Department of Health and Human Services

Public Health Service

National Cancer Institute

National Cancer Advisory Board

Summary of Meeting
May 26-27, 1987
Building 31, Conference Room 6
National Institutes of Health
Bethesda, Maryland

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The National Cancer Advisory Board (NCAB) convened for its 62nd regular meeting at 8:30 a.m., May 26, 1987, in Building 31, 6th Floor, Conference Room 6, National Institutes of Health (NIH). Dr. David Korn, Chairman, presided.

Board Members Present

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

Absent

Dr. Howard Temin

President's Cancer Panel

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

Absent

Dr. Armand Hammer

Ex Officio Members

Dr. David P. Rall, NIEHS
Dr. Dorothy A. Canter, NIEHS
Dr. Ralph E. Yodaiken, DOL, OSHA
Captain Stephen R. Veach, DOD
Dr. Richard J. Greene, VA
Dr. Lakshmi Mishra, CPSC
Dr. Mary Ann Danello, FDA
Dr. Beverly Berger, OSTP

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

Liaison Representatives

Dr. Eve Ida Barak Briles, Assistant Program Director, Cell Biology Program, Division of Cellular Biosciences, National Science Foundation, Washington, D.C., representing the National Science Foundation.

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

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

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

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

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

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

Members, Executive Committee, National Cancer Institute

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

In addition to NCI staff members, meeting participants, and guests, a total of 32 registered members of the public attended the meeting.

I. Call to Order, Opening Remarks, and Consideration of the December 8-10, 1986, and February 2-4, 1987, NCAB Meeting Minutes--Dr. David Korn

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

The minutes of the December 1986 and February 1987 NCAB meetings were unanimously approved.

The Board, NCI staff, and all others assembled for the meeting observed a moment of silence in memory of Dr. Tim Lee Carter, NCAB member, who died in March 1987.

In observance of the 50th anniversary of the founding of the National Cancer Institute, a videotaped message from Mrs. Nancy Reagan was presented. She expressed pride in the NCI and the research it has supported, and conveyed wishes from the President and herself for continued success.

II. Future Board Meeting Dates

Dr. Korn called the Board members' attention to the following confirmed future meeting dates: September 28-30, 1987; November 16-18, 1987; February 1-3, 1988; May 9-11, 1988; September 26-28, 1988; and December 5-7, 1988. Proposed dates for 1989 are February 6-8, May 15-17, September 18-20, and December 4-6.

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

Dr. Longmire read a prepared report from Dr. Armand Hammer, PCP Chairman, who could not be present.

The PCP held its first 1987 meeting on March 16 at the Jonsson Comprehensive Cancer Center, University of California at Los Angeles (UCLA), where presentations focused on the continuing theme, "Innovations in Cancer Treatment." Reports were heard on the use of human monoclonal antibodies in cancer diagnosis and treatment (six of eight patients have responded with 50 percent or more reduction in tumor mass); the promising results achieved in in vitro testing of the human granulocyte macrophage colony stimulating factor (final results of trials now underway are expected in about a year); and studies of tumor infiltrating lymphocytes and IL-2 in humans.

At future meetings, the Panel will concentrate on the latest developments in the treatment of one or two specific cancers, bringing together experts for a full exchange of information, plans, and progress. The next meeting of the Panel, scheduled for June 22 at the University of Pittsburgh,

will focus on colorectal cancer and drug resistance. Board members were invited to attend. Dr. Hammer acknowledged, on behalf of the Panel, Dr. Fisher's assistance in arranging the meeting.

Referring to his predictions in February of a year of challenges and productivity, Dr. Hammer cited, in particular, the April report of the Government Accounting Office (GAO), which called into question NCI's claims of progress over the last three decades in treating cancer. He expressed his belief that the GAO report was too pessimistic and that recent developments, especially the work done with biological response modifiers, have justified the claims of significant progress. Dr. Hammer drew attention to inconsistencies in the report and expressed concern about the possible negative effects on the general public. He pointed out that the first paragraphs of the report and headlines of the newspaper articles are also likely to cause public concern, discouragement, and confusion. While various articles did present rebuttals by NCI and others, the initial impressions are likely to be lasting. Dr. Hammer added that statistics can be open to many interpretations but the interpretations made by the GAO investigators were unfair and misleading. He suggested that NCAB's planned regional public participation meetings, such as the one to be held in Los Angeles later in the year, could serve a very useful purpose in communicating balanced information to the public.

Turning to his prediction of progress in 1987, Dr. Hammer noted the encouraging reports heard at the Panel's March meeting and the progress made in characterizing the cancer cell and understanding its mechanism of action. In the treatment area, he cited reports in the New England Journal of Medicine (NEJM) by Dr. Steven Rosenberg (NCI) and Dr. William West (Biological Therapy Institute) and their colleagues, which reaffirm positive results achieved in the treatment of advanced cancer patients using IL-2 with and without LAK cells. In an editorial in the same issue of the NEJM, Dr. John Durant wrote that he felt the results achieved by Drs. Rosenberg and West and their colleagues justified the vigorous national pursuit of that therapy. Dr. Hammer praised Dr. DeVita and the NCI for taking a very important step in requesting that the Food and Drug Administration (FDA) move LAK/IL-2 to a modified group C category, making it available to the 38 comprehensive and clinical cancer centers. He expressed his belief that the NCI proposal was carefully crafted and designed to maintain stringent controls and appropriate data reporting. FDA approval of the NCI request will allow many additional patients with advanced malignant melanoma and kidney cancers, diseases for which effective treatment does not exist, the opportunity to receive IL-2 therapy. The increased numbers of patients participating in trials will make further refinement of the therapy possible. Dr. Hammer expressed the hope that the cancer centers will be able to move quickly to enroll qualified patients so that IL-2 therapy, like chemotherapy, surgery, and radiation, soon will be standard treatment and available to all who need it.

Information Item

As an information item, Mrs. Brown called attention to the booklet that had been distributed titled "Confronting Cancer through Art." She explained this was a catalog of works by cancer patients in an art exhibit mounted by Debra Breslow, Director of the Art that Heals Program at UCLA's

Jonsson Comprehensive Cancer Center. The Program encourages patients to express themselves in painting, drawing, or writing as a means of coping with difficult periods in their illness. Mrs. Brown reminded the Board that part of the Cancer Program focuses on providing psychological support to cancer patients. The catalog, selling for $11, is also a fundraising item that can be used by other cancer centers and cancer organizations. Anyone interested in obtaining additional information or hosting a traveling exhibit of the works in the catalog should contact Ms. Breslow at UCLA.

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

Dr. DeVita welcomed former NCI Directors, Dr. Carl Baker and Dr. Frank Rauscher, who were present for the events commemorating the Institute's 50th anniversary. Dr. DeVita, in noting that he would discuss the by-pass budget as a separate segment of his report, stated that it was a particularly important year for the by-pass budget as the Cancer Act will be up for reauthorization in 1989. The budget is based on the philosophy that to effectively address the cancer problem and achieve the goals for the year 2000, an influx of resources is needed comparable to that which occurred in the early 1970s.

Dr. DeVita announced that Dr. Howard Temin, an expert in virology and a Nobel laureate from the University of Wisconsin, had been appointed to fill Dr. Tim Lee Carter's position on the Board. Dr. Temin was one of the investigators who discovered the enzyme reverse transcriptase.

As part of the commemorative activities, Congress passed Public Law 100-24 designating May 1987 as the National Cancer Institute month. Dr. DeVita read the following part of President Reagan's proclamation issued on the occasion of NCI's 50th anniversary:

> The NCI's basic research over the past 15 years has brought about unparalleled understanding of the cancer cell and extraordinary insights into cellular biology. Applying knowledge now at hand could cut the annual death rate by 50 percent by the year 2000.

Dr. DeVita also thanked the many organizations that had helped celebrate the 50th anniversary, including the American Association for Cancer Research, the American Society of Clinical Oncology, the Oncology Nursing Society, the American Academy of Dermatology, the American Association of Cancer Institutes, the International Union on Cancer, and the Coalition for Cancer Research. He noted that much of NCI's history was chronicled in the May issue of the Journal of the National Cancer Institute in the reprint of the speech given by Mr. Benno C. Schmidt at the December NCAB meeting, plus reprintings of the Cancer Acts, and comments by Dr. DeVita. Dr. DeVita also announced that Mr. Schmidt and Congressman Paul Rogers would receive the Year 2000 Awards and noted that Mr. Richard Bloch's second annual Fighting Cancer Rally will take place on May 31.

In commenting on staff appointments, Dr. DeVita said that Ms. Iris Schneider had been promoted to the position of Assistant Director for

Program Operation and Planning. Ms. Judith Whalen will be the new Planning Officer and Executive Secretary of the NCAB Subcommittee on Budget and Planning. The organization of all animal research components into the Office of Laboratory Animal Science has been completed. This Office, headed by Dr. John Donovan, is located in the Office of the Director and provides for centralized administration and direct scrutiny of animal research issues. Changes in administrative staff included the loss of Mr. Steve Fica to the National Heart, Lung, and Blood Institute; the appointment of Mr. Don Christoferson, formerly Administrative Officer of the Division of Cancer Treatment (DCT), as Deputy Associate Director for Administrative Management, NCI; and the appointment of Mr. Larry Ray, formerly Administrative Officer of the Division of Extramural Activities (DEA), to replace Mr. Christoferson in DCT.

New Items

Dr. DeVita said that with respect to the IL-2 and LAK therapy, the Institute realized that data from the trials indicated that it was appropriate to move this therapy into the group C category, meaning that these are agents showing some effect against cancers for which there are no other effective therapies and thus should be dispensed for use. This was based on the results of national studies of IL-2 and LAK, which achieved a 30 percent overall response and 10 percent complete remission rate in treatment of advanced melanoma and kidney cancer. Dr. DeVita said that the remissions occurred in patients with very bulky pulmonary metastases and liver and bone metastases. These data reflect early clinical trials in which IL-2 and LAK therapy was used only for a single cycle.

To increase the availability of the therapy to the 13,000 patients per year with advanced melanoma and kidney cancer, NCI asked the FDA to approve group C prime or limited distribution to the comprehensive and clinical centers. FDA approved the request, and on May 12, NCI met with the Cancer Centers to discuss implementation of the program. Dr. DeVita said about 20 of the centers will participate, and $1 million has been moved from the clinical trials reserve fund to cover start-up costs.

The FDA's newly published rule for distribution of materials in early stages of clinical trials, referred to as the reproposal, is similar to NCI's group C program. Dr. DeVita said the reproposal would not influence the IL-2/LAK program because this therapy can only be made available to those institutions that have the facilities to grow LAK cells. Dr. Maryann Roper in the Office of the Director can provide information on the new FDA rule.

In referring to the cancer meetings, Dr. DeVita said Dr. Fisher's presentation on positive adjuvant studies in colorectal cancer was a highlight of the American Society of Clinical Oncology meeting. A follow-up study is planned, but Dr. DeVita said the real issue is to get more patients on those studies. Of about 60,000 eligible colon cancer patients nationwide each year, only about 1,000 patients per year are entered on the studies. One reason for the President's Cancer Panel's meeting in Pittsburgh is to focus attention on those studies and on the issue of rapidly accruing more patients.

Dr. DeVita said the group C prime issue was also associated with these studies because methyl CCNU, which was synthesized by Dr. Montgomery and is one of the drugs shown to be effective in Dr. Fisher's study, had been removed

from the market several years ago because of second tumor causation in some circumstances. There is a debate on how to provide access to this drug without damaging the clinical trials program. NCI and FDA are still discussing mechanisms for its distribution.

As the final new item, Dr. DeVita announced that a new Cancer Atlas would be released on June 9. This series of color-coded maps of cancer mortality shows trends for the U.S. white population for three decades: 1950 to 59, 1960 to 69, and 1970 to 79. The Atlas on the black population will be released next year. The Atlas includes maps for aggregate mortality and 33 separate cancers. Dr. DeVita said the maps identify hot spots for investigation and are very useful research tools. He stated that one of the earlier cancer maps had led to the observation that there were clusters of lung cancer mortality on the east coast and southeast coast which were found to be associated with World War II shipyards and exposure to asbestos. Because of the political implications of these maps, NCI will hold briefings for members of Congress. Dr. DeVita said Board members would be sent copies of the Atlas and acknowledged the efforts of Drs. Joseph Fraumeni, Robert Hoover, Thomas Mason, and Linda Pickle in the preparation of the maps.

Follow-up Items

General Accounting Office Report

Dr. DeVita next discussed the General Accounting Office (GAO) report and the problems in using statistics to evaluate the National Cancer Program. These problems relate to the use of different endpoints, e.g., mortality and survival rather than considering incidence, mortality, and survival together as the NCI annual Statistics Report does, the lag time in collecting and analyzing data, use of different study methodologies, potential biases in interpretation, and misinterpretation by the media and the public. Dr. DeVita stated he had been contacted by some of the individuals who had been interviewed by the GAO, and they had expressed the view that the negative tone of the report was not consistent with what they had said to the GAO investigators. The only recommendation in the report was that NCI should point out the potential biases in interpreting its annual report to the NCAB. Dr. DeVita said that, in fact, last year's annual report did include a discussion of bias in the introductory section.

Nutrition

Dr. DeVita reported that at the urging of Dr. James Wyngaarden, Director, NIH, he and Dr. Claude Lenfant, Director of the National Heart, Lung, and Blood Institute, have arranged with the Institute of Medicine to have a conference on evaluating data to develop dietary recommendations. Board members will receive an agenda for the December 4-5, 1987, conference.

Dr. DeVita said a press conference had been held in March to announce the NCI/Giant Food project to evaluate the impact of food labeling on consumer purchases. Special emphasis is focused on the fat and fiber content of food. One hundred stores in the Washington area have the food labeling program, and 100 stores in the Baltimore area are serving as controls. Samples of the information that Giant is distributing were provided to Board members.

Board members also received a booklet titled "Wave 2," which is the follow-up survey on attitudes towards cancer and, in particular, diet and cancer prevention. Although the public seems to have more knowledge on cancer, many people are still quite pessimistic about being able to take actions on their own to prevent cancer.

Frederick Cancer Research Facility

Dr. DeVita said the recompetition for the Frederick Cancer Research Facility (FCRF) program is nearly complete. Contractors for a 7-year period will be selected in July.

A basic research portion of the FCRF Program, headed by Dr. George Vande Woude, was recently site-visited by a group constituted by the FCRF Advisory Committee. Dr. DeVita reported that the Program had received the highest accolades.

AIDS

Dr. DeVita said Dr. Temin has agreed to chair an NCAB Subcommittee on AIDS. As the Board had previously discussed, it was felt that the Subcommittee was needed to provide guidance on NCI's relationship with other Government Agencies involved in AIDS research and on how to apportion resources between AIDS and cancer research. The Subcommittee's mission statement and list of members were distributed to the Board.

Dr. DeVita announced that a settlement had been reached with the Institut Pasteur on the lawsuit over the discovery of the AIDS virus. Negotiations have been concluded with Hoffman-LaRoche on licensing of dideoxycytidine and NCI has announced its intention to award licenses for two related compounds, dideoxyadenosine and dideoxyinosine. Also on the subject of AIDS, Dr. DeVita said the Institute is actively looking for an Associate Director for Biological Carcinogenesis. He invited Board members to suggest candidates.

Public Participation Hearings

Dr. DeVita expressed enthusiasm about the first of the Public Participation Hearings scheduled to occur on September 22 in Los Angeles. He suggested that issues related to survival statistics and other areas of high public concern may well be raised and offered to provide whatever information may be required.

Community Clinical Oncology Program

Dr. DeVita said the Community Clinical Oncology Program (CCOP) has been found to be very effective in accruing patients, following protocols, and accurately collecting data. In the recompetition of the Program, the Division of Cancer Prevention and Control (DCPC) Board of Scientific Counselors (BSC) recommended inclusion of a cancer control component in the mission of the CCOPs, making them slightly more expensive per unit. Although an additional $1 million was added to the approximately $10 million allocated to the Program, the number of CCOPs able to be funded is lower than before. Dr. DeVita said the Executive Committee had added another $1 million and will attempt to fund

more CCOPs before the end of the year, although there are many competing requests. He assured the Board that NCI is pleased with the Program and anticipates strengthening of the Program over the years. Dr. DeVita mentioned the difficulties in setting priorities for Programs when there are so many worthwhile and promising avenues to pursue with limited resources.

Cancer Centers Program

Dr. DeVita reviewed several items on the agenda and proposed the re-formation of the NCAB Cancer Centers Subcommittee. Several issues need to be considered including criteria for designation as a comprehensive cancer center, the organizational framework for the Centers Program, and the role of centers in the National Cancer Program. In response to a question from Dr. Mihich about how many of the centers are engaged in the full spectrum of activities including cancer control, outreach, patient care, and research, Dr. DeVita said the 20 comprehensive centers have these activities described in their mission. However, the roles of each of the four types of centers need to be redefined.

Points raised in discussion included the following:

- The position of Chief, Surgery Section, Clinical Investigations Branch has been advertised but not filled. NCI would welcome efforts by Board members to aid in recruiting. The elevation of the position to the DCT Associate Director is not justified by the size of the program, but could be considered if a new person develops the program in size and scope.

- The Soviet Union has been informed that the United States is very upset over the allegations that the AIDS virus was developed by the United States as a harrassing agent. In some cases, the United States has stated that there can be no collaboration on virologic research until there is a retraction of that assertion.

- A consensus conference on statistical reporting might be a means of clarifying issues associated with the interpretation of cancer statistics.

- Private groups, such as Biotherapeutics, charge patients about $30,000 for what is called private support of research and then make biologic treatments available to them. Third-party carriers will often pay for therapeutic agents on group C and expenses for patients in cancer centers.

- Twenty centers will be giving IL-2/LAK cell therapy under group C and six centers are already part of the national study group. Other centers are involved in research to develop and improve the therapy.

- A balanced research program, which can achieve progress in meeting the goals for the year 2000, must include all treatment modalities, which often involve overlapping scientific disciplines and the development of new types of scientists.

- Part of the year 2000 plan involves information transfer to private physicians and the public, which is a costly application effort. The plan was based on budget projections that may need to be revised.

Legislative Update--Dr. Mary C. Knipmeyer

Dr. Knipmeyer referred to the Legislative Update Report and invited Board members to contact her for additional information. Dr. DeVita testified at Appropriation Hearings in March, and Dr. Chabner testified at a hearing in April on exchange of U.S. and Soviet medical research information and human rights considerations. The focus of the hearing was on cancer patients who want to emigrate or visit the United States for cancer treatment.

Dr. Knipmeyer noted that 25 bills have been introduced on AIDS since the beginning of the 100th Congress. Several relate to establishment of various commissions, and President Reagan has announced his intention to form a Presidential Commission on AIDS. Dr. Knipmeyer said that Senator Kennedy had introduced a bill to enhance AIDS research at NIH, which would also establish an AIDS Advisory Board to NIH as a whole, with some members appointed by the Secretary and a number of ex officio members named in the statute.

Other bills mentioned by Dr. Knipmeyer related to animal welfare, cancer screening and prevention, nutrition, construction, pain management, and radiation compensation. Bills on occupational cancer, especially on the issue of worker notification, are receiving significant attention. Dr. Knipmeyer said that she is following these bills to determine whether NCI would need to change procedures used in occupational epidemiology studies. Dr. Knipmeyer also commented on the Family and Medical Leave Act, a bill aimed at establishing standards to allow workers to take leave when a family member is seriously ill.

Dr. Knipmeyer pointed out that the letters and calls from Congress in support of CCOPs are mostly generated by CCOP applicants calling or writing Congress. In conclusion, Dr. Knipmeyer said the Congressional breakfast had to be postponed because of logistical problems.

Board members asked for additional information on several bills listed in the Legislative Update Report, including a bill on imposing trade quotas unless foreign markets are opened to U.S. cigarettes, the University Research Facility Revitalization Act, Representative Oakar's bill on breast cancer screening, and a Laetrile bill. Dr. Knipmeyer said that as it is early in the session, many bills have been introduced, but little action has occurred on most of the bills.

Budget Update

Before reviewing the by-pass budget, Dr. DeVita stated that Dr. Wyngaarden had provided the report on apportionment requested by Congress. Dr. Wyngaarden also sent a letter to the Office of Management and Budget (OMB) through the Department requesting that NIH return to apportionment on an Institute by Institute basis, and he is still awaiting a reply.

Dr. DeVita stated that the philosophical intent of the by-pass budget is to refuel the revolution in both basic research and the application of the

results of basic research. The 1989 by-pass budget supports research to a greater degree than in recent years and continues to build networks for the application of the results of the research.

In reviewing the current situation, Dr. DeVita said the Institute was operating under the 1987 continuing resolution budget of $1.403 billion which includes the Administration's advanced appropriation concept whereby $64 million was proposed to be shifted from 1987 to the 1988 budget. Congress has rejected that proposal. The President's 1988 budget of $1.366 billion is essentially a flat budget from the 1987 budget, but requires some downward negotiation of competing grants and some increases for AIDS.

Most of the increase in the 1987 budget went into the research project pool. Cancer centers will be funded at about 85 percent of recommended levels. Centers have not been funded at their full recommended levels for several years now.

Funds for the Cooperative Groups increased in 1987 with the addition of about $7 million of the $20 million Congressional increase for clinical trials. Dr. DeVita said research and development contracts increased largely because of expanded AIDS activity and IL-2/LAK trials. The intramural research program received a modest increase. However, Dr. DeVita called attention to the fact that the cancer prevention and control budget in 1980 was about $75 million, compared to the 1987 budget of $66.5 million. The 1987 NCI budget also includes about a million dollars for specific antiviral agent research projects funded through the Office of the Director, NIH.

Dr. DeVita stated that the 1989 by-pass budget represents about a 50 percent increase over the President's 1988 budget. The assumptions on which the 1989 by-pass budget of $2.055 billion are based include the following:

- Fund 50 percent of approved research project grants at recommended levels
- Support trainees through the National Research Service Awards (NRSA) program at 1,600 per year
- Increase the number of cancer centers by 50 percent by 1992
- Increase support for cancer prevention and control by 60 percent
- Double the number of patients treated by Clinical Groups by 1992
- Add $10 million for the instrumentation needs of the extramural community
- Request 2-year obligating authority for construction projects
- Provide funds for upgrading and expansion of biomedical research computing capabilities as a special initiative.

In discussion of these assumptions, the following points were made:

- Some funds for a special initiative would go toward preliminary steps needed for sequencing the human genome

- The assumptions are directly related to the current situation in basic research and the year 2000 goals

- Research project grants are currently funded at about 95 percent of recommended levels

- Funding for cancer centers is negotiated down about 15 percent from recommended levels

- A major challenge is increasing the number of patients on clinical trials

- Resolution of the apportionment issue would permit flexibility in remedying any discrepancies in funding.

It was stated that the Subcommittee on Planning and Budget evaluate the impact of the deficits between by-pass budgets and actual budgets on the year 2000 plan.

Dr. DeVita next reviewed budget projections for 1989 to 1993. The 1993 budget is projected at $3.104 billion. The 1988 President's budget includes about $85 million for AIDS research by NCI. Dr. DeVita said the 1989 by-pass budget assumes a 50 percent increase in AIDS research.

V. Tumor Autocrine Motility Factor: Role in Invasion--Dr. Lance Liotta

Dr. Liotta presented recent data on the identification and characterization of a new protein factor, autocrine motility factor (AMF), which is secreted by tumor cells, binds back to the same tumor cells through a cell surface receptor, and profoundly stimulates their motility. He described his group's hypothesis on the biochemical basis of metastases as a three-step cascade involving attachment of a tumor cell to the extracellular matrix through specific cell surface matrix receptors; local proteolysis by secretion of proteases that break down the matrix; and migration of the tumor cell into the zone of lysis broken down by the proteases. In examining the question of what regulates tumor cell motility, AMF was consistently found by assay in a modified Boyden chamber and identified from a variety of murine and human tumor cells. This factor markedly increases (up to 400-fold) locomotion of the cells, mainly random locomotion.

Dr. Liotta stated that AMF has a molecular weight of approximately 50,000. It is stable in alkaline pH, but inhibited by very low pH and destroyed at 100°C. It is not inhibited by protease inhibitors, RNAase or DNAase, but proteinase K destroys its activity.

Dr. Liotta's group has sequenced the first 19 amino acids of AMF and thus determined that it constitutes a unique protein. They have used this protein sequence to make an oligonucleotide probe and extract a gene clone, which can be used to determine whether the expression of AMF genes is amplified in more aggressive tumor cells and to produce large amounts of AMF for therapy studies.

Dr. Liotta noted that AMF differs from factors to which leukocytes respond. Antibodies to AMF inhibit tumor cell migration but not leukocyte migration. AMF binds to one major class of binding sites on the cell surface. Therefore, it seems that two gene products are involved: one that encodes for AMF itself and one that encodes for the AMF receptor.

Dr. Liotta stressed that understanding the pathways through which AMF works may provide clues to rational design of pharmacological inhibitors of tumor cell motility. Dr. Liotta's group studied major types of second messenger receptor pathways (transducer pathways) thought to be involved in tumor cell growth, including the cyclic-AMP pathway, the IP3 pathway, phospholipase A2 in the membrane methylation pathway, and a cyclic-GMP pathway. It was shown that AMF probably works through the IP3 pathway by causing a cytoskeletal alteration and cell shape change, and through the phospholipase A2 pathway by inducing methylation and causing a change in membrane lipid fluidity.

To determine how AMF is augmented in certain experimental systems, members of Dr. Liotta's group are studying ras oncogene transfection in suitable recipient cells. After ras oncogene transfection, these cells produced up to a 400-fold increase in AMF.

Dr. Liotta's group also examined the ability of AMF to stimulate production of pseudopodia, a prominent feature of cell locomotion. They developed a new assay for measuring pseudopodia, using a filter with pores too small for a whole cell to move through. Thus, it was possible to isolate pseudopodia to study their biochemical make-up and gain greater understanding of the mechanism by which pseudopodia are extended in response to AMF. In the presence of motility factor antibody, production of pseudopodia and cell migration were inhibited.

Dr. Liotta's group also found that AMF stimulates cell migration independent of the adherent substratum. They hypothesize that the pseudopodia may be sense organs enriched for certain cell receptors and that the cell may use the pseudopodia to sense its environment and to determine the direction of cell migration.

In summarizing the characterization of AMF, Dr. Liotta stated that AMF is distinct from known growth factors, serum factors, or formal peptides, and that it is markedly induced following ras transfection leading to the expression of the metastatic phenotype.

Dr. Liotta then described an application of AMF in the diagnostic setting. The production of motility factors was measured in urine samples of patients with transitional cell bladder carcinoma in a study with Dr. Brian Liu at UCLA. The following unpublished data were presented by Dr. Liotta. It was found that urine samples from controls never contained motility factor; samples from patients with Stage D transitional cell carcinoma had the highest level of AMF; samples from patients with Stage II transitional cell carcinoma showed AMF; and samples from patients with carcinoma in situ also showed a statistically significant increase in AMF. Dr. Liotta noted that while the amount of factor produced may be related to the volume of the tumor mass, a quantitative relationship between tumor aggressiveness and the amount of

factor has not yet been established. He stated that studies of the biochemical mechanisms related to the intrinsic ability of a tumor cell to invade may lead to the discovery of factors that are augmented in actively invading tumor cells. These "tumor invasion markers" have several potential applications. For example, in immunohistology, antibodies to these factors may be useful for identifying more aggressive tumors, which would have a higher proportion of cells staining positive for the marker. Evaluating the level of expression of the gene for this factor or its receptor in a tumor might ultimately be used to predict tumor aggressiveness. This factor could also be used as a serum or urine marker, and antibodies to it could be useful in detecting occult metastases.

Dr. Liotta closed his presentation by describing possible applications of this research to cancer therapy and prevention. He stated that the development of a drug to inhibit tumor cell invasion might be particularly useful in diseases such as preinvasive nevus syndrome, carcinoma in situ, and basal cell carcinoma. This type of agent might also inhibit tumor angiogenesis and help to prevent local recurrence after surgical therapy. Dr. Liotta concluded by noting that AMF may play a role in the actual growth of metastases, and therefore inhibition of the invasive phenotype may arrest growth of metastases, not just prevent the development of new metastases. He emphasized that continued study of biochemical mechanisms involved in tumor invasion would focus on developing inhibitors of invasion.

Points raised in discussion included the following:

- This motility factor is not unique to tumor cells. Endometriosis and trophoblastic invasion are possible areas for further studies of AMF.
- Some cancer cell lines have shown heterogeneous response to motility factors.
- AMF stimulates migration independent of the adherent substratum.
- It appears that a whole cascade of events takes place, unrelated to the immune system, through ras oncogene induction of metastases. The underlying genetic mechanisms will be the subject of further investigation.

VI. New Program Project Guidelines--Dr. Robert Browning

Dr. Browning reviewed the progress made in implementing the recommendations of a recent Program Project Working Group as presented to the Board at the February 1987 meeting. He emphasized that the new Program Project Guidelines distributed to the Board were based on the recommendations of the Working Group to:

- Increase interaction between program staff and applicants and between program and review staff
- Conduct all reviews by special review committees

- Discontinue automatic site visiting of amended applications

- Implement various operating level changes to effect a smooth transition to the one-tiered review system in the specified time period of approximately one year.

Outlining the timetable for implementation, Dr. Browning noted that the applicants should have the new Guidelines by July/August 1987 in order to prepare applications by the February 1, 1988, deadline. In October 1988, the Board would see the first reviews of applications prepared according to the new Guidelines.

Dr. Browning stressed that the new Guidelines incorporate the recommendations from discussion at the February 1987 Board meeting, the new instructions from the research grant application form (PHS 398), and information from several NIH-wide policy and procedure documents, as well as the recommendations of the recent Program Project Working Group. Drafts of the new Guidelines were reviewed by the NCI Chiefs of Programs Directors, the Working Group, and the NCI Executive Committee.

To address the recommendation to increase productive interaction between program staff and applicants, the new Guidelines stress the importance of the letter of intent. The Guidelines also delineate the appropriate roles of NCI staff to improve the interaction between review and program staff.

Dr. Browning noted that the greatest concern voiced at the Board's February 1987 discussion of the Guidelines was the potential loss of a pool of reviewers experienced in the review of P01 applications. He noted that the Grants Review Branch is soliciting the assistance of former P01 committee members and P01 grantees and establishing a communication network through a newsletter and mailings of NIH publications such as the Peer Review Notes and the NIH Guide. Ad Hoc Advisory Groups drawn from the pool of P01 reviewers will be convened periodically to provide advice on special problems that arise in the P01 review process.

In discussion following Dr. Browning's presentation, concern was raised over the ability of special review committees to rate the relative merit of program project grants within the same discipline. Mrs. Bynum emphasized the important role of NCI program staff in developing funding plans for recommendation to the NCI Executive Committee to maintain a broad awareness of individual grants. She noted that, at present, the program has three committees and 25 percent of grants are reviewed by special review committees from which to intercalate scores. It was clarified that if a single project within the entire program project detracts in some way from the whole, the entire project will be downgraded. Mrs. Bynum emphasized that the object of the revised Guidelines was to obtain better informed reviews by utilizing review groups with specific scientific expertise as well as understanding of the program project review process in a single-tiered system.

The Board unanimously approved a motion that the new P01 Guidelines be approved, with the provision that the Board review the Guidelines in three years and that a report on progress under the new Guidelines be given in the interim. The Division of Extramural Activities will pursue development of evaluation criteria for the Guidelines.

VII. Intramural Nutrition Laboratory, Division of Cancer Prevention and Control (DCPC): Status Report--Dr. Malden Nesheim

Dr. Nesheim, Director of the Division of Nutritional Sciences at Cornell University and Chairman of the DCPC ad hoc Subcommittee organized to address the proposal for establishing an NCI intramural nutrition laboratory, outlined the Subcommittee Report distributed to the Board. He noted that the members of the Subcommittee representing a broad cross section of the nutrition community were closely involved with NCI staff in the review and revision of the Report.

The Subcommittee unanimously recommended that an intramural nutrition laboratory be established at NCI. The principal rationale underlying this recommendation was the potential importance of environmental factors including diet on the incidence of certain types of cancer and the potentially great influence on prevention strategies. The Subcommittee felt that given the structure of the NCI, an intramural laboratory devoted to nutrition would enable design of a stronger extramural program and overall nutrition program with long-term support. Dr. Nesheim stated that the Subcommittee felt that the ability to integrate an NCI intramural nutrition laboratory with other basic research laboratories at NCI offers a unique opportunity for scientific interaction not fully available outside of this type of institutional framework. The Subcommittee also recognized the need to develop a new cadre of researchers. They felt that such an intramural program at the NCI would have a particularly important effect on the overall development of the study of diet, nutrition, and cancer.

The Subcommittee recommended that the laboratory be located with other NCI laboratories at the Frederick Cancer Research Facility in Frederick, Maryland, and include major sections on basic nutrition research, nutritional epidemiology, and clinical/metabolic studies. Interaction with other intramural basic sciences laboratories was emphasized. Dr. Nesheim stated that in FY 1988 it would be important to identify a director of the laboratory, some of the key scientific and administrative staff, and a board of scientists to advise on program development. The annual funding for the fully staffed laboratory can be anticipated to be about $15 to $20 million.

In discussion following Dr. Nesheim's presentation of the Subcommittee Report, Dr. Greenwald noted that the proposed nutrition laboratory would be the first laboratory within DCPC, and thus it would be particularly important to integrate it with other NCI basic sciences laboratories. Several Board members noted that the clinical component of the proposed laboratory required further definition. Dr. Nesheim stated that the clinical facility should be located within the laboratory at Frederick and would involve studies mainly with normal population groups; the possibility of working with the local community hospitals in Frederick was raised.

In response to Dr. DeVita's question about the likelihood of NCI attracting top quality scientists for the nutrition laboratory, Dr. Nesheim noted that a group of nutritionists as well as a group of scientists in other disciplines would be required. He stressed that establishing the appropriate direction for the laboratory in relation to the approach of the nutrition community would be a key factor.

The Board unanimously approved a motion to endorse the concept of establishing an NCI intramural nutrition laboratory and to allow a specific request for funding during the next round of Congressional hearings.

VIII. Core Grant Guidelines for Review of Core Support for Non-Peer Reviewed Clinical Research--Dr. Jerome W. Yates

Dr. DeVita prefaced Dr. Yates' presentation of the proposed amendments to the Center Core Grant Guidelines by outlining the review process of any such amendment. He stated that all suggested modifications must be approved by the Executive Committee and the DCPC Board, which includes Center directors and organizations, as well as the NCAB.

Dr. Yates explained that the revisions address five areas related to the issue of providing core program support for clinical research activities in cancer centers. The first limits the amount that may be requested in an application to a maximum 50 percent increase above the previous award. The revised Guidelines state that the Cancer Centers Branch will, in very unusual circumstances, consider requests for ceilings exceeding the standard.

An addition to the second guideline relating to shared resources in clinical research support addresses the issue that clinical research should be reviewed in a way not entirely dependent on existing R01-P01 support, as is true for the other programs in the core grant. A revision to the third area addresses the issue that protocols involved in a core grant must have Institutional Review Board (IRB) approval and must demonstrate that they are supported by other sources.

The fourth area addresses the issue of reviewers' responsibilities and indicates that the review committee should be composed of investigators with expertise in clinical research who can provide a judgment on the scientific merit of the protocols themselves. The final item states that the same standards for reviewing protocols in the CCRC will be used for reviewing protocols in the cancer centers.

Dr. Yates concluded by emphasizing that these changes represent a deviation from the usual review procedure for the core grants, which are built on a foundation of peer-reviewed P01 and R01 awards. These changes focus on a scientific review of clinical research before awarding program support.

Dr. Korn expressed concern that supporters of studies considered part of the pool of projects within a core grant review should bear an appropriate allocation of indirect cost assessment, particularly in the case of support from the pharmaceutical industry. After considerable discussion of this point, Dr. Yates pointed out that core support is largely for data management, and statistical and computer support within the centers, and that reviewers, in evaluating research projects, should take indirect costs for individual projects into consideration and try to ensure that the drug companies are contributing their share to the support of these costs.

The Board unanimously approved the revisions to the Core Grant Guidelines.

IX. Centers Program - Board of Scientific Counselors' Report, Division of Cancer Prevention and Control--Dr. Virgil Loeb

Dr. Loeb stated that he was speaking for the DCPC Board of Scientific Counselors because he chairs the Subcommittee on the Centers and Community Oncology Program. The Subcommittee includes three cancer center leaders (Drs. John E. Ultmann, James F. Holland, and Paul F. Engstrom) and participants in community outreach and clinical research programs (Drs. Robert J. McKenna and Lloyd K. Everson). Dr. Loeb is an independent practitioner working in an academic medical center. Other expert guests were invited to the May 7 Subcommittee meeting to discuss the role, status, and organizational location of the Cancer Centers Program.

Dr. Loeb noted that in addition to the different types of centers (comprehensive, clinical, laboratory, and consortial), there is also heterogeneity within each type. Representatives from several centers gave presentations at the DCPC Board of Scientific Counselors meeting and raised the following issues:

- The relationship of clinical centers to universities contributes to the variability among the centers
- There have been only modest increases in funding for the cancer centers program during recent years
- Because of funding constraints, centers have found it difficult to initiate new programs or respond to new initiatives
- Funds for construction and training are critical to continued growth and evolution of the centers program
- The type of center must be considered in relation to expectations for cancer prevention and control research
- The distinction between prevention and control research and community-related activities is important
- Consortiums, involving organizations other than universities, can facilitate cancer control and research activities.

Dr. Loeb then summarized the main conclusions of the BSC deliberations:

- The DCPC Board of Scientific Counselors has a keen interest in the centers program. The BSC Subcommittee on Centers and Community Oncology helps the BSC to give attention to centers issues.
- While the prime function of the centers is to support fundamental research, the centers have an important responsibility for clinical research, and some, certainly the comprehensive centers, should have prevention and control research and community outreach responsibilities.

- The concept of comprehensiveness and the status of comprehensive centers should be clarified (the original criteria for comprehensive centers were developed in 1973 and revised in 1979).

- Comprehensiveness is not now one of the review criteria used in renewing core grants for centers designated as comprehensive.

- Maintaining the centers program within DCPC may help the centers fulfill their responsibilities for cancer prevention and control research.

- The cancer centers program should have greater visibility and would benefit from additional funds.

In conclusion, Dr. Loeb said that the DCPC Board welcomes advice and is willing to continue to explore the best ways of strengthening the centers program and its relationship to other NCI activities.

Several Board members spoke in support of the centers program and recognized its achievement in integrating cancer research into major university research programs. One suggestion for strengthening the program was the designation of a high-level advocate for the centers in a new administrative structure; another was more direct participation of NCI on an administrative level within the centers to support a more uniform national approach to the cancer problem. The question was raised of how many of the non-comprehensive centers perform cancer control activities and cancer control research. Dr. Yates replied that in terms of cancer control or early detection activities, the distinctions between comprehensive centers and clinical centers become blurred, and the issue becomes whether the research expectations of the centers should be redefined.

Dr. DeVita suggested that because the issues extended beyond an organizational move for the centers program, an NCAB subcommittee should be established to redefine comprehensiveness and examine the issues of visibility, uniformity, diversity, and independence within the overall context of the National Cancer Program. Other issues to be examined would include clarification of the prevention and control research responsibilities, the establishment of centers in areas where none currently exist, and methods for evaluating the centers.

A motion was made, seconded, and unanimously approved to establish an NCAB subcommittee to include members from the DCPC Board of Scientific Counselors and other appropriate individuals.

X. Report of the Subcommittee on Environmental Carcinogenesis--Dr. Roswell Boutwell

Dr. Boutwell began the Report of the Subcommittee on Environmental Carcinogenesis by stating the Subcommittee's charge: "To study national needs and problems in environmental carcinogenesis and to monitor progress in this area." At the May 25 meeting of the Subcommittee, Dr. Joseph Fraumeni of NCI's Epidemiology and Biostatistics Program described the structure of the program and stated that the program is concerned with a wide range of

cancer risk factors, of which the evaluation of occupational hazards is but one component. The objective of the program in occupational epidemiology is not only to identify preventable cancer hazards, but also to generate insights into the origin of cancer.

Dr. Boutwell reported that Dr. Aaron Blair, Chief of the Occupational Studies Section, discussed the various NCI studies on formaldehyde and the considerable controversy that arose over the interpretation of results of the most recent study. As a result, the Epidemiology and Biostatistics Program developed guidelines for initiating, conducting, and reviewing large cohort studies with potential economic and political consequences. These new guidelines have been applied to the design of large cohort studies of workers exposed to acrylonitrile and methylene chloride. The guidelines provide for the establishment of advisory panels and protocol review by interested parties including unions, industry, consumer groups, Government agencies, and other organizations.

Dr. Boutwell said the Subcommittee had unanimously approved a motion stating that the Epidemiology and Biostatistics Program of the NCI has been responsive to the concerns raised as a result of the Formaldehyde Cohort Study, that the Subcommittee endorses the Program's approach to occupational cancer studies and looks forward to the final evaluation of the acrylonitrile and methylene chloride studies. Dr. Boutwell, in emphasizing the importance of the epidemiology program, pointed out that epidemiologic studies in humans have been responsible for the discovery of nearly all human carcinogens. Dr. Adamson added that a future agenda item for discussion by the Subcommittee would be naturally occurring toxins and carcinogens and man-made pesticides found as food residues.

Dr. Ralph E. Yodaiken, ex officio member from the Occupational Safety and Health Administration (OSHA), read a statement supporting the concerns raised by labor unions and some industry about NCI's activities in the occupational health field. He questioned the need for NCI to study workers' exposures to chemicals that are already regulated by OSHA and studied by the National Institute for Occupational Safety and Health (NIOSH). Dr. Yodaiken also expressed concern about the studies being conducted in China of workers exposed to high levels of benzene.

In response, Dr. Adamson stated that NCI performs studies not only because of regulatory concerns but to study the carcinogenic process and generate insights into the origins of cancer. Board members expressed support for NCI's epidemiology program and the need for more information beyond the requirements of regulations and standards. Dr. Adamson reiterated that the study protocols are sent to all relevant Government agencies, including OSHA, for review, and to labor unions, industry, and international organizations.

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

XI. Public Participation Hearings Report--Mrs. Nancy Brinker and Mrs. Helene Brown

Mrs. Brinker reported that a successful planning meeting had been held in Los Angeles, presided over by Mrs. Brown. She invited Board members to attend the first Public Participation Hearing, which will be held in Los Angeles on September 22, 1987.

Mrs. Brown said the recent planning meeting for the Los Angeles Hearing involved all the California cancer centers, the state and county Departments of Health, the Medical Association, the Consortium of Black Institutions, members of the Hispanic community, Health Maintenance Organizations, and representatives of the Los Angeles AIDS program and free clinics. Representatives from neighborhood health coalitions will be asked to testify. One outcome of the Hearings will be the compilation of information from the local communities about their perspectives on meeting the year 2000 goals, especially those for cancer prevention and screening.

Mrs. Brown said that additional assistance would be needed by NCAB members organizing local hearings. Dr. DeVita said the Institute would provide the necessary support.

A second Hearing is tentatively scheduled for the third week in October in Atlanta. Mrs. Brinker said information on the Los Angeles Hearing would be presented to the Board at the September 28-30, 1987, NCAB meeting. The first two Hearings will be reviewed at the November 16-18, 1987, NCAB meeting and a decision made about whether to proceed with four more Hearings.

As followup, Dr. Korn described a Conference on Cancer in Minorities, sponsored by M.D. Anderson Hospital, that he and Mrs. Bynum attended in April. The Conference brought together a broad spectrum of health care professionals who are trying to bring good health practices and access to medical care to grassroots minorities. The topics covered the gamut of problems, including education, public awareness, fighting advertising lobbies, smoking and alcohol problems, etc. Mrs. Bynum noted the participation of several NCI staff and said her presentation dealt with NCI's goals for reducing cancer incidence and mortality among minority populations. Reaching the year 2000 goals requires focusing on the populations with the highest risk. A major problem remains one of establishing credibility in the local communities.

Dr. Strong said a second Conference on Cancer in Minorities is to be held next year. Participants will be asked to return to evaluate what they learned from the first Conference, describe what they have been able to implement, and identify changes that have occurred. There will also be consideration of future conferences in various parts of the country.

XII. New Business--Dr. David Korn

Subcommittees

As noted by Dr. DeVita, Dr. Howard Temin, who was recently appointed to the NCAB, will chair the Subcommittee on AIDS. Dr. Korn distributed a

draft charge to the Subcommittee and asked that Board members provide comments to Mrs. Bynum. He also distributed a proposed roster of NCAB Subcommittee assignments, including the new Subcommittee on AIDS. In addition, he asked for suggested participants for the reactivated Subcommittee on Centers.

Future Agenda Items

Dr. Korn said the September meeting is two-and-a-half days and asked if Board members would like to have an indepth review of some part of the scientific program. Suggestions of topics are welcome.

In reviewing the list of proposed agenda items, it was suggested that the item on "Status and Function of the NCI within the NIH in Light of the Prerogatives Afforded NCI by the National Cancer Act" be consolidated with the item on "Linkage of the Goals for the Year 2000 and the By-pass Budget."

New items suggested included the following:

- Chromosomal analysis and DNA probe detection of gene rearrangements (in terms of classifying neoplasms and the impact of the classification on selection of therapy and prediction of behavior) Possible speaker--Dr. Janet Rowley, former NCAB member.

- Deletion of segments of chromosomes and effects on gene expression.

XIII. Closed Session

The rest of the second day of the meeting was closed to the public as it was devoted to the Board's review of grant applications. The applications reviewed numbered 1,766, requesting support in the amount of $229,876,359. Of these, 1,416 were recommended for funding at a total cost of $163,397,598.

XIV. Adjournment

The open session of the 62nd meeting of the NCAB was adjourned at 9:15 a.m. on Wednesday, May 27, 1987.

September 9, 1987
Date

David Korn, M.D.