal of two intramural contracts, one to provide mouse plasmacytomas and special strains of mice to the scientific community, and the other to provide special inbred strains of mice used to study the immune response and transplantation.

Finally, Dr. Scharff stated that although the year was particularly difficult because of uncertainties in funding, enormous scientific progress was achieved. He mentioned, for example, the problem of malignant transformation and the studies that have shown that particular growth factors are required to stimulate the proliferation and ultimate differentiation of cells of different lineages.

The following points were raised in discussion:

- Any money resulting from commercial uses of products, tests, etc. developed by the Government goes to the Department of the Treasury although individual NCI scientists can receive a small percentage of the royalties

- Organ-targeted research is needed, as well as research on the natural history of cancer and causative factors in metastasis

- The use of magnetic resonance imaging of heavy metal tagged monoclonal antibodies is at present hindered by a technical problem, i.e., more than 1,000 substitutions per antibody molecule would be needed to improve the resolution of existing MRI

- A localizing fluorescent marker is needed to improve detection of cancer cells; this requires monoclonal antibodies having both specificity and affinity.

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

Dr. Chabner described the mission of the Division of Cancer Treatment (DCT), which is to develop new therapies for cancer in the fields of surgery, radiotherapy, cytotoxic chemotherapy, hormonal therapy, and biological products. He then presented an organizational chart of the DCT, detailing

the five programs within the division. Staff appointments included the following: Dr. Gregory Curt, Deputy Director; Dr. Marcia Browne and Dr. Eddie Reed, Special Assistants in preclinical and clinical areas in the Office of the Director; Dr. John Antoine, from the University of New Mexico, Director of the Radiation Research Program; and Dr. Dan Longo, Associate Director for the Biological Response Modifiers Program, replacing Dr. Ronald Herberman who accepted the position of Director of the Cancer Center at the University of Pittsburgh.

Principal organizational changes in the past year included the establishment of a Regulatory Affairs Branch in the Cancer Therapy Evaluation Program (CTEP) to handle relations with the Food and Drug Administration, and the reorganization of the intramural laboratories for drug development and pharmacology, in the Developmental Therapeutics Program (DTP). The restructuring of the laboratory effort resulted in the creation of the Laboratory of Biological Chemistry and the Laboratory of Pharmacology and Experimental Therapeutics.

Dr. Chabner reported that the FY 1986 DCT budget, estimated to be $330.386 million, compared to $331 million in FY 1985, would be a relatively level budget with a small increase in the intramural research program, primarily for additional support for the lymphokine-activated killer (LAK) cell research. A projected decrease in diagnostic research was based on the President's budget level.

Dr. Chabner then presented the scientific highlights, noting that developments in the Clinical Oncology Program (COP) would be the main emphasis of this program overview. He said that Dr. Samuel Broder, Associate Director of the COP, had played the lead role in the development of new therapies for AIDS with his discovery of two promising compounds, suramin and Compound S, now in clinical trials. After reviewing the various COP components, Dr. Chabner proceeded to highlight recent accomplishments in each COP Branch:

- NCI-Navy Medical Oncology Branch--identification of C-myc, N-myc and L-myc oncogenes, which appear to be over-expressed in two-thirds of patients with small cell lung cancer and associated with a very aggressive clinical disease and a lack of response to therapy.

- Pediatric Oncology Branch--great progress in the treatment of Ewing's sarcoma with a protocol of initial chemotherapy, followed by radiation therapy and chemotherapy, and then total body irradiation followed by rescue with transplantation of autologous bone marrow harvested from patients prior to initi in patients with neuroepithelioma.

- Medicine Branch--intensive study of ovarian cancer and trials with cis-platin and cytoxan, with emphasis on attempting to suppress the renal toxicity caused by cis-platin. A new protocol for the treatment of locally advanced breast cancer, has

achieved remarkable improvements in response and local control rates. The new protocol uses aggressive chemotherapy upfront in a number of cycles, followed by radiation and/or surgery. (Mrs. Kushner noted that the treatment is chemohormonal as the cells are primed with premarin and tamoxifen.)

- Clinical Pharmacology Branch--investigations of the reasons for drug failure; studies of the cell membrane proteins and relationships between an enzyme, protein kinase C, and drug resistance in breast cancer cell lines; the development of imaging agents for magnetic resonance.

- Radiation Oncology Branch--use of hematoporphyrins for treatment of intraperitoneal tumors.

Attention was turned to the Developmental Therapeutics Program, which is responsible for drug development efforts. He stated that the major concern of the DTP in FY 1985 had been the change in the screening systems from the murine leukemias to the use of human tumor cell lines as the primary screen. In another area, Dr. Robert Gallo's work on HTLV-III and AIDS vaccine development were given high priority in the program. Six new compounds were produced by the DTP in FY 1985, including flavoneacetic acid, which has been entered into clinical trials, and Aza-Ara-C, which is targeted for clinical development.

In the Radiation Research Program, the major project has been the development of neutron therapy facilities. Of the four facilities built with NCI funds--University of Washington, M.D. Anderson, UCLA, and Fox Chase--the first two are operational, the third one is scheduled for completion in early 1986, and the fourth one had repeated failures due to a machine design problem and is being terminated. Five Phase I protocols and several Phase III protocols in neutron therapy are underway, of which the most promising are in salivary gland tumors and prostate cancers.

Dr. Chabner proceeded to present a brief description of the clinical trials currently monitored by the Cancer Therapy Evaluation Program (CTEP), which is responsible for managing extramural trials for the DCT. Current clinical trials of new agents include the following:

- TAC monoclonal antibody (Dr. Tom Waldmann)

- Pseudomonas toxin conjugated to anti-TAC antibody

- IL-2 combined with LAK cells (Dr. Steve Rosenberg)

- Recombinant interferon, which is highly active in hairy cell leukemia

- Human colorectal monoclonal antibody, used in diagnostic imaging experiments

Among the extramural clinical studies sponsored by the CTEP, Dr. Chabner briefly described the following:

- An Intergroup study of leuprolide + flutamide in Stage III prostate cancer, to test this combination versus the use of leuprolide alone

- A Phase I trial of hexamethylenebisacetamide (HMBA), a differentiating agent

- A study of bone marrow transplantation in solid tumors undertaken by two newly formed, major consortia

- A study of the N-myc gene in neuroblastoma in the Children's Cancer Study Group. Findings show that the number of copies of the N-myc gene indicates the degree of aggressiveness of the tumor. Multiple copies of N-myc are associated with rapid progression of neuroblastoma.

Dr. Chabner thanked Dr. Wells and the Board of Scientific Counselors for their support and acknowledged the importance of the Board's assistance.

DCT Board of Scientific Counselors--Dr. Samuel Wells

Dr. Wells reviewed the composition of the DCT BSC, noting the various areas of expertise represented by Board members. In 1985, the BSC conducted intramural research site visits to the Pediatric Branch of the Clinical Oncology Program and the Laboratory of Molecular Pharmacology. Site visits planned for FY 1986, will be to the Medicine Branch, COP, and the Radiation Oncology Branch, COP, and the Laboratory of Tumor Cell Biology, DTP.

Dr. Wells noted scientific presentations made to the BSC during the year with particular attention to two areas which were of special interest to the Board--advances in the cellular biology of lung cancer, presented by Dr. John Minna, and adoptive immunotherapy with LAK cells and IL-2, by Dr. Steve Rosenberg.

In other activities, the DCT Board, through its Surgical Oncology Research Development Subcommittee (SORDS), was instrumental in developing a new support mechanism for surgical oncology. Dr. Wells announced that this new training grant, providing five years of support, would be advertised in the coming weeks. He closed his presentation with an expression of the Board's concern over the reduction in DCT's personnel and the potential consequences of this policy on the development of the intramural program.

The following points were raised in discussion:

- Tumor debulking is a major therapeutic component of the regimens in pediatric sarcomas but is of value only in relatively small tumors

- Microsurgical techniques for getting rid of cancer cells have made great advances but detection techniques must be improved

- Studies are needed on the late effects of radiation

- The SORDS committee is responsible for the evaluation of possible mechanisms for enhanced funding and research development in surgical oncology

- Only 5 breast cancer patients have been treated with the leucovorin and 5 Fu combination and data suggest that leucovorin enhances the effectiveness of 5 Fu.

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

Dr. Fischinger announced that Dr. Werner Kirsten, Chairman of the Frederick Advisory Committee, was not able to leave Wisconsin because of adverse weather conditions.

He reviewed the organization of the FCRF noting that as Deputy Director, NCI, he will maintain supervisory authority over the facility but day-to-day management will be through the General Manager in close cooperation with the Contracting Officer representing the Research Contracts Branch of the NCI. The FCRF is a government owned-contractor operated (GOCO) facility that provides rapid response to Institute needs. The facility consists primarily of contractor operations funded through five contracts, which are scheduled for recompetition soon, initial aspects of the concept review having been completed. The next contract year cycle will begin on September 27, 1987. The contracts are presently held by the following companies:

- Litton Bionetics, Inc. (LBI)--provides capabilities for basic research that complements the intramural program

- Program Resources, Inc. (PRI)--provides operations and technical support

- Harlan Sprague-Dawley--animal production (approximately 600,000 rodents per year)

- Information Management Services, Inc.--computer support

- Data Management Services, Inc.--library maintenance.

In response to a question about how purchase of LBI by a foreign company would affect the operation, Dr. Fischinger said the Department of Health and Human Services is considering how to handle the situation.

In addition to the contractor operations, the FCRF houses NCI laboratories (DCE, DCBD, and DCT) as well as laboratories of the National Institute of Allergy and Infectious Diseases (NIAID), and the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS). Dr. Fischinger emphasized that the support services provided at FCRF are used by the intramural laboratories on a voluntary basis and must therefore be competitive with outside firms in terms of rapid response, quality, and cost. The support operation has expanded greatly and is expected to reach $9 million in 1986 for the 15 support services that are currently operational.

Dr. Fischinger outlined the new initiatives at the FCRF as follows:

- NCI supercomputer (Laboratory of Mathematical Biology, DCBD)--construction was funded intramurally; to be operated by a unit of PRI which will also develop some of the software; the building to house the computer is essentially complete and operations will begin soon

- Lymphokine activated killer cell project (Surgery Branch, DCT)--at present the only support provided is the growth of cells for reinfusion; but plans are that patients will also be treated at the Frederick Memorial Hospital

- Development of the in vitro drug screening program (Developmental Therapeutics Program, DCT)--still in preliminary stages but the capacity exists for significant expansion of this program

- Fermentation Production Program (PRI)

- Recombinant DNA laboratory (PRI)--constant and continually escalating requests in this area led to development of this service which will be almost unlimited in terms of production capacity, capable of progressing stepwise from very small laboratory quantities to very large amounts.

Next, Dr. Fischinger reviewed the Basic Research Program, pointing out highlights of the current scientific investigations. He stated that Dr. George Vande Woude, Principal Investigator, has assembled a highly qualified group of investigators to head the laboratories as follows:

- Laboratory of Eukaryotic Gene Expression (Dr. Jeffrey Strathern, yeast geneticist)--conceptualization of the manner in which control of sequential events occurs in cell division.

- Laboratory of Molecular Virology and Carcinogenesis (Dr. Stephen Oroszlan, peptide chemist)--discovery of interesting facets of gene organizations in retroviruses.

- Laboratory of Chemical and Physical Carcinogenesis (Dr. William Lijinski, expert on chemical carcinogenesis)--represents a major Institute effort in the investigation of nitrosamines; work with nongenotoxic substances that are known to be carcinogens.

- Laboratory of Genetics and Recombinant DNA (Dr. Stuart Austin, bacterial physiologist)--basic prokaryotic investigations dealing with the transport of molecules to the cell surface.

- Molecular Mechanisms of Carcinogenesis Laboratory (Dr. George Vande Woude, molecular biologist)--isolation of an oncogene called met located on chromosome 7, a tyrosine kinase whose sequencing seems to resemble an insulin receptor. Dr. Fischinger reported that it is quite clear now that the met oncogene can be used as a probe to diagnose cystic fibrosis prenatally and that, by using a technique called "walking" the gene, it should soon be possible to identify carriers of the gene as well (about 1 person in 20 in general North European and American populations are carriers and the disease occurs in one in 1,600 births).

- Mammalian Genetics Laboratory (Dr. Neal Copeland, mouse geneticist)--devised a process called "hybrid dysgenesis" for generating mutant mice almost at will; also able to generate transgenic mice which should make it possible to establish a library or bank of them, using frozen embryos, for use in many research areas.

The establishment of an X-ray crystallography cell biology laboratory is projected. One way to study small protein products is to crystallize them and use an X-ray diffraction technique for analysis, a process requiring analysis of numerous computer graphics.

The mission and actions of the Frederick Advisory Committee were reviewed. It is composed of 11 members, ad hoc representatives from the DCT, DCBD, and DCE BSCs (to integrate programs), and an ex officio member from the NCAB. The Committee reviews contract concepts, reviews management of the FCRF, provides scientific review of the Basic Research Program, and advises on new research support efforts. In 1985, the Committee performed concept reviews for the AIDS vaccine development subcontracts for PRI, emphasized the need for continued and extended stability of the FCRF, and suggested AIDS and X-ray crystallography as new support areas. Scientific reviews of the Photocarcinogenesis and Photoimmunity Section and the Laboratory of Chemical and Physical Carcinogenesis led to elimination of the former and affirmation of the latter as a key laboratory for the Institute, containing elements that are unique in the world. The Committee also reviewed the program of the Laboratory of Molecular Virology and Carcinogenesis.

In his review of the estimated FY 1986 budget figures as compared with actual FY 1985 amounts, he stated that the Basic Research Program has increased at the prescribed 2 1/2 percent rate. A total of $3.6 million is projected for AIDS vaccine development.

The following points were made in the discussion:

- Non-NCI Institutes reimburse the FCRF for services and overhead. Divisions of the NCI pay only for services; the Office of the Director, NCI, pays overhead.

- The Management and Support line item in the FCRF budget includes the costs of building maintenance, engineering, radioactive waste disposal, and other costs of maintaining the 60-building, 70-acre operation, as well as the overhead.

- The cost of maintaining an intramural laboratory at Frederick is almost equal to the cost of maintaining one on the NIH campus.

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

Dr. Greenwald characterized the Division of Cancer Prevention and Control (DCPC) as the effector arm of the NCI. The Division has three major program areas and Biometrics and Surveillance and Operations Research Branches. Staff changes and additions have included the following: Dr. Charles Smart, Community Oncology and Rehabilitation Branch Chief; Dr. David Byar, Biometry Branch Chief; Dr. Charles Brown, Section Head for Biostatistical Methodology and Cancer Control Epidemiology in the Biometry Branch; Dr. Larry Kessler, Section Head for Operations Research in the Surveillance and Operations Research Branch (SORB); Dr. Thomas Marciniak, Head of the Computer Systems Section, SORB; and Mr. J. Henry Montes, Board of Scientific Counselors Executive Secretary in the Office of the Director.

The Surveillance and Operations Research Branch in the Director's Office works on the details relating to the Year 2000 goals and has been developing computer models for use in estimating impact of the cancer program on incidence, morbidity, and mortality nationwide. One model can be used in the field to help local authorities work out programs to achieve an impact in their own areas.

The Biometry Branch performs research on methodology related to specific research projects. The clinical trials in cancer prevention, which are now being done for the first time in history, are very complex and require careful methodological design.

In describing the highlights of the Smoking, Tobacco, and Cancer Program, it was noted that several dealt with smokeless tobacco: an RFA on prevention and cessation of use of smokeless tobacco; a January 1986 NIH consensus conference on smokeless tobacco; and key participation in the

preparation of a Surgeon General's Report on Smokeless Tobacco. Other activities involve smoking prevention/cessation programs for minorities; a community-based intervention research program aimed at heavy smokers; and investigation of tobacco production and consumption in selected developing countries. Public opinion is changing in recognition of the dangers of smoking and the use of smokeless tobacco.

The Prevention Program includes the following branches: Diet and Cancer, Chemoprevention, Cancer Detection, and Cancer Prevention Studies and Occupational Cancer. Dr. Greenwald cited the nearly two dozen chemoprevention trials using a few synthetic retinoids and naturally occurring substances (beta-carotene, vitamins A, C, and E, and selenium compounds). Several of these have produced some evidence of an effect on potential markers of premalignancy in humans. While the changes in cellular indicators have yet to be validated, the trials will be continued to test for a lowering of cancer incidence and have contributed greatly to the knowledge needed for designing better future trials. Studies on dietary fiber are also in progress.

The feasibility study for low fat diet intervention in women at high risk for breast cancer ("Women's Health Trial") has succeeded in reaching the desired accrual level of 300 women who have uniformly achieved the diet faster and at a better level than anticipated, and have maintained it for four months. Whether such a diet can be maintained over the long period necessary for successful completion of the trial is unclear, and other methods/issues have yet to be addressed in the feasibility phase. The DCPC plans to continue the feasibility phase of both this study and the low fat intervention trial for women with Stage II breast cancer (Nutrition Adjuvant Study) for a few months and seek guidance from the DCPC BSC before coming to the NCAB with a report in February or May.

In the Centers and Community Oncology Program, Dr. Greenwald noted the increased flexibility given Center Directors as a result of the change in core grant guidelines. He stated that a large proportion of the patients now in the community hospital studies under the Community Clinical Oncology Program are going on to NCI-supported clinical trials.

Highlights of the Cancer Control Science Program included the recompetition of the Cancer Communication System and the award of 16 contracts; the development of a cancer control initiative involving primary care physicians; a program with Giant Foods to stimulate change in purchase behavior; establishment of technical liaison with State health agencies; and various programs on cancer control in minority populations. A new Cancer Control Science Associates Training Program was developed and the first three Associates recruited.

In discussing the budget, it was pointed out that about one-fourth of the DCPC budget of $251 million is devoted to Cancer Prevention and Control, with the remainder used mainly to fund the Cancer Centers, Organ Systems, Cancer Training, and Construction Programs. Dr. Greenwald expressed concern about the relatively level estimated FY 1986 budget at a time when

it is necessary to maintain the initiatives in prevention trials and prevention research.

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

Dr. Bettinghaus stated his view that reaching the Year 2000 goals would require effective work by all of NCI, but particularly the DCPC because some of the most difficult problems left to solve are communications problems. He stressed the diversity of specialties represented on the DCPC BSC and described how this diversity was partly responsible for the establishment of BSC subcommittees, which preliminarily screen concepts before they are presented to the full Board. Ad hoc committees also supplement the regular review processes. The four ad hoc committees for 1985 were the Policy Advisory Committee for the low fat breast cancer trials; a site visit team for the intramural review of the Cancer Prevention Studies Branch; a Task Force on Cancer Control in the Black Population; and a newly formed Committee on Cancer Screening Research and Application.

Referring to the site visit of the Cancer Prevention Studies Branch, it was stated that the report of the reviewers was generally favorable, but it suggested that the Branch needs more personnel. The Biometry Branch will be visited in 1986.

A review of the achievements of the DCPC noted particularly the Cancer Communication System and the effectiveness of a single number, nationwide, for the cancer hot line, 1-800-4-CANCER. It was emphasized that the present quality of the program should be maintained under any kind of future change in the system.

Mention was made of a two-day meeting that was held to develop a cancer control initiative involving primary care physicians. Several RFPs have resulted and several concepts are likely to be approved by the Board to address the issue of how to involve primary care physicians in the entire range of cancer activities.

The discussion dealt mainly with the status of negotiations with the American Cancer Society about the transfer of the Cancer Communication System. If any transfer were to occur, it would probably involve only a part of the system, perhaps only the telephone line.

X. Organ Systems Program

Introduction--Dr. James Karr

Dr. Karr presented an overview of the Organ Systems Coordinating Center (OSCC) activities for the past year and reviewed the responsibilities and structure of the Organ Systems Program (OSP). A report was distributed to the Board that included a summary of OSCC activities, details on each of the five programs, and reports from the conferences on the feasibility of

adding working groups on the upper aerodigestive system and central nervous system. The NCAB will be asked to act on the feasibility reports in February.

The OSCC is administered through the Organ Systems Section of the Cancer Centers Branch, DCPC, and is advised by a seven-member board chaired by Dr. William Shingleton. Five Working Groups, each comprised of a chairperson, 14 members, an OSCC scientific administrator, and an NCI program director, have been established. The Working Groups are responsible for planning and identifying research opportunities through a multidisciplinary approach. The OSCC prioritizes the plans identified by the Working Groups, develops documentation of concepts, and fosters interaction among the Working Groups, NCI, and the biomedical community.

During the past year, 1 Request for Application (RFA) was released, 21 applications were received, and 5 institutions were awarded funding. Four other concepts were presented to and approved by Boards of Scientific Counselors, three of which will be released as Program Announcements (PA), and one as an RFA in large bowel cancer.

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

- The length of time from concept initiation in the Working Groups to grant award was of concern to Board Members (two years for Flow Cytometry in Bladder Cancer). The delay was eventuated by personnel vacancies at the NCI, specifically the lack of an Executive Secretary to deal with this project. The Board expressed the hope that this time period would be greatly reduced in the future.

- About 20 concepts might be submitted to NCI during the next year. Dr. Karr estimated that this is the maximum number the current review system can handle.

Dr. Karr's overview was followed by progress reports of the Working Group chairpersons.

Working Group on Prostate Cancer--Dr. Donald Coffey

Dr. Coffey stressed that although prostate cancer is the second leading cause of cancer death in men, there is relatively little research funding for the disease and, perhaps consequently, very few research workers in the field.

During the past year, the Working Group has reviewed 35 work statements from the former program. These were reduced to five and two have been submitted to the NCI. One on metastases in prostate cancer was submitted to the Board of Scientific Counselors, DCBD for consideration as a program announcement and approved. The other deals with noninvasive methods to quantify tumor burden as an important research priority. A future joint workshop with the five Working Groups will focus on stromal epithelial interaction. Dr. Coffey concluded that program stability and funding increases are urgently needed.

The discussion following the presentation focused on the need to continue evaluating the OSP structure and funding priorities.

Working Group on Bladder Cancer--Dr. Gloria Heppner

Dr. Heppner reported that the Working Group is focusing on "transitional" science to link clinical and basic research. An RFA on automated flow cytometry has been approved by NCI, and five awards have been made to form a network for research in this area.

The following concepts are being developed:

- Pharmacokinetics and other aspects of intravesical chemotherapy
- Bladder cancer markers as prognostic indicators and as monitors to response to therapy
- Collaborative research on carcinogenesis and oncogenesis in animal models or in human systems
- Role of radiation in combination therapy.

Dr. Heppner stressed that the Group requires a firm funding commitment, as does the entire OSP.

Working Group on Pancreatic Cancer--Dr. James Jamieson

Dr. Jamieson reported that the less than 1 percent 5-year survival for pancreatic cancer reflects a lack of knowledge about the etiology and early diagnosis of the disease and the poor response to any kind of therapy. He estimated that only about 20 grants in the United States are studying pancreatic cancer, and he stated that there is a problem related to the level of support.

The priorities identified by this Group include:

- Research on molecular biological probes to define methods for earlier diagnosis
- Identification of animal models of pancreatic cancer
- Case control studies to identify environmental factors and, thus, to develop future prevention programs
- Definition of the effect of identified risk factors on pancreatic function
- Study of the etiology and control of pain in pancreatic cancer.

The Group, therefore, will focus on concepts in etiology and earlier diagnosis and will be holding workshops on the neurobiologic and physiologic basis of pain and on the use of modern imaging techniques (e.g., NMR). At present, there are no RFA concepts under review.

Dr. Jamieson emphasized the need to attract young investigators to the field by assuring research support and an appropriate review mechanism.

Working Group on Breast Cancer--Dr. Elinor Spring-Mills

At the first meeting of the Breast Cancer Working Group in November 1984, eight areas of breast cancer research were identified and prioritized. The first four of these areas were developed and presented at the second meeting and workshop entitled, "Tumor Markers and their Significance in the Management of Breast Cancer," in March 1985. A summary of that workshop--which was divided into the three areas of 1) circulating tumor markers, 2) breast cancer antigens, and 3) estrogen metabolites and estrogen-induced proteins--will be published in Breast Cancer Research and Treatment in January 1986. The priority areas presented at the March Working Group meeting and those subsequently developed include:

- A concept on histologic and mammographic characteristics of the normal human breast throughout the life cycle, which was sent for NCI review in September 1985.
- A work statement on the radiographic appearance of the breast with aging, which was recently approved by the Working Group.
- A joint effort among U.S. and European investigators to characterize circulating antigens further and to compare and evaluate the reagents used by different laboratories.
- A concept on factors influencing the susceptibility of the breast to carcinogenesis, an animal model. This has been sent to NCI for final development.
- A research initiative on the interactions among dietary factors in the prevention of mammary carcinogenesis, this has been approved for release as a Program Announcement.

Recently, the Working Group also had a workshop on nipple aspirates. Summaries from the workshop will be reviewed for future publication in Breast Cancer Research and Treatment. Work statements that were presented include:

- The transformation of normal breast cells by identifiable factors, which will be further defined and submitted to a Board of Scientific Counselors in the spring of 1986
- Oncogene expression and malignant phenotypes in breast cancer cells

- Stromal epithelial interactions, which will be further developed at the April 1986 workshop with the five Working Groups

- Risk assessment associated with histologically defined categories of benign proliferative breast disease and other factors influencing breast cancer risk.

The Breast Working Group has also identified six work statements that will be presented at 1986 meetings of the Group. Five work statements have been transmitted to NCI for concept review and one PA will be issued in January 1986.

The Group plans to hold at least one meeting per year at a cancer center or in conjunction with a major breast cancer meeting to increase interaction with the biomedical community. A workshop is planned on hormonal factors that may affect breast cancer. In the future, Dr. Spring-Mills said the Group will try to increase the number of initiatives in breast cancer treatment, prevention, and control. She re-emphasized the need for increased funding and improvement of the review process for solid tumor research.

Working Group on Cancer of the Large Bowel--Dr. Glenn Steele

Dr. Steele stated that the Working Group aims to focus on "transition" areas to link clinical and basic research. The following have resulted from the Group's activities over the past year:

- An RFA on markers of premalignancy and colon cancer, which is budgeted for $1 million/year for 3 years

- A Program Announcement on drug resistance mechanisms.

The Group has also identified the following future research initiatives:

- Definition of subsets of patients with a clinically, very poor prognosis, especially those patients with undifferentiated tumors, and young women with mucinous tumors

- Role of calcium in the development of colorectal cancer

- Evaluation of the extent of surgery required for various types of tumors.

The Group's goal is to obtain an incremental increase in available funds for RFA/RFP submissions of about $6 million within 2 years. To achieve this goal, the Group will continue workshop initiation, design of seminars, and its own research.

Dr. DeVita thanked Dr. Karr and Working Group Chairs for their presentations.

XI. Cancer Statistics Seminar

Overview of NCI Cancer Surveillance--Dr. Edward Sondik

Dr. Sondik distributed copies of the 1985 Annual Cancer Statistics Review, which is based on 10 percent of cancer cases in the United States. The Surveillance, Epidemiology, and End Results (SEER) Program provides data on incidence and survival, while mortality data are derived from the National Center for Health Statistics. SEER participants include: the San Francisco/Oakland SMA, Connecticut, metropolitan Detroit, Hawaii, Iowa, New Mexico, Seattle/Puget Sound area, Utah, metropolitan Atlanta, and a small area of rural Georgia, Puerto Rico, and New Jersey. Thus, SEER is not a random sample, but rather reflects the U.S. population as a whole. Some populations are, however, under-represented (e.g., Hispanics).

Members of the SEER staff were introduced: Dr. John Young, in charge of the SEER Program; Ms. Lynn Ries, in charge of survival data; and Mr. John Horm, in charge of incidence and mortality.

A significant change from the 1984 statistics was noted: a 4 percent decrease in lung cancer incidence in white males, which correlates with changes in smoking behavior. The following 10-year trends shown in the report were discussed:

- A 70 percent increase in incidence and mortality of lung cancer in both black and white females
- A 20 percent higher incidence of lung cancer in black than in white males, which reflects an equivalently higher prevalence of smoking among black men
- A gradual increase of about 4.7 percent in the incidence of colorectal cancer, with a 5.3 percent decrease in mortality
- A slight increase in breast cancer incidence, with relatively constant overall mortality and survival rates--but including a 6 or 7 percent decline in mortality for women younger than age 50
- A 26 percent increase in incidence and a 48-49 percent increase in survival in prostate cancer in all age groups.

Three major factors that determine when and if research results have an impact on mortality were discussed: 1) applicability of research results; 2) the degree to which research advances are applied; and 3) impact of past treatments on mortality in a given year, i.e., the treatment used at the time of diagnosis.

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

- Rural blacks seem to be under-represented in the SEER Program and require further study

- It was proposed that the Community Clinical Oncology Program (CCOP) could be more generally included in the SEER registry.

The Implications of Cancer Statistics for Cancer Research Direction--Dr. John Cairns

Dr. Cairns began by analyzing the impact of chemotherapy on cancer mortality, drawing first on the data of Dr. Robert Miller at the NCI on modern treatments for cancers that affect children under age 15 years. By examining data from 1950-1979, he illustrated that the favorable impact of new treatment for acute leukemia was seen fairly quickly between 1965 and 1970 in the United States. However, he pointed out that the impact of new treatments is easier to see more quickly in smaller, more self-contained European countries than in the United States. For example, in Norway, the success of treatment for acute childhood leukemia was shown very rapidly in cases diagnosed between 1963 and 1967, shortly after the advances reported about 1960.

Although cancer incidence is increasing, mortality has remained constant. Dr. Cairns discussed the American Cancer Society's (ACS) five-year projected estimates of mortality and explained that their accuracy is due to the fact that they are based on the assumption that there will be no change in mortality and on estimates of how many people will be at risk for specific cancers at specific ages.

Dr. Cairns drew a historical analogy between current trends in cancer mortality rates and deaths from tuberculosis in England and Wales that occurred between the middle of the 19th century and the present. The current decline in cancer mortality among the younger age groups (e.g., leukemia and Hodgkin's disease in patients less than age 30 years) with an increase in incidence and mortality among the old compares to a similar period when the mortality and incidence of tuberculosis declined among the young after a cleaner environment, the widespread use of X-rays, and successful chemotherapy were introduced, while the mortality from tuberculosis among the old still reflected the previous era. Thus, he predicted that cancer mortality will decline as the young reach middle- and old age.

Dr. Cairns concluded that successful cancer treatments (e.g., tamoxifen for breast cancer) are sometimes developed outside of clinical cancer trials of chemotherapeutic agents and urged that basic biomedical research should not be "plundered" to support more trials of these agents.

A Clinical Research Perspective on Cancer Statistics--Dr. Emil Frei, III

Dr. Frei focused first on acute lymphocytic leukemia (ALL) in children and curative cancer chemotherapy which includes the three components: producing a complete remission, dealing with residual microscopic tumor, and maintaining complete remission. Drawing on data from the Acute Leukemia Group B from about 1965 to the present, he illustrated that at about 4 or 5 years--or 1-2 years after stopping therapy--there is a "disease-free survival

plateau" when patients are no longer at risk of relapse. When considering the disease-free survival plateau as an expression of cure, one needs to look at the number of patients on the plateau and the number of years since therapy. The fact that it was not until about 15 years after the initiation of the St. Jude's clinical trial in 1965 that the 1980 mortality from ALL showed a 50 percent overall decline illustrates that there is a substantial lag period even for this disease which is largely treated in centers. After treatment, there is an exponential decrease in the proportion of patients who fail--a "maximum recurrence time," after which the risk of failure is less than 5 percent. The maximum recurrence time is about 1-2 years for rapidly progressing cancers in the younger age groups (e.g., ALL, testicular cancer, Hodgkin's disease) versus about 4 years for carcinoma of the colon and much longer for breast cancer. This factor influences when a trial will be mature enough to evaluate the disease-free survival plateau and, therefore, when the results will be extrapolated to the community.

Dr. Frei also discussed the rationale behind increasing the numbers and types of drugs in combination chemotherapy. Combinations of three or four agents, particularly those with different mechanisms of action and dose-limiting toxicities, allow drugs to be delivered at full dose, deal with the problem of resistance to individual drugs, and attack the heterogeneous variants of the tumor population. Dr. Frei illustrated this point using the results of the MOPP chemotherapy for Hodgkin's disease, which showed that while the partial response rate was about 50 percent and the complete response rate very low for individual agents, the complete response rate was 70 percent and the disease-free survival plateau was 40-50 percent for the four-drug program.

In adjuvant chemotherapy for solid tumors, the importance of delivering chemotherapy early to deal with micrometastatic disease and to stage reduce the primary to facilitate cure by local treatment was stressed. The success of this strategy was illustrated by the following:

- In a clinical trial of chemotherapy given before local treatment of head and neck cancer at the Dana Farber Cancer Institute, in patients who achieved a complete response to chemotherapy, the disease-free survival plateau was about 85 percent; for those who achieved a partial response after chemotherapy, the plateau was about 50 percent; and for those who did not respond, the survival curve was about 10-20 percent, or the same as in those patients who received only local therapy.

- In bladder cancer, single-agent chemotherapy is effective in 20-40 percent of patients, but results in few complete responses. However, initial studies with combination chemotherapy have shown response rates as high as 50-70 percent and complete response rates of 25-40 percent.

For most cancers, Dr. Frei suggested that the disease-free survival plateau time to mortality is 5 to as much as 20 years--being short in rapid cancers (e.g., ALL) and relatively long when the disease is indolent (e.g.,

breast cancer). He noted that the quality of life for cured patients with cancer is, in general, very good, and emphasized the importance of cancer treatment research and agreed that basic science and prevention research should not be compromised. Attention was called to the interrelationships of scientific research in many fields and across many disciplines.

The Inferences of Cancer Statistics for Breast Cancer--Dr. James Holland

Dr. Holland based his discussion of breast cancer therapy on the premise that in treating solid tumors mathematical models can be constructed to account for the number of tumor cells and to inaugurate treatment accordingly. These models reflect those developed in curative strategies for acute lymphocytic leukemia.

Dr. Holland compared the data from a five-drug study similar to Dr. Richard Cooper's adjuvant chemotherapy regimen including cyclophosphamide, methotrexate, 5-fluorouracil, vincristine, and prednisone (CMFVP) to that from Bonadonna's study including cyclophosphamide, methotrexate, and 5-fluorouracil (CMF). Bonadonna's study, including breast cancer patients with four or more positive lymph nodes, compared mastectomy plus axillary dissection and 1-year CMF treatment to surgery only. Half of the patients who did not receive chemotherapy relapsed in 1 year and three-quarters relapsed by 3 years. Patients receiving CMF showed a dramatically improved response rate, while those in Dr. Holland's study receiving the five-drug CMFVP regimen showed a significantly superior survival rate at 4 years. However, Dr. Holland pointed out that a survey conducted by the American Society of Clinical Oncology showed that 51 percent of oncologists still use CMF for this group of patients, and therefore, are a generation behind current studies.

The results of the CMFVP studies led to a further study, which was designed based on the suggestion that CMFVP fails in some patients because a resistant subpopulation of tumor cells develops. In this study, the patients were randomized either to continue on the CMFVP regimen or after 8 months to shift to a four-drug, Adriamycin-based regimen. The results have shown that at 4 years the two-treatment regimen shift is significantly more effective than the continuation of the five-drug treatment. Ongoing studies, depending on an even more intensive use of CMFVP in a shorter time and then a much higher dose of Adriamycin, have increased the response rate to 85 percent with 40 percent complete remissions.

These principles have been applied to trials of Stage III and IV ovarian cancer, showing a significantly higher response rate in patients receiving either Adriamycin and cis-platin, or cyclophosphamide, Adriamycin, and cis-platin than in those receiving thiotepa and cis-platin, or cis-platin alone. Ongoing studies show a further improvement in response rate in patients receiving hexamethylmelamine-containing regimens (i.e., hexamethylmelamine, cyclophosphamide, Adriamycin, and cis-platin) compared to those receiving Adriamycin and cis-platin only. However, hexamethylmelamine has not been patented, and therefore is not available for extended study.

Dr. Holland concluded that better results are obtained when adjuvant treatment is begun early when there is a major impact of dose and schedule change, allowing for higher doses and combinations of drugs to attack the variant tumor cell populations. Comments following this presentation included the following points:

- Aggressive physician education programs are required to encourage more doctors to participate in clinical protocols and speed the dissemination of current results to the community. For example, Dr. DeVita commented that most patients with diffuse large cell lymphoma receive a chemotherapeutic regimen that cures perhaps half the number cured by the state-of-the-art program.

- There may be a general misconception by the lay press and public that tamoxifen is the drug of choice for all post-menopausal breast cancer patients with positive nodes. This may contribute to reluctance on the part of patients and doctors to enter current trials of multiagent chemotherapy.

An Epidemiological and Cancer Control View of the Statistics--Dr. Phillip Cole

Dr. Cole first analyzed the way in which a higher proportion of the population began to reach the maximum life expectancy between 1900 and the present. Between 1900 and 1950, the "sanitary revolution" added 18 years of life expectancy to childhood and only 3 to adulthood. From 1950 to 1970, only 2 years were added to life expectancy--1 to childhood and 1 to adulthood. From 1970 to 1984, 4 years, 1 in childhood and 3 in adulthood, were gained. Thus, a higher and higher proportion of the gain is going into adulthood, reflecting a strong decline in deaths from heart disease and cerebrovascular disease, and lesser declines for accidents and pneumonia. A decrease in cancer mortality is not yet contributing to increased life expectancy.

He suggested that in order to influence cancer mortality rates, the cancer program must impact mainly breast and colon cancer in women and prostate and colon cancer in men--the common cancers in an aging population. He emphasized that the aging of the population is the most important factor in the cancer experience in the United States, and if rates remain constant, both cancer incidence and mortality will increase. The effects of advances in cancer treatment occur slowly, with most of the advances improving the quality and duration of life rather than curing the disease.

Dr. Cole stressed the need for a recommitment to the idea of prevention and the continued development and evaluation of screening. He also strongly emphasized a need for even distribution of care and education to the general population. Some studies were cited in the southeastern United States that indicate that good quality care is inaccessible to about 75 percent of the population.

Treatment Research--Dr. Bruce Chabner

Dr. Chabner briefly addressed several points related to the importance of treatment research. He expressed disappointment that the 1985 SEER survival statistics do not reflect recent substantial treatment progress. For example, the 40 percent 5-year survival rate now achieved using combination chemotherapy in advanced ovarian cancer (as reported by Dr. Holland) was not seen in the SEER statistics, as only 60 percent of the patients with this stage of disease received any form of chemotherapy. This and other examples such as testicular, small cell lung, and breast cancers indicate the underutilization of current treatments and a considerable time lag in application of treatment advances.

Dr. Chabner pointed out that treatment research has remained at about 28 percent of the total NCI budget for the past 5 years and that the treatment budget, in fact, includes basic research (e.g., the discovery of HTLV III, and studies of gene amplification as an outgrowth of treatment research investigating methotrexate resistance). He emphasized the cooperative exchange of advances in cancer treatment and in basic research.

Adjuvant Therapy of Breast Cancer--Dr. Marc Lippman

Dr. Lippman stressed that a decline in breast cancer mortality is not reflected in the SEER data because of a lack of widespread dissemination of the results of successful clinical investigation and thus a lack of their application in the community. Data presented at the recent Breast Cancer Consensus Conference (September 9-11, 1985) showed statistically significant declines in mortality from breast cancer of 24 percent in women under 50 and of 8 percent for women over 50. Although these results from Richard Peto's analysis of all randomized studies of adjuvant chemotherapy for breast cancer worldwide were extremely encouraging, Dr. Lippman said they reflect the results of many methods of breast cancer treatment and, in fact, represent the lowest common denominator of effect. Included in Peto's analysis, for example, are trials involving simply single agents and nonintense regimens. Dr. Lippman compared the 8 percent overall reduction in mortality for women over 50 reported from Peto's analysis to the results at 3 years of a National Surgical Adjuvant Breast Project (NSABP) trial including a regimen of L-PAM, 5-fluorouracil, and tamoxifen, plus the very active drug, Adriamycin. The NSABP trial showed an extremely significant improvement in survival for women receiving the regimen including Adriamycin, compared to those receiving the regimen without Adriamycin.

Dr. Lippman emphasized that there is also a significant relationship between disease-free survival from breast cancer and the amount of drug(s) the patient receives. He stated that only a small minority of women receive close to the amount of drug that they can safely tolerate and that increased drug intensity has already been proven to induce better responses.

Discussion Following Presentations

Although the details of several studies were discussed in relation to the applicability of the SEER data to current oncology practice, the discussion that followed the Panel's presentations focused on the following major points:

- As most patients start chemotherapy after leaving the hospital, the capability of the SEER data abstraction system to track patients once they leave the hospital should be analyzed and improved. At present, SEER collects data from only the first course of therapy and only for those patients whose discharge notes indicate that chemotherapy will be given on an outpatient basis.

- Dr. Cairns agreed that his statements about the increased risks of leukemia among patients who received adjuvant chemotherapy for breast cancer were based on worst case data in other diseases. Data in breast cancer studies indicate the risk is less than 1 percent. He indicated he chose this data to be sure patients were alert to the danger, however small.

- Studies have shown that involvement in a clinical trial, in itself, increases survival and this, among other factors, complicates extrapolation of results of clinical trials to the general population. However, to avoid bias in extrapolation, "defined populations" that are representative of the chosen generalized population are used.

- Application of results of adjuvant studies and diffusion of therapies in the community is very slow, and thus the SEER data do not reflect state-of-the-art medical oncology practices. The American Society for Clinical Oncology is undertaking patterns of care studies to evaluate actual practices in the community.

- The SEER Program requires more information about rural blacks and Hispanics, two groups that are thought to be under-represented.

- Costs for screening (e.g., mammography) and for adjuvant therapy (e.g., tamoxifen for breast cancer) are not reimbursed by many insurance companies and this may contribute to lack of use in the community. Further study on generalized cost reduction of both screening and chemotherapeutic agents was urged.

- The Physician Data Query (PDQ) program should play an important role in increasing and speeding the dissemination of clinical treatment advances.

- The need for continued direction in research on the major cancers in older populations--lung, colon, breast, and prostate--was stressed, and the importance of the Organ Systems Program in this research was underscored.

- The central point of all of the speakers--the importance of the link between research results and general oncology practice and of optimizing that link--was re-emphasized. Much of the work in creating this link and in epidemiology studies of its effects on mortality require appropriations in the control and contract lines.

XII. Symposium on Biologics, Cytokines, Lymphokines, Modulators

Dr. Longo presented a brief synopsis of biological therapy and noted that it appears to have joined the ranks of surgery, radiation, and chemotherapy as a legitimate mode of cancer treatment. This is especially true with the application of modern molecular biology, biochemistry, and cell biology techniques. He said that although traditionally biological therapy has been thought of as immunology therapy, many biological agents have direct effects on tumor cells as well as indirect effects in stimulating the immune system.

Dr. Longo mentioned two lymphokines reported in the last year to have antitumor effects, cytolysin and leukoregulan, and added that biological therapy should include nonimmune-mediated and nonimmune cell sources of biological materials. In addition, Dr. Longo cited developmental biology as an area that may yield new cancer treatment techniques and agents. Currently, the Biological Response Modifiers Program (BRMP) is studying oncogene expression and neuroendocrine relationships with the immune system.

Tumor Necrosis Factor--Dr. Carl Pinsky

Dr. Pinsky gave a brief history of research on tumor necrosis factor (TNF) which was discovered about 15 years ago in Dr. Lloyd Old's laboratory. TNF produced in the serum of mice that were pretreated with Bacillus Calmette-Guerin (BCG) and endotoxin was first shown to cause necrosis and regression of meth-A sarcoma in mice. These results were reproducible in rats and rabbits, and the necrotizing effects of the serum from BCG plus endotoxin-treated animals was also shown *in vitro*.

Dr. Pinsky described the initial difficulties of distinguishing the direct cytotoxic effects of TNF from those of endotoxin or lipopolysaccharides. Presently, many of the effects of TNF are known and how these compare to the effects of endotoxin is better understood. For example, TNF has direct cytotoxicity on tumor cells *in vitro*, but endotoxin does not; endotoxin affects T-cell differentiation, but TNF does not. There are also a number of immunologic effects that differentiate TNF from endotoxin.

TNF was initially purified from serum by passage through sephadex columns and various gels and the resulting product was purified 800 times. Use of the highly purified TNF resulted in complete regression of meth-A sarcoma in mice, identical to results with serum. However, Dr. Pinsky cautioned that TNF could not be expected to be a universally useful agent either in vitro or in vivo, as there is a wide range of sensitivity of human and animal tumor cell lines and wide range of tumor growth inhibition.

Dr. Pinsky described how Genentech has been able to produce TNF from a peripheral human blood cell line that is more than 4,000 times more pure than the original TNF. Using this, and several other approaches, a number of biotechnology firms have produced recombinant TNF from E. coli. This recombinant human TNF has been found to be active in mouse tumors, although there are differences between human and mouse TNF. Human derived TNF is synergistic in its effects with interferon in vitro. On the other hand, in vivo studies show that the effects of human TNF and recombinant mouse gamma interferon are synergistic for toxicity, but not, as yet, for tumor regression. These toxic effects are not produced with intraperitoneal administration. He added that, in mice, recombinant TNF seems to have more toxicity than natural TNF. Cachectin, produced by stimulation of macrophages in the mouse by endotoxin, has been found to be identical to TNF. One needs to be cautious in clinical trials, therefore, because recombinant human TNF (cachectin) is probably the effector molecule of hypotensive shock.

Phase I trials are just beginning, and dose-finding and safety studies are underway. Two clinical trials are in progress in Japan, and studies in the United States are being conducted at Roswell Park, Dana Farber, Memorial Sloan-Kettering, M.D. Anderson, and Wadley Institutes. So far no antitumor effects have been reported, although such effects would be unlikely at this early stage.

The following points were raised in discussion:

- Little is known about the human toxicity of TNF, although hypotension, chills, and fever are being observed fairly regularly
- TNF has definite effects in the B16 metastatic model
- TNF should be studied as a biological response modifier at doses several logs lower than the maximum tolerated dose and studied for its direct cytotoxic effects at the maximum tolerated doses
- Hemorrhagic necrosis seems to occur only in the meth-A transplant in Balb/C mice, not in metastatic tumors
- A possible immune aspect of the TNF effect needs to be studied
- Cachectin/TNF is an incredibly active biological compound, the activities of which are only beginning to be understood; its possible use in weight reduction should be viewed cautiously

- TNF is an exciting compound because of its possible dual role--as a direct cytotoxic agent on a limited number of human tumors and as a possible prototype of a biologic response modifier--however, it is not ready to be routinely used in cancer treatment

- The dose-limiting toxicity of TNF will probably not be weight loss but hypotension

- Phase II trials might begin in early or mid-1986.

Lymphokine-activated Killer Cells and Interleukin-2: Update on Clinical Results--Dr. Steven Rosenberg

Dr. Rosenberg summarized animal studies and presented data on 25 patients that were published in the New England Journal of Medicine on December 4, 1985. The approach is to enhance the antitumor activity of the patient's own immune cells ex vivo and use them to mediate antitumor effects in the body. Lymphocytes are removed from the blood by leukapheresis, incubated in interleukin-2 (IL-2) to give them antitumor activity, and then reinfused into the patient.

Animal studies were begun in 1978 and the results of one early experiment were described in which mice showed a dramatic reduction in the number of metastases after treatment with lymphokine-activated killer (LAK) cells and IL-2. Both LAK cells and IL-2 were required to mediate the antitumor effects. Dr. Rosenberg described the mechanism as having three phases: 1) LAK cells with antitumor reactivity proliferate under the influence of IL-2; 2) proliferating LAK cells maintain their antitumor reactivity and are responsible for the antitumor effects; and 3) the proliferating LAK cells die and resolve completely when IL-2 administration is stopped.

Dr. Rosenberg explained how the human trials of LAK and IL-2 began. In the initial testing in Phase I studies, LAK cells and IL-2 were administered separately to determine the maximum tolerated doses of each. Treating patients with activated lymphoid cells alone began in 1981 and involved 27 patients. These cells were activated in phytohemagglutinin, as not enough recombinant IL-2 was available at the time. In this trial no antitumor effects were seen; however, it was demonstrated that one could transfer up to 2 x 10^{11} activated lymphocytes to a patient with minimal toxicity.

A study in 39 patients was then performed using first natural IL-2 and then recombinant IL-2. No antitumor effects were seen in any patient. Toxicity from recombinant IL-2 included fever, chills, malaise, and diarrhea, which Dr. Rosenberg said could be managed by appropriate medications. The major dose-limiting toxicity to IL-2 alone or with LAK cells is fluid retention. All side effects are completely resolved as soon as IL-2 is stopped.

In November of 1984 Dr. Rosenberg was given approval to start the combined therapy, using the following protocol:

- IL-2 administration for several days to boost the number of lymphokine-activated killer cell precursors in the peripheral blood
- Removal of lymphocytes by leukapheresis for 5 days in a row
- Incubation of lymphocytes to produce LAK cells (3 to 4 days)
- LAK cells infused intravenously with the IL-2 every 8 hours.

In many patients this cycle is repeated. Since the time of the first trial, the protocol has evolved and now uses three times the amount of IL-2 as was used initially.

Of the first 25 patients, 11 have had objective regressions of their cancer with one patient showing a complete regression of all metastatic cancer. Dr. Rosenberg pointed out that responses have been seen in four different tumors: malignant melanoma, colorectal cancer, renal cell cancer, and primary lung adenocarcinoma. All patients had advanced cancer and metastatic disease and had failed all other forms of therapy.

The treatment of several patients was then described:

- A 29-year-old woman with multiple subcutaneous nodules of metastatic melanoma on her arm, thigh, back, and buttock who had undergone surgery and interferon therapy with no response--a complete regression of all metastatic melanoma and remains free of disease.
- Another patient with melanoma, whose biopsies showed that the LAK cells penetrated the melanoma and disrupted the architecture--categorized as a nonresponder with less than a 50 percent regression.
- A 41-year-old male with five pulmonary metastases from a rectal cancer, who had undergone abdominoperineal resection, resection of lung metastases, and had received chemotherapy with 5-fluorouracil and mitomycin-C and had failed all--three of the five tumors completely regressed and the other two partially regressed; after a second course of therapy, and further shrinkage, the remaining nodules were resected and now this patient is disease-free.

Dr. Rosenberg showed x-rays following this last patient throughout treatment, and other patients whose tumor nodules had regressed significantly. Since the original 11 responders, two additional patients have responded.

Dr. Rosenberg then suggested a variety of future efforts using this approach: use of allogeneic LAK cells in humans; direct arterial infusion (a regression of a hepatic lesion has been observed in one patient treated by direct arterial infusion); and expansion of LAK cells in vitro to form LAK cell lines so repeated leukapheresis would not be necessary.

To date, all studies indicate that the smaller the tumor burden, the more profound the antitumor effect and the higher the cure rates. Therefore, Dr. Rosenberg would like to try the therapy in patients with Stage II disease. Because LAK cell therapy does not depend on the immune competence of the host, it is an ideal therapy to combine with chemotherapy and radiation therapy. Dr. Rosenberg then said that intraperitoneal instillation of LAK cells and IL-2 can have profound effects on intraperitoneal disease and should be considered for treatment of ovarian and colorectal cancer.

Dr. Korn and other Board members congratulated Dr. Rosenberg for his selection as co-recipient of the Hammer Cancer Research Prize.

The following points were raised in discussion:

- Breast cancer patients are being sought for treatment with this type of protocol.
- It appears that it is the transferred LAK cells within the tumor that are mediating the antitumor effects.
- It is believed that the LAK cells can recycle and lyse more than one target.
- With the LAK cell plus IL-2 therapy, patients generally gain four to five pounds in a month. Weight gain due to fluid retention, is lost as soon as IL-2 is stopped. There is no hair loss as in chemotherapy.

Combined Modality Treatment--Dr. Robert Wiltrout

Dr. Wiltrout presented an overview of combined modality treatments being investigated in the Experimental Therapeutics Section of the Biological Response Modifiers Program. These preclinical experiments are combinations of the immunotherapeutic protocols currently being developed and traditional methods of cancer treatment.

Dr. Wiltrout stated that since most life-threatening tumors, particularly the solid tumors, are often complicated by metastases in vital organs, the traditional approach of monitoring the effects of biological response modifiers (BRM) only in the blood or lymphoid organs may not be the best approach. For this reason, one major aspect of study will be the ability of BRMs to induce immunomodulation in nonlymphoid organs.

A second problem area, using the immune system to treat cancer, has two major aspects: activating cells to have cytotoxic effect and getting those cells to the cancer site. The ability of various BRMs to change the distribution of lymphoid cell populations from one area to another in vivo is being studied.

The third problem area and the focus of Dr. Wiltrout's talk is evaluation of combination approaches. For example, well known chemotherapeutic approaches are being used in conjunction with BRMs and chemotherapeutic drugs are conjugated to tumor-specific monoclonal antibodies.

Another approach, the combination of chemotherapy with adoptively transferred cytotoxic lymphocytes, is being evaluated on the basis of the following parameters:

- Is there an additive or synergistic effect using chemotherapy and adoptive transfer of LAK cells?
- Is the efficiency of this treatment the same at different stages of tumor development?
- Is this therapy efficient in different tumor types in different locations?
- What are the mechanisms of action by which chemotherapy and adoptive immunotherapy (ACIT) complement each other?

Dr. Wiltrout then described the renal carcinoma animal model, which is staged like human renal cell cancer. The first step, in designing a combination approach is to find a chemotherapeutic regimen for treatment of renal cancer. On the basis of in vitro testing, Adriamycin was picked as the chemotherapeutic drug. Lymphocytes are extracted and incubated in IL-2 for 24 hours. This is done because cells in culture for 3 to 6 days tend to migrate to the lung and liver but not to the lymph nodes. After reinfusion of the treated lymphocytes, IL-2 is given supplementally to boost the lymphocytes' cytolytic and proliferative potential.

Dr. Wiltrout said that in the first set of experiments control mice given 100,000 tumor cells died within 38 to 40 days. Mice treated with transferred cytolytic lymphocytes and IL-2 had extended survival times but ultimately died of the cancer. Mice treated with relatively high doses of Adriamycin had significantly extended survival times, and 20 percent were cured of early disease. The treatments given in combination, however, resulted in a 70 percent cure rate, even with suboptimal doses of Adriamycin.

The next set of experiments described by Dr. Wiltrout tested the combined therapy against more advanced stages of disease, which are more likely to be similar to clinical situations. Dr. Wiltrout said no long-term cures were induced. However, most mice were dying from peritoneal tumors, suggesting that the intravenous administration had controlled systemic disease. Therefore, intraperitoneal adoptive chemoimmunotherapy was used

to treat early peritoneal disease. Cure rates of 85 to 100 percent were obtained with this combination therapy.

In studies of more advanced disease, it was necessary to remove the tumor bearing kidney but this did not effect a cure. However, after nephrectomy, when chemoimmunotherapy was given both intravenously and intraperitoneally, an 80 percent cure rate was seen. When cured animals were rechallenged with tumor, no specifically cytolytic protective T-lymphocytes were generated. Similar results were obtained for stage III disease. Dr. Wiltrout emphasized the importance of treating disseminated disease by bicompartmental administration of adoptive chemoimmunotherapy to reach all tumor sites and all foci of tumor growth.

Dr. Wiltrout stressed that adoptive chemoimmunotherapy is more effective for treating established disease than either chemotherapy or adoptive immunotherapy alone. Both cytotoxic lymphocytes and IL-2 are required for successful treatment. Dr. Wiltrout concluded that combination approaches may be especially useful because of the heterogeneity of tumor cells and the frequent dissemination of tumors to various anatomical sites.

The following points were raised in discussion:

- The animals did not retain fluid because the doses of IL-2 are smaller in the combined therapy
- Lymphocyte cells in culture for several days tend to localize in the lung and liver when reinfused
- Human IL-2 was used in the mouse studies, which should be considered in analyzing results.

Interferon in Hairy Cell Leukemia--Dr. Jeffrey Clark (for Dr. Steis)

Dr. Clark briefly described hairy cell leukemia and stated that his presentation would be on B-cell cases, which constitute the great majority of cases. In the past, splenectomy has been the principal treatment for hairy cell leukemia because it serves to remove the primary source of destruction of platelets and granulocytes and decrease the total body burden of hairy cells. About 75 percent of patients respond to splenectomy for variable amounts of time; however, one-third to one-half will require further therapy within 5 years. Dr. Clark said that until recently no treatment (combination therapy, chemotherapy, or leukapheresis) was universally applicable to all patients post-splenectomy.

In the past two years, with the use of deoxycoformycin and alpha-interferon, the treatment of hairy cell leukemia has become much more effective. Deoxycoformycin is a chemotherapeutic agent that has shown good results. Alpha-interferon is a natural glycoprotein secreted by leukocytes in response to viral infections and has a broad range of cytostatic and immunomodulatory effects.

Dr. Clark reported that 118 of 126 (94 percent) patients with hairy cell leukemia have had some response to alpha-interferon treatment. However, it is still too early to know the complete remission rate or duration of remission. The early indications are that the duration of response seems to be contingent on continued treatment with alpha-interferon. Dr. Clark said patients receive 3 million units of alpha-interferon injected subcutaneously on a daily basis for 4 to 6 months, followed by a three times per week schedule indefinitely.

In evaluating the responses, a complete remission is defined as the absence of any hairy cells in the bone marrow and improvement in the peripheral blood counts, and partial remission is defined as a greater than 50 percent reduction in hairy cells in the marrow and improvement in the peripheral blood counts. Of the 50 patients treated in Phase II, over half had prior splenectomy and 40 percent had not had any prior therapy. Dr. Clark said that of the 36 evaluable patients, 3 are in complete remission, 11 have had partial response, and overall, 34 of the 36 have had either stabilization of their disease following interferon or some response. Two patients have experienced progression of disease following interferon therapy.

Dr. Clark said the time to response is variable but is often longer than would be expected with a chemotherapeutic agent. In general the hairy cell counts of patients with this therapy come down relatively rapidly, however, the rise in granulocytes tends to be less rapid. The response of platelet counts has been variable from patient to patient.

The primary toxicity has been flu-like symptoms, similar to those observed in other patients treated with interferon, but they have not been dose limiting. The most persistent symptoms are fatigue and anorexia, but the majority of patients are able to return to work while on treatment.

Dr. Clark said that an integral part of the clinical trials is the elucidation of basic cellular mechanisms and the monitoring of the patient's response to treatment. Hairy cell leukemia cell lines have been established in laboratory research and are potentially a very useful tool for study of mechanisms.

The preliminary data suggest that alpha-interferon is well tolerated and very effective in the treatment of the majority of hairy cell leukemia patients who have progressive disease post-splenectomy. The long-term impact of this treatment is not yet known, and the additional role of deoxycoformycin in combination in initial treatment is also not known but planned for study.

The following points were raised in discussion:

- Dr. Clark said that he gets patients from all over the country and said that a randomized study is being done extramurally

- Neither the presence or absence of the spleen or the number of interferon receptors on the hairy cells are good predictors of responses to treatment

- As deoxycoformycin is considered specific for T cells, its use in hairy cell leukemia was based on empiric observations.

L-Histidinol--Dr. Robert Warrington

Dr. Warrington presented data to support the observation that the amino acid analog L-histidinol is able to protect normal cells of tumor-bearing mice from anticancer drugs, while at the same time increase the capacity of those drugs to destroy the tumor cells. He added that this approach increases the specificity and efficacy of drugs.

Anticancer agents are usually very toxic either to specific tissues or in general. Their toxicity is a result of antiproliferative action. He suggested that if an agent could arrest proliferation of normal cells, then the proliferation-dependent anticancer drugs would only affect the cancer cells. This would increase the drug's specificity so that the dose could be increased.

This selective cell cycle arrest state is achieved by taking advantage of the fact that normal cells remain quiescent when deprived of certain amino acids, yet cancer cells continue to divide. L-histidinol is an amino alcohol analog of the amino acid L-histidine and competitively inhibits histidyl-tRNA synthetase. This essentially prevents cells from using the essential amino acid L-histidine.

To verify this approach in tumor-bearing animals, it had to be shown that histidinol protects normal cells and enhances the killing of the tumor cells. Animals were treated with anticancer drugs and after 24 hours femur cells were removed and their clonogenicity determined by a relative cell survival assay. The proper amount of L-histidinol eliminated the toxicity of cytosine arabinoside, 5-fluorouracil, and methotrexate. Mice given supra-lethal doses of 5-fluorouracil were protected from its toxicity when L-histidinol was also administered. Histidinol is effective in protecting normal cells against the general toxic effects of anticancer drugs.

To determine whether L-histidinol also enhances the killing of cancer cells, animals were injected with transplantable leukemias and then various anticancer drugs were administered, either with L-histidinol or without. When animals were given cytosine arabinoside and L-histidinol, a protective effect on normal cells was seen, and the ability of the drug to kill tumor cells was increased. These effects have been verified with other anticancer agents, including 5-fluorouracil, a number of alkylating agents, and some antitumor antibiotics. The most dramatic responses have been seen with L-histidinol and BCNU. Similar trials were done in metastatic models and a significant reduction in the number of metastases was observed with the combined treatments.

L-histidinol can increase the specificity and efficacy of a variety of clinically relevant anticancer drugs, but Dr. Warrington cautioned that it is not known whether this approach will be applicable to human chemotherapy. He stated that these experiments have demonstrated that the toxic

effects of anticancer drugs can be modulated. Future studies will be done using human tumor cell lines.

The following points were raised in discussion:

- The histidinol is administered two hours before the anticancer drug, with the drug, and three times after the drug administration for a total of five 5 mg doses
- L-histidinol enables higher concentrations of some drugs to be used and for other drugs, enhances the effectiveness of a given concentration
- Studies have not yet been done using solid tumors
- L-histidinol seems to be a fairly strong sedative, but toxic effects have not been observed below the maximum tolerated dose
- Preclinical toxicology testing remains to be done.

Monoclonal Antibodies: Introduction--Dr. Dan Longo

Dr. Longo presented an overview of monoclonal antibodies and strategies for their clinical use. Using a slide of a monoclonal antibody of the IgG subtype, he noted the light and heavy chains, both having two segments. One segment has a relatively constant amino acid sequence and the other, at the amino terminal, has variable sequences of amino acids that allow that portion of the molecule to accept different configurations. These different configurations allow for the specificity of binding of the antibody molecule. The capacity to make a wide range of monoclonal antibodies is genetically programmed.

The constant portion of the antibody molecule determines the function of the antibody and is the part to which complement binds. In general, antibodies are modified by conjugating them with toxins, isotopes, or drugs, which need to be attached to the constant portion of the molecule. The potential cytotoxic mechanisms include the fixation of complement to lyse cells and the activation of endogenous cytotoxic cells, such as T cells, natural killer cells that have FC receptors and macrophages that have FC receptors and can recognize a tumor cell bearing an antibody. In addition, antibodies can activate the reticuloendothelial system to serve more of a scavenger function.

There is also excitement about developing monoclonal antibodies to physiologically important molecules on the cell's surface. For example, growth factor receptors, which may be expressed differently on tumor cells and normal cells, appear to be able to be blocked with monoclonal antibodies, and that blockage is associated with a change in the biochemistry of the cell and its proliferation capacity. There is also the possibility that monoclonal antibodies can be used to induce long-term tumor immunity.

The research of Dr. Hilary Koprowski at the Wistar Institute who is using anti-idiotype monoclonal antibodies was described. He believes he has found a tumor antigen, and he has made an antibody to it and a second monoclonal antibody that recognizes the first one. For the second anti-idiotype antibody to interact with the first antitumor antibody, it has to have a structure very similar to the primary tumor antigen. Dr. Koprowski believes that by using the second antibody and the anti-idiotype, long-term tumor immunity in patients with colon cancer can be induced. Other research is focusing on the use of monoclonal antibodies to specifically deliver drugs, toxins, and radioactive isotopes to the tumor.

Dr. Longo described some problems associated with monoclonal antibodies. First, the technology is best developed for making murine monoclonal antibodies, but the human body recognizes them as foreign and they are not circulated or metabolized like normal human IgG. Also there are differences between the constant portions of murine and human antibodies that result in many murine antibodies being poor activators of human effector mechanisms. In clinical trials, patients have been able to make an antibody against the murine antibody, which diverts the murine antibody from going to the tumor site.

There are also potential problems with human antibodies largely because it is difficult to select an antitumor-specific cell and immunize a human against a tumor. There are also technical problems that involve the lack of availability of a truly excellent fusion partner to generate the monoclonal antibodies. The majority of human antibodies described to date have been derived by exposing human cells to the tumor antigen in vitro. This primary immune response involves mostly antibodies of the IgM heavy chain class, the first strike antibody in the defense mechanism but one that does not get out of the vascular system effectively. Also, because it is a primary response and there has not been an opportunity for clonal selection of cells that produce an antibody of higher specificity, the IgMs have a limited effector function and are not capable of eliciting antibody-dependent cytotoxicity mechanisms.

Due to the heterogeneity in the expression of antigens on the surfaces of tumors, there are problems with any antibody type. After treatment with a particular antibody, the fraction of cells that lose the target of the antibody can increase. Another important problem is that the tumor membrane is fluid and dynamic, and tumor cells secrete many of the target antigens for which monoclonal antibodies can be made. These secreted target antigens distract an intravenously administered monoclonal antibody from getting to its target.

Additional problems concern the conjugation chemistry. If a bond between a toxin and an antibody is broken in vivo, free toxin could be released and produce unacceptable toxicity. In most biodistribution studies, the vast majority of conjugates are found in the liver and do not track to the tumor cells. In general, only about 5 to 10 percent of an injected dose of a monoclonal antibody can be found associated with the tumor.

A problem with monoclonal antibodies as drug carriers is that there are between 500 and 100,000 target antigens on tumor cells. If, in the optimal case, one molecule of drug is attached to a monoclonal antibody, then the molecules of the drug delivered to the cell would correspond to the numbers of tumor antigens. However, the transport mechanisms of many drugs are much more efficient and the use of monoclonal antibodies as carriers may not enhance tumor specificity.

In spite of these problems, Dr. Longo stated that much progress is being made. The following speakers described successful use of monoclonal antibodies in preliminary clinical trials.

Human Use of Anti-Idiotype Antibodies--Dr. Ronald Levy

Dr. Levy summarized the clinical trials being performed at Stanford with monoclonal antibodies against surface molecules on tumors of patients with B-cell lymphoma. He stated that B-cell malignancies provide good study opportunities because they are tumors of the system that actually makes antibodies. About 80 percent of patients with malignancies of the lymphoid system have tumors that make immunoglobulin molecules and put them on the surface membrane of the cells or secrete them into the serum. The advantage is that each tumor cell makes only one immunoglobulin molecule, and every progenitor of the cell makes exactly the same immunoglobulin molecule. If an antibody is made against the immunoglobulin molecule in the variable region--the idiotypic determinant--that antibody will be able to differentiate between tumor cells and normal cells. The problem is that every patient's tumor is different, requiring a different antibody.

This problem has been approached by creating a heterohybrid between the human tumor cell and a mouse cell that secretes large amounts of antibody, thus tricking the cell into becoming a large-scale synthesizer and secreter of the antibody that was formerly only on the surface of the tumor cell. The molecules can be isolated in pure form and used to immunize mice to make the antibodies, which are very good at distinguishing between tumor and normal cells. Dr. Levy described this technique as a way of isolating tumor cells for genetic analysis.

Clinical trials have involved infusing custom-produced antibodies to assess their ability to attack or direct an attack against the tumor in vivo. Dr. Levy described the course of treatment for the first patient treated, over 4 years ago. The mouse antibody was successful in clearing from the serum circulating protein made by the tumor and at that point, the tumor began to regress. The patient remains in complete remission. The results with this first patient were the best that have been obtained.

In a second patient with a very high level of circulating leukemic cells, antibody was infused in increasing doses until an excess of antibody was achieved. The tumor cells then disappeared from the blood and bone marrow for some months thereafter. Another patient with a B-cell lymphoma received several weeks of treatment with a custom-made monoclonal antibody and experienced a major reduction in tumor size.

Summary data on the treatment of 13 patients scored in terms of clinical response were presented. The results were described as heterogeneous, with some patients having significant regressions of their tumor and others having little or no response to the antibody infusion. In analyzing a number of parameters, Dr. Levy said a rough correlation was found between the number of T cells in the tumor and the outcome in terms of response to therapy. The two patients who responded best had more T cells in their tumor than tumor cells, indicating an immunologic response by the patient against the tumor before the antibody was administered. The T cells that are killing the tumor may recognize the idiotypic determinant on the surface of the tumor cell.

Dr. Levy emphasized the complexity of the situation in which patients, tumors, and antibodies all have unique characteristics. It has been found that cells in the tumor population are heterogeneous in terms of their expression of target at which antibodies are directed. The targets are heterogeneous in terms of the molecular details of the amino acid sequence of the determinant that the antibody looks at. This explains why in some patients tumors initially respond to treatment but then recur. After treatment some cells still have immunoglobulin molecules but do not express the exact determinant that the antibody reacts with. The antibody is not effective in eliminating cells that do not have the particular determinant for which it is specific.

To study this mutational process that allows some cells to escape from the antibody treatment, genomic DNA was extracted, and cloned. It was thought a single amino acid change in the second hypervariable region of the immunoglobulin gene accounted for the escape. However, it was also found that the host was allowing mutations to occur in some regions but not in others. The growth of mutants that destroy the immunoglobulin molecule binding site is inhibited by the host. Evidence implies the existence of some anti-idiotypic network of responses in the host that interacts with the tumor.

Therapeutic strategies that are being studied include developing multiple anti-idiotype antibodies that recognize different portions of the molecule and combining anti-idiotype treatment with other biologicals and chemotherapy.

The following points were raised in discussion:

- About six months are required to make an antibody, which must be custom-made for each patient and each clone
- With no treatment, patients can change from idiotype positive to idiotype negative during the time it takes to make the antibody
- T cells do not bind well to soluble antigens and probably do not have receptors that specifically recognize the determinant

- Studies are planned to use IL-2 to try to activate T cells surrounding the tumor cells

- Mechanisms of responses of the tumor cells to the antibody are largely unknown

- Lymphocytic lymphomas are the sixth commonest tumor as a cause of death in the United States, and the median age of occurrence is about 46

- Most follicular B-cell lymphomas have not been cured with chemotherapy

- There is evidence that there may be synergistic effects between interferon and the antibodies.

Marrow Purging of Tumor Cells--Dr. John Kersey

Dr. Kersey summarized the process of bone marrow transplantation and noted that all cells of the lymphoid system have their origin in the bone marrow. Potentially any disease that involves the various cells of the lymphoid system could be treated by bone marrow transplantation. He discussed leukemia in relation to both autologous and allogeneic marrow transplantation and the use of marrow purging to circumvent the problems that arise when there is no matched donor or to prevent graft versus host disease.

Bone marrow transplantation is used to treat both acute and chronic leukemias because the patients suffer from a very high risk disease and the particular chemotherapy or radiotherapy is very toxic to the marrow. Dr. Kersey described patients with high risk acute lymphoblastic leukemia who relapsed after conventional therapy and had a dismal prognosis. A comparison was made of the results of allogeneic marrow transplantation using a matched sibling donor with a new approach in which the patient's marrow is purged of leukemic cells and then infused back into the patient, autologous marrow transplantation.

The new approach involves three monoclonal antibodies that bind to leukemic cells in the patient's marrow but do not bind to stem cells. About 85 percent of the patients have B-cell acute lymphoblastic leukemia and about 15 percent have T-cell acute lymphoblastic leukemia, which requires different antibodies. The bone marrow is removed from the patient in remission and treated to remove red cells and collect the mononuclear cells that contain a mixture of stem cells and leukemia cells. The marrow is then treated with the antibodies and complement and frozen. The patient receives a very high dose of chemotherapy and radiation therapy to eliminate whatever residual tumor exists. The patient's purged marrow is reinfused.

In experiences over the past 3 years, patients with HLA/MLC matched sibling donors received allogeneic transplants and those without such donors received autologous transplants. There was essentially no difference in the survival of the two groups of 44 patients each, who received the two types of transplants: about one-third of the patients are surviving at 3 years. Although the numbers are small and followup short, there is a good probability that the patients who have not experienced any disease after one and a half years are going to be cured. No significant differences in survival were found between patients receiving the autologous and allogeneic transplant methods.

Graft versus host disease, which occurs in 30 to 70 percent of matched allogeneic bone marrow transplants was discussed. This very serious complication can result in tissue damage, immune deficiency, and, in some cases, death. There is evidence that the T-lymphocytes from the donor bone marrow are playing a major role in this graft versus host disease and therefore, to prevent the disease, efforts have been made to eliminate these T-lymphocytes. The antibodies used for removing T-leukemia cells have been used to remove immunocompetent T-lymphocytes from the donor bone marrow. To enhance the killing, toxins are conjugated to the antibody. One such toxin is ricin, derived from the castor bean and probably the most potent known toxin. The killing is done by inhibition of protein synthesis so that the cell becomes protein-starved.

Antibody ricin conjugates have been used to treat the donor bone marrow of 17 patients undergoing allogeneic transplantation. Seven of these patients were beyond the age of 30 and therefore had a very high risk of developing severe and fatal graft versus host disease. None of the patients treated developed fatal graft versus host disease. The patients experienced no toxicity from the ricin because it was removed before the marrow was infused into the patient. Dr. Kersey concluded that the approach is potentially very useful and may be expanded to develop immunotoxins that can be used in vivo.

The following points were raised in discussion:

- This approach is similar to and complementary with the flow cytometry approach for detecting different types of cells and then destroying them by various means, such as lasers
- It is not clear which cells are responsible for graft versus host disease and which are responsible for graft versus tumor effects and whether the two are different
- No patients have been encountered who did not have enough bone marrow to undergo this treatment
- Patients who receive allogeneic transplants may experience a very profound immune deficiency for up to 2 years

- About 1 month of hospitalization is necessary for autologous transplantation, costing about $75,000

- Autologous marrow transplantation is being tried in some very high risk patients with acute lymphoblastic leukemia in first remission

- About one-third of the 88 patients in the study had undergone extramedullary relapse and after marrow transplantation, their risk of relapse was slightly higher.

Human Use of Anti-GD3--Dr. Alan Houghton

Dr. Houghton presented background information and Phase I clinical trial data on the monoclonal antibody, anti-GD3. Mice were immunized against malignant melanoma and the antibody was harvested from hybridomas. The antibody R24 recognizes the GD3 glycolipid and is very specific against melanoma, but does react with normal cells, including melanocytes, astrocytes, and islet cells in the pancreas and adrenal medulla. Dr. Houghton said over 200 melanomas have been examined and all but 3 have reacted with the antibody.

In the experiments conducted, it has been found that while GD3 is expressed at low levels on the normal cell, there is increased GD3 expression on melanoma cells. The antibody is very effective in killing melanoma cells in a variety of ways. The antibody prevents melanoma cells from attaching to surfaces and causes them to aggregate. It has also been found that the antibody probably reacts with a small proportion of the T-cell population and leads to T-cell stimulation.

This antibody has been administered at four dose levels in 21 patients. The total doses were from 10 to 20 mg/m2 per patient up to 600 to 800 mg/m2 per patient over the total treatment period. Patients who received lower doses experienced hives and itching, especially around tumor sites and those who received higher doses experienced more severe urticaria, as well as nausea, vomiting, and diarrhea. Of the first 12 patients treated, 6 treated with low doses experienced some regression in tumors for varying periods of time, and 4 had a 50 percent reduction in all measurable lesions. However, tumors have recurred in all patients after varying intervals. At higher doses, an antitumor effect was seen in only one patient.

While peak serum levels or peak steady-state levels of antibody were related to the amount of antibody given, by the end of the second week of treatment, the levels of antibody decreased rapidly. All patients developed IgG antibodies against the mouse protein usually within 10 to 18 days. Among the melanoma cell lines, there is heterogeneity of the expression of the antigen. A description was given of a phenomenon known as antigenic modulation in which the antigen actually disappears from the tumor cell when the tumor cell is attacked by the antibody. Progression of the tumor or

recurrence of the tumor after treatment generally did not result from outgrowth of GD3 negative cells. The cells that grew after treatment usually continued to express the antigen, although in one patient GD3-negative cells were found, perhaps indicating that some cells escaped.

The amount of antibody reaching the tumor was found to be related to the dose given. However, within a given tumor some areas react very strongly with the antibody and other areas very weakly or not at all.

Possible mechanisms of the antibody effect on the tumors are being investigated. The antibody fixes complement, and it is known that the antibody can destroy tumor cells if effector cells are present. Increased numbers of mast cells, which carry immune mediators, including histamine, are also seen and would explain the hives and itching. Some of the complement components can activate mast cells, which could lead to a more chronic inflammatory response and later infiltration of lymphocytes. These lymphocytes were found to have a TA positive phenotype and in one patient a series of cloned T-cell lines was established that killed her own tumor.

Dr. Houghton said work is in progress to investigate the use of this antibody in conjunction with other therapies. In vitro data suggest that Adriamycin can potentiate the cytotoxic effect of this antibody quite dramatically. There are also plans to further study the role of the T cells and to consider monoclonal antibody plus interleukin-2 therapy.

The following points were raised in discussion:

- Patients were sequentially allocated to dose groups on the basis of observed toxicity

- In attempts to couple the antibody to other agents, such as toxins, substantial reactivity of the antibody is lost.

Antibodies Conjugated to Toxins--Dr. Ira Pastan

Dr. Pastan stated that he and Dr. Mark Willingham have been studying how antibodies and immunotoxins interact with cells. He summarized how immunotoxins work and said that ultimately some fraction of the internalized immunotoxin gets into the cytoplasm and can kill the cell catalytically. Toxins that have been studied include diphtheria, ricin, and pseudomonas exotoxin (PE).

One model that has been used is adult T-cell leukemia because of the existence of the antibody to the TAC receptor, which is expressed in fairly high numbers in such leukemias. Also this leukemia is a very aggressive disease with no satisfactory treatment. The PE-anti-TAC was first shown to be active in vitro; toxicity studies then were done in monkeys, and two patients were recently treated.

The first patient was a typical HTLV-I positive and had a white count of about 18,800 and more than 50 percent of his circulating cells were TAC-positive. The patient was given two treatments of PE-anti-TAC, and after the first treatment, the number of white cells and TAC-positive cells fell, but went back up after a few days. The second treatment had no effect, perhaps due to the fact that starting at day 8, the level of interleukin-2 receptors in this patient's blood rose substantially and antibodies to the pseudomonas toxin developed.

Therefore, in treating a second patient, the doses were given closer together in hopes of avoiding this response. Although the data are incomplete, the patient experienced some liver toxicity with a 4 mg dose administered over a few days. This particular PE-anti-TAC preparation also produced liver toxicity in monkeys. As a different PE-anti-TAC preparation was used in each patient, efforts are now underway to determine why the preparations varied and why the second one elicited liver toxicity.

Dr. Pastan also described experiments on an ovarian cancer model using a pseudomonas exotoxin conjugated to an antibody to the transferrin receptor. This model was chosen because ovarian cancer is a disease that is often restricted to the peritoneal cavity, and it was thought that by injecting immunotoxin into the peritoneal cavity, large molecules could escape slowly and bone marrow damage would be limited by dilution. When this antitransferrin PE immunotoxin was injected into nude mice intraperitoneally, tumor cells growing in the intraperitoneal cavity were killed, but the same cells growing extraperitoneally were not killed. If tissues that are at risk near the peritoneal cavity are found to be transferrin receptor negative, Phase I trials will be initiated next year.

The following points were raised in discussion:

- The mechanisms by which the second preparation of immunotoxin damaged the liver are unknown; no damage to the reticuloendothelial system was seen

- Immunosuppression is being considered as a means of avoiding the production of immunotoxin antibodies.

Imaging and Therapy with Radiolabeled Antibodies--Dr. Steven Larson

Dr. Larson said radiolabeled antitumor antibodies have been used to target human tumors in vivo. In a patient in whom radiolabeled antibody was given by intraperitoneal catheter, antibody was seen binding to tumor deposits, as verified by surgery, in the liver and the spleen. When the peritoneal cavity was washed to eliminate some unbound activity, the radioactive antibodies remained tightly bound to the tumors. In this patient, other diagnostic tests (NMR and CT) were negative at the time when this test was positive. Surgery confirmed that the radionuclide antibody test had detected occult disease.

In principle, the radiolabeled antibodies are clinically useful for two purposes: 1) to diagnose undisclosed tumor by labeling the antibody like a tracer and injecting the antibody into the patient where it circulates through the blood and tissue and interacts with the specific antigen so that radioactivity accumulates at the tumor site; and 2) to use these antibodies to target killing doses of radiation. The hope is that these radiolabeled antibodies can ultimately be used to detect a few milligrams of tumor in a living system. At present, further research is needed to develop better targeting of the radioactive antibody to the tumor with as little as possible going to normal tissues. An important theoretical advantage is that many solid tumors and hematopoietic malignancies, for which only modest therapy is currently available, could potentially be diagnosed and treated with this approach if on-going research proves to be successful.

In regard to clinical studies at NIH, antibodies antimelanoma, anticolon and antiovary, and antibody to T cells (hematopoietic tumors) have been studied. Using antimelanoma antibodies and a rotating gamma camera, excellent images of tumor location in the liver were obtained as a tomographic picture much like a CT scan. This method can be used to image tumors very early after injection of the antibody. A variety of special radionuclides such as I123, In111 or TC99m are most suitable for this kind of imaging because they emit radiation of the right wave length (energy). Indium-111-T-101 has resulted in excellent targeting to T-cell malignancies, cutaneous T-cell lymphoma, chronic lymphocytic leukemia, etc. after intravenous injection in some patients. In the future, research will continue on ways to link the best radionuclides for diagnostic purposes to antibodies, because to be optimally useful, considerable effort should be expended to improve present preparations.

In patients found to have sufficient localization of tumors, therapy with radioactive antibodies has been given. Only one melanoma patient had a particularly dramatic response to treatment that was of about 4 months in duration. There are considerable problems remaining with this approach, however, including the variability of tumor response to radiation. Also I-131 is not ideally suited as an antibody label for therapeutic uses because it has an associated gamma decay which causes marrow suppression and toxicity. Future plans are to use pure beta-emitters to deliver radiation in a more localized way, within about 10 cell diameters of the site of origin. Another potential method is the use of alpha-emitters as therapy radionuclides, to take advantage of the selectivity and an excellent tumor killing effect that has been demonstrated in vitro with the bismuth-210, for example. Other alpha emitters that are being studied as potential therapeutic labels are astatine-211 and lead-210.

A number of factors have been found to affect the uptake of radiolabeled antibody in the tumor, including the type and dose of the fragment, the radiolabel itself, and the delivery to the tumor. Increasing the content of antigen on the tumor by stimulation with interleukin-2 is being studied as a possible way of increasing tumor uptake of the radiolabeled antibody. Antibody availability for clinical trials has also been a problem in the past, but new methods promise to reduce this problem in the future.

The following points were raised in discussion:

- Problems with the preparation of the antibody administered by the subcutaneous route have hindered a pilot study to visualize internal mammary nodes

- The choice of the radionuclide is determined by the metabolism of the antibody: short-lived therapeutic radionuclides can be used to target hematopoietic malignancies

- The ratio of radiation deposited in the tumor to the radiation deposited in the radiosensitive organs determines the success or failure of the technique.

Dr. Korn and members of the Board then expressed their appreciation to Dr. DeVita, Dr. Chabner, and Dr. Longo for the excellent presentations.

XIII. Adjournment

Mrs. Bynum announced that a new system for distribution of materials using truncated summary statements and microfiche will be initiated in January. Board members will receive portable microfiche readers.

The 56th meeting of the National Cancer Advisory Board was adjourned at 11:35 a.m., Wednesday, December 4, 1985.

1/29/86
Date

David Korn, M.D.