Department of Health and Human Services

Public Health Service

National Institutes of Health

National Cancer Institute

National Cancer Advisory Board

Summary of Meeting
May 9-11, 1988
Building 31, Conference Room 6
National Institutes of Health
Bethesda, Maryland 20892

Department of Health and Human Services
Public Health Service
National Institutes of Health
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Summary of Meeting*
May 9-11, 1988

The National Cancer Advisory Board (NCAB) reconvened for its 66th regular meeting at 8:30 a.m., May 9, 1988, in Building 31, 6th Floor, Conference Room 6, National Institutes of Health (NIH). Dr. David Korn, Chairman, presided.

NCAB Members

Dr. Roswell K. Boutwell
Dr. David G. Bragg (absent)
Mrs. Nancy G. Brinker (absent)
Mrs. Helene G. Brown (absent)
Dr. John R. Durant (absent)
Dr. Gertrude B. Elion
Dr. Bernard Fisher
Dr. Phillip Frost (absent)
Mr. Louis V. Gerstner, Jr. (absent)
Dr. David Korn
Dr. Walter Lawrence, Jr.
Dr. Enrico Mihich
Mrs. Irene S. Pollin
Mrs. Barbara I. Shook
Dr. Louise C. Strong
Dr. Louis W. Sullivan
Dr. Howard M. Temin
Dr. Samuel A. Wells

President's Cancer Panel

Dr. Armand Hammer (absent)
Dr. William P. Longmire
Dr. John A. Montgomery

Ex Officio Members

Dr. Dorothy A. Canter, NIEHS
Captain Stephen R. Veach, DOD
Dr. Ralph Yodaiken, DOL
Dr. Richard Greene, VA
Mr. John Whalen, NIOSH
Dr. Lakshmi Mishra, CPSC

Members, Executive Committee, National Cancer Institute, NIH

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

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

Liaison Representatives

Ms. Delores Espasza, President-Elect, Oncology Nursing Society, Cambridge, Massachusetts, representing the Oncology Nursing Society for Ms. Deborah Mayer.

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

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

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

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

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

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. Margaret Sharke, Scientific Program Director, American Cancer Society, New York, New York, representing the American Cancer Society for Dr. John Laszlo.

Ms. Shirley Shelton, Associate Director for Practice Activities, American College of Obstetricians and Gynecologists, Washington, D.C., representing the American College of Obstetricians and Gynecologists for Dr. Warren H. Pearse.

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

Ms. Kerrie Wilson, Coordinator of Public Issues, American Cancer Society, Washington, D.C., representing the American Cancer Society, New York, New York, for Mr. Alan C. Davis.

In addition to NCI staff members, meeting participants, and guests, a total of 21 registered members of the public attended the meeting.

I. Call to Order, Opening Remarks, and Consideration of February 1-3, 1988, NCAB Meeting Minutes--Dr. David Korn

Dr. David Korn, Chairman, called the 66th meeting of the National Cancer Advisory Board (NCAB or Board) to order and welcomed Board members, the President's Cancer Panel, liaison representatives, guests, staff of the National Cancer Institute (NCI), and members of the public. He announced the reappointment of Dr. Howard M. Temin, who had been appointed to complete the term of the late Dr. Tim Lee Carter, and the appointment of Dr. David G. Bragg, Professor and Chairman, Department of Radiology, University of Utah School of Medicine; Mr. Louis V. Gerstner, Jr., President, American Express Company, New York City; Dr. Walter Lawrence, Jr., Professor of Surgery and former Director, Massey Cancer Center, Medical College of Virginia; and Dr. Samuel A. Wells, Jr., Bixby Professor of Surgery, and Chairman, Department of Surgery, Washington University School of Medicine, St. Louis, Missouri. He noted that an additional appointment was forthcoming.

Approval of the February 1988 minutes was postponed until the Wednesday, May 11, session.

II. Future Meeting Dates

Dr. Korn called Board members' attention to the following confirmed meeting dates: September 26-28, 1988; December 5-7, 1988; February 6-8, 1989; May 15-17, 1989; September 18-20, 1989; and December 4-6, 1989. Proposed dates for 1990 are January 29-31, May 14-16, October 1-3, and December 3-5.

III. Report of the President's Cancer Panel--Dr. William P. Longmire, Jr., for Dr. Armand Hammer

In Dr. Armand Hammer's absence, Dr. William Longmire read the report of the President's Cancer Panel as prepared by Dr. Hammer. To begin his report, Dr. Hammer announced that President Reagan had just renominated Dr. Longmire for a third term as a member of the President's Cancer Panel. He commended Dr. Longmire's contribution to the work of the Panel and extended congratulations to him on everyone's behalf.

Dr. Hammer reported that on April 11, the Panel received the report from Dr. Vincent DeVita on the impact of the National Cancer Act on the ability of the NCI to achieve its mission. He noted that a report covering the issue of reauthorization of the National Cancer Act had been requested so that the Panel could take the case for reauthorization to appropriate members of the Administration and Congress. Dr. Hammer reported that he had transmitted the report to Senator Edward Kennedy, Chairman of the Senate Labor and Human Resources Committee, on behalf of himself and the other Panel members. He said the transmittal letter emphasized the Panel's interest in retention of such special authorities as Presidential appointment of the Panel, members of the NCAB, and Director of the NCI. He added that the Panel also emphasized in the letter the importance of the bypass budget provision and recommended that the Director retain the authority to appoint advisory committees necessary to conduct the business of the Institute and peer review of the intramural program. Dr. Hammer stated that he requested that the report be entered into the record of the hearing held on

S.2222, the National Research Institute Reauthorization Act. The report and the Panel's recommendations were also sent to Representative Henry Waxman, Chairman of the House Subcommittee on Health and Environment, for consideration in that committee's hearing on the reauthorization and to Dr. Robert Windom, Assistant Secretary for Health and Human Services (HHS).

Dr. Hammer noted that the Senate Committee had made no significant changes in the Act, and it was learned that HHS did not intend to oppose reauthorization; House Committee action is pending. Dr. Hammer stressed the need to continually defend the special authorities of the National Cancer Act whenever they are challenged.

Turning next to Panel meetings, Dr. Hammer reported that the first meeting of 1988 was held at Columbia University Cancer Center in New York City, where the Panel heard presentations on novel strategies for cancer therapy based on protein kinase C, oncogenes in human cancer as a possible approach to antiviral therapy, recent advances in radiation therapy, and developments in the use of colony stimulating factors. The next meeting of the Panel is scheduled for May 17 at the University of Wisconsin's Clinical Cancer Center in Madison, Wisconsin. Presentations will include a report on chemical carcinogenesis by Dr. Henry Pitot, former Chairman of the NCAB, and reports covering intraoperative radiotherapy, therapeutic advances in breast cancer, breast cancer prevention, and antitumor effects of interleukin-2 with acceptable toxicity. Dr. Hammer noted that the Panel hopes to visit many different areas of the country in the course of its public meetings.

Next, Dr. Hammer reported that on March 29, scientists from the United States and the U.S.S.R. held a teleconference that was broadcast live by satellite from the National Library of Medicine and Moscow to 1,500 hospitals and health care facilities in the United States (via the Hospital Satellite Network), 57 countries in Europe, Africa, and the Middle East (via Worldnet), and an estimated 150 million people in the U.S.S.R. Details of the conference were arranged by Dr. Hammer's office working closely with the United States Information Agency. The conference was an outgrowth of a 1985 treaty signed by President Reagan and Soviet General Secretary Mikhail Gorbachev calling for increased cooperation in the areas of the arts and sciences, and it featured opening messages from the two leaders and welcoming remarks from Dr. Hammer. The panelists included Drs. DeVita and Steven Rosenberg from the United States and Drs. Nikolai Trapeznikov and Nikolai Napalkov of the Soviet Union. Dr. Hammer noted the special interest afforded Dr. Rosenberg's first public discussion of his work with tumor-infiltrating lymphocytes (TILs). Dr. Rosenberg stated that TILs have greater potency and less toxicity than lymphokine-activated killer cells and reported that he had treated nine patients with advanced melanoma with preliminary results that show evidence of substantial regression of the tumors.

Finally, Dr. Hammer brought the Board up to date on the progress toward his recently announced goal of raising additional funds for the NCI in the expectation that such funds would be matched by the Government with funds separate from the NCI appropriation. He announced that a not-for-profit corporation called "Stop Cancer" has been set up in California to collect the funds, with Mr. Denver Frederick as Executive Director. Dr. Hammer pointed out that Mr. Frederick's experience with fundraising includes his work with Mr. Lee Iacocca on the Statue of

Liberty-Ellis Island project, and he stated that a preliminary meeting has resulted in many ideas and pledges of assistance for the project. He said specific plans and proposals will be put into effect in the near future.

In the meantime, Dr. Hammer reported that he has been assured the support of both Democrats and Republicans, in particular, Representatives William H. Natcher and Tony Coelho and key members of the Senate. In addition, he noted a letter from Speaker of the House Jim Wright expressing his full support of the proposed plan to raise $500 million from the private sector to be matched by $500 million in public funds and his promise of help in assuring that Congress enacts appropriate legislation to provide the funds. Details of the legislation remain to be worked out, but Speaker Wright indicated that the intention was to provide funds in addition to those normally appropriated to the NCI in the course of normal budget increases and that all funds raised by the project would be given directly to the NCI.

In the discussion, it was suggested that public funds, if obtained to match private funds, be allocated so that they are not linked to expenditure within the fiscal year unless there is continuity in these extra public funds.

IV. Director's Report, National Cancer Institute--Dr. Vincent DeVita

Dr. DeVita began his report by welcoming the new Board members and expressing gratitude to the President, his staff, and the personnel staff of the Department for their outstanding appointments. In particular, he noted the efforts of Ms. Debi Zuloaga of the Secretary's Advisory Committee Office. Dr. DeVita also congratulated Dr. Hammer on his upcoming 90th birthday. For the benefit of the new Board members, Dr. DeVita outlined the format of his reports: information on staff and organizational changes, followup on issues previously discussed before the Board, a budget presentation, and discussion of new items. In addition, Dr. Mary Knipmeyer usually presents a legislative report. He announced that an orientation session would be held for new Board members before the next meeting.

Dr. DeVita pointed out the unique role of the Board system. The major functions of the NCAB are to approve the funding of peer-reviewed grants and to assist in overall allocation of resources, particularly on issues that overlap Divisions. He said that the Divisions and the Boards of Scientific Counselors (BSC) of the NCI are unique within the organization of the National Institutes of Health because they have intramural and extramural responsibilities. The Boards review concepts for contracts and requests for applications and conduct the intramural site visits, a process developed by the NCI. The Institute tries to coordinate the NCAB and the BSCs by regularly sending materials to inform them of each other's activities, such as lists of concepts approved by the divisional Boards. Dr. DeVita emphasized that the Boards' activities are conducted in public, and he urged NCAB members to attend BSC meetings. In addition, in November of each year the NCAB hears a program review presented by Division Directors and the Chairpersons of their Boards of Scientific Counselors along with scientific presentations on a specific subject and a report from the Organ Systems Program.

Dr. DeVita stated NCI's Board system is unique in that the chairpersons are all outside people, whereas in other Institutes the chairpersons of the Councils are the Institute Directors. He underscored the value of being able to seek advice from someone outside the Institute and in that regard congratulated Dr. Korn on his reappointment as Chairman of the NCAB.

New Items

Dr. DeVita announced that Dr. Robert Gallo had been elected a member of the National Academy of Sciences and was awarded the Japan prize of $676,000 with six other scientists, including Dr. Luc Montaigner. Dr. Werner Kirsten was named the new Associate Director for the Frederick Cancer Research Facility (FCRF).

In noting organizational changes, Dr. DeVita said that in view of the importance of prevention clinical trials, a Cancer Prevention Clinical Trials Branch would be established in the Division of Cancer Prevention and Control (DCPC). He said the infrastructure exists within DCPC to build trials in an orderly way and pointed out that 38 trials are planned through 1989. Dr. DeVita suggested that a positive prospective study in prevention will put much pressure on the system to develop more prevention strategies.

A Review Logistics Branch has been established in the Division of Extramural Activities (DEA) to develop and test new procedures for improving the quality of grant and contract reviews. Dr. DeVita said a search will take place for chiefs of the new Branches in DCPC and DEA.

The final organizational change reported by Dr. DeVita was the establishment of an NCI task force on AIDS vaccine development that would be chaired by Dr. Gallo. The task force will cut across divisional boundaries, and its staff will be from the NCI and FCRF. *Ad hoc* members from pharmaceutical companies and extramural investigators from the United States and other countries will be included on the task force. Dr. DeVita also noted that Dr. Kirsten will assume overview responsibility for AIDS research in general and will represent NCI on the Departmental and NIH AIDS task forces.

Followup Items

Dr. DeVita said Dr. Brian Kimes would describe the meeting of the Organ Systems Working Group chairpersons on April 25 and the changes that had occurred. The first subcommittee meeting for the review of the Cancer Centers also took place in April, and a definition of a Comprehensive Cancer Center was drafted. Dr. DeVita emphasized that NCI has full confidence in the Cancer Centers Program and that the review is meant to streamline the program to help meet the goals for the year 2000.

Dr. DeVita said the NCI reorganization plan is still under evaluation, but decisions will not be made affecting the Cancer Centers Program or the Organ Systems Program until those reviews are completed. A decision about the Epidemiology Program also has not been made. At the June retreat, the Executive Committee will consider transferring the International Cancer Information Center and the Cancer Information Service to the Office of Cancer Communications. Dr. DeVita said any major changes would first be discussed with the chairpersons of the NCAB and of the BSCs.

With respect to the Women's Health Trial, Dr. DeVita said the Executive Committee had agreed to give $454,000 for the orderly conclusion of the trial and some further data collection. Exit meetings will be held for all women who had been involved in the trial so they will understand why the trial is not continuing. Self-help information will be provided to those women who want to continue on low-fat diets. Dr. DeVita said some new information related to the development of markers is coming out of the trial and may be the subject of future presentations to the Board.

believes that if doctors have access to state-of-the-art cancer treatments through PDQ, they will not put patients on clinical trials. The Cancer Centers that have not submitted protocols to PDQ are Johns Hopkins, the Mayo Clinic, University of Miami, University of Pennsylvania, Wayne State University, Columbia University, and the Illinois Cancer Council.

Next, Dr. DeVita announced that the first issue of the new *Journal of the National Cancer Institute* was published on March 7. He acknowledged the efforts of Dr. Robert Wittes, Dr. Peter Greenwald, and Ms. Sue Hubbard. He said the response from the scientific community had been excellent; there are 6,000 paid subscribers and 3,000 additional copies are distributed to libraries and Federal agencies. Because of the large number of papers submitted, the acceptance rate is about 20 percent. Dr. DeVita noted that the first issue had contained two very exciting articles by Dr. Bernard Fisher on the positive adjuvant therapy studies for colon and rectal cancer. Information will soon be released on another positive study.

Patient Accrual to Clinical Trials

Dr. DeVita recalled that discussion of patient accrual to clinical trials was being added to his report because of the importance of getting patients into the trials. He said that the centers, except for those that belong to a Cooperative Group, are not playing a major role in accruing patients to clinical trials. The Centers Subcommittee's draft definition of "comprehensiveness" includes a role in providing resources for clinical trials. Nonetheless, Dr. DeVita said the failure of the clinical trials program to complete studies in a timely manner is an unpopular issue in the cancer treatment community, and regular public reports to the NCAB are a means of dealing with the problem.

As indicated by Dr. Wittes at the last NCAB meeting, efforts are being made to change the terms of awards for the Cooperative Groups to a per case payment basis, which should serve as a stimulus to put patients in clinical trials. Dr. DeVita said details of a group grant would be discussed at the closed session. In addition, the terms of award for Cooperative Groups are being changed to provide authority for terminating studies that are not accruing or studies that are duplicative. The Office of Cancer Communications has been working with centers to try to define what they need and what is needed to get the public involved. There have been favorable newspaper articles on clinical trials that have resulted in increased referrals. Dr. Wittes will meet with the press and make presentations at meetings. Also, protocol searching of PDQ has gone up 76 percent in the last year, which underscores the need to have protocols from the Cancer Centers included.

Using slides, Dr. DeVita discussed annualized data comparing the first three months of 1988 with the first six months of 1987. The number of Phase III studies, which compare new therapy to a standard therapy, was reduced, with 15 studies closed. The average accrual rate in the groups increased 15 percent and 178 percent for the high priority protocols. Looking at the data on a group basis, Dr. DeVita pointed out that between the Children's Cancer Study Group and the Pediatric Oncology Group, more than 40 percent of all children with cancer go on protocols. He suggested that was an explanation of why mortality from childhood cancer is rapidly decreasing. Although there are increases in accrual in other groups, the total number of patients on protocols compared with the number of cancer patients remains quite low. Fewer than 1 percent of eligible patients with common cancers actually go on protocols. Except for the

Dr. DeVita noted information in the Board book on the Office of Technology Transfer established in the Office of the Director. This new office has responsibility for implementing the Stevenson-Wydler Technology Transfer Act. Of the 91 patents that are bringing in royalties to NIH, 51 are NCI patents. Dr. DeVita said there would be a presentation on all the non-Federal sources of funds at the fall NCAB meeting.

NCI is implementing the NCAB decision on PO1 review, and all scheduled PO1 reviews will be *ad hoc* reviews. Dr. DeVita said that although other Institutes are using the same process as NCI, NIH has not fully approved this process. The issue is to be discussed by the Peer Review Committee established by Dr. James Wyngaarden, Director, NIH.

As requested by the Senate Appropriations Committee, a committee was established under the auspices of the NCAB to consider the proper measures of progress in cancer research. The committee is chaired by Dr. Lester Breslow, and members include Mrs. Helene Brown, Dr. Bernard Fisher, and Dr. John Bailar. Dr. DeVita said the committee had completed a draft report, which provides useful information on the strengths and weaknesses of incidence, mortality, and survival statistics as well as other criteria or indirect indications of progress that should be routinely developed and presented to the public. The report will be sent to the Board as soon as it is completed.

Dr. DeVita said five public participation hearings had been completed, with exciting results. A followup evaluation will be made to determine what impact the hearings have had in the five cities. This evaluation will be presented to the Board at the fall meeting. Dr. DeVita suggested that if additional hearings are held, they should address the issue of clinical trials.

In light of the lack of funds for construction in the 1988 and 1989 budgets, the Senate asked NIH to assemble a committee to consider the question. The committee, of which Dr. Korn was a member, recommended that NIH should have a general, extramural construction authority, that those Institutes that have construction authority (NCI, the National Heart, Lung, and Blood Institute, and the National Eye Institute) should maintain it, and that the authority should be expanded to other Institutes as needed. It is not yet known how Congress will respond to these recommendations.

Dr. DeVita next discussed the Physicians' Data Query (PDQ) and stated that hours of use have increased 53 percent over March of 1987 and number of users has increased 38 percent. The biggest increase (about 42 percent) has been among those who use lay codes, i.e., the lay public and science writers. One enhancement to the PDQ system is the addition of board certification information to the directory file. Another enhancement is the addition of the protocols of the European Organization for Research on Treatment for Cancer (EORTC). This will increase the worldwide utility of the PDQ system. Dr. DeVita also noted that PDQ is now on CD-ROM so that it will be available without having to use phone lines. Also with respect to PDQ, Dr. DeVita announced that an external advisory board, chaired by Mrs. Brown, has been established to help modify the statements in the information for patient files so that lay people can use the system and understand the contents. These modifications are expected to be completed at the end of 1989.

Dr. DeVita pointed out that although all protocols funded by the Government and all European protocols through EORTC are included in PDQ, some of the Cancer Centers still have not submitted their voluntary protocols. He said that Dr. Charles Moertel

National Surgical Adjuvant Breast and Bowel Project (NSABP), accrual to the high priority protocols remains problematic.

Following Dr. DeVita's presentation, a question was raised about the donation of private funds to NCI. Dr. DeVita answered that in the case of Mr. Leonard Abramson, who donates approximately $1 million a year for breast cancer research, some of the funds go to Dr. Marc Lippman, who headed the Breast Cancer Group, and other funds go to other investigators in NCI. Because Dr. Lippman is leaving NCI, an arrangement has been made whereby some of the funds will go with Dr. Lippman and the rest will remain at NCI.

In discussing other new items, Dr. DeVita announced that thanks to Mr. Alan Kay and donations from the Merck Company, a children's inn will be built on the NIH campus. The construction of the 36-room building to house the families of children being treated at NIH is completely supported by private funds.

Dr. DeVita said two new Government Accounting Office (GAO) investigations are in progress. One is on funding for AIDS grants. The other is a followup of the earlier GAO report on the failure of breakthroughs in clinical trials to be translated to general clinical practice. Dr. DeVita said it is not known exactly what data are under scrutiny, but it is understood that Representative Waxman will hold hearings on the subject in June.

NCI has been through the House and Senate appropriation hearings and the Senate reauthorization hearings. Dr. Greenwald represented NCI at hearings by the Senate Committee on Governmental Affairs on the issue of the link of diet to cancer.

NCI also participated in a number of town meetings, including a meeting on tobacco use in Hispanics and blacks organized by Dr. Louis Sullivan. Dr. DeVita also mentioned the teleconference with the Soviet Union and said that the Soviets were very interested in the fact that American doctors generally tell patients they have cancer because Soviet doctors generally do not. He expressed the hope that future teleconferences would allow more opportunity for questions and answers.

Dr. DeVita then brought up a major issue of concern: The number of full-time equivalent (FTE) positions has decreased by 13 percent from 1984 to 1988, even though NCI's budget has increased by 47 percent. Considering the increase of 71 FTEs for AIDS research, then the number of FTEs has decreased 16.8 percent since 1984. Dr. DeVita said the Institute was approaching the point of not being able to manage its resources with the available number of FTEs. He said the bypass budget specifies the number of FTEs that are needed to do the required work.

With respect to the FY 1989 budget, Dr. DeVita said the Office of Management and Budget (OMB) had requested an increase for NIH. Also, OMB dropped the apportionment approach of pooling all NIH budgets. Dr. DeVita expressed gratitude to the President's Cancer Panel and the Board for allowing the issues surrounding apportionment to be aired publicly.

Budget Update

Dr. DeVita said that NCI's FY 1989 budget is $1.593 billion, including AIDS. It was requested that all AIDS activities be consolidated in the Office of the Assistant Secretary, a step that has not been approved by Congress. The FY 1989 budget represents a 8.5 percent increase with AIDS and 6.5 percent without AIDS. By mechanism, the largest increase (12.6 percent, or $85 million) is to the grant pool; however, it will still be necessary to negotiate reductions for grants--13 percent for competing grants and 7 percent for noncompeting grants. Dr. DeVita said that at the Congressional hearings, he had presented NCAB's view that more attention should be focused on funding grants near their full level rather than on the number of grants.

The FY 1989 budget includes a 1 percent increase for Cancer Centers, which will require that center grants be funded at approximately 30 percent lower than recommended levels or that fewer grants be funded. Dr. DeVita pointed out that because of the increase to the RO1 pool, most of the remainder of the budget is relatively flat. The overall increase to R&D contracts is 9.1 percent, but if AIDS is removed, the increase is 1.4 percent. The increase to intramural research, without AIDS, is 2.7 percent. Once again there are no funds for construction, which Dr. DeVita described as a serious problem, including the use of such funds to maintain FCRF.

In discussing the AIDS budget, Dr. DeVita pointed out that grants are projected to increase faster than contracts and intramural research. There may be a problem with referral guidelines to ensure that appropriate NCI AIDS applications are not sent out of NCI. Researchers who are working on cancer-related subjects need assurance that they will have access to grant funds. Dr. DeVita attributed the increase in AIDS contracts to NCI's management of the AIDS Drug Development Program.

As the final point of the budget update, Dr. DeVita noted that while the total number of grants for FY 1989 is increased, the number of competing grants is decreased by approximately 61 grants. This occurs because one year's funded applications become noncompeting grants in the subsequent year and increase the commitment base, thus decreasing the number of competing applications that can be funded. Dr. DeVita said that while this is not an ideal situation, it is not true that all new research occurs in the competing grant pool.

In discussion, the following points were raised:

- It is not expected that the new central AIDS coordination office in the NIH Director's office will affect NCI's authority to perform needed research.

- NCI resources are being devoted to AIDS research without appropriation compensation, especially in terms of FTEs.

- Congress has held back funds for construction so that it can study the construction issue. It is not satisfied with the committee convened, at its request, by the NIH and has requested a report from the Secretary. The NIH advisory group on construction recommended that NIH receive an independent construction authority but that the existing construction authorities of other Institutes should not be impaired. Senator Kennedy's reauthorization bill is compatible with these recommendations.

- The bypass budget includes a five-year plan for renovation and upgrading at FCRF.

As an additional new item, Dr. DeVita mentioned that a number of studies in the United States and Europe of Stage I (node-negative) breast cancer using adjuvant chemotherapy or hormonal therapy have become positive. The NCI Executive Committee agreed on the need to make public service announcements (PSAs) but felt that there was also a need to inform doctors of the finding. After consulting Dr. Arnold S. Relman of the *New England Journal of Medicine* so as not to jeopardize future publication of the papers, and after pursuing various information dissemination options (e.g., at professional society meetings), NCI decided to mail a report of the data to the 12,000 physicians listed on PDQ. Dr. Wittes will present the information to the Board.

Trials to Improve the Quality of Life for Cancer Patients--Mr. Richard Bloch

Mr. Richard Bloch announced a new initiative to enroll cancer patients on a protocol designed to improve their quality of life. Those who agree to go on the trial will make a commitment to do everything in their power to fight cancer. The commitment will entail such things as not smoking, keeping doctors' appointments, taking necessary treatments, eating a well-balanced diet, relaxing, and openly discussing cancer with family and friends. The trial has been planned and will be run by Dr. Carl Hansen, a medical oncologist in Kansas City; Dr. James Collins, Chairman of the Psychology Department at the University of Missouri in Kansas City; and Ms. Rosemary Padburg, an oncology nurse and head of the Cancer Center at St. Luke's Hospital. Mr. Bloch said that he and his wife are financing the effort.

The hoped-for outcome is that patients will have a better quality of life and better survival when they actively and positively fight their cancer. Oncologists will ask patients whether they want to go on the trial but assure them that no matter what their decision, they will receive state-of-the-art treatment for cancer. Mr. Bloch said that while the trial will start slowly, his goal is to accrue 25,000 patients, with more in the control group. Every patient who goes on the trial must have a qualified second medical opinion and receive the state-of-the-art treatment listed in PDQ. Mr. Bloch expressed the hope that the Board would support the concept.

In response to questions, Mr. Bloch said experts in several fields have been working on the development of the trial. The network of participating physicians will be all oncologists who are willing to participate. Patients will fill out a form indicating their willingness to participate, and the physicians will be asked three times a year about their patients' medical status. The trial will be offered to patients with all types of cancer.

V. Legislative Update--Dr. Mary Knipmeyer

Dr. Knipmeyer stated that the Senate Committee on Labor and Human Resources had approved a bill to reauthorize NIH, which preserves the authority of NCI and incorporates some proposed changes that have been endorsed by the President's Cancer Panel and the NCAB. Authorization levels for FY 1989 are set at $1.853 billion, $88 million of which would be for cancer control. The bill also establishes a deafness institute and authorizes a $150 million construction program for NIH. Dr. Knipmeyer noted that Senator Kennedy, referring to himself as an architect of the National Cancer Act, pointed to several indices of progress and said he was pleased to renew the Act.

The House NIH reauthorization bill has not been introduced, and it is not known whether there will be hearings.

Dr. Knipmeyer said that the Senate had passed the Acquired Immunodeficiency Syndrome Research and Information Act of 1987. That bill requires NCI, in consultation with the NIH Director, to establish a clinical care unit for AIDS patients at the Clinical Center and authorizes needed personnel. The bill requires new resources above and beyond resources already allocated for NCI's cancer and AIDS research at the Clinical Center. Other provisions of the bill include an expedited seven-month review period for AIDS research project applications that are submitted in response to solicitations, authorization of NIAID construction activity for AIDS research, and designation of the NIH Director as the coordinator of all NIH research on AIDS. In addition, the bill specifies that a core national program on AIDS be established at the National Institute of Allergy and Infectious Diseases (NIAID).

On tobacco issues, Dr. Knipmeyer stated that a bill had been introduced to increase the excise tax on smokeless tobacco, with revenues going directly into a trust fund at NCI. She clarified that smoking is now banned on all flights scheduled for two hours or less, or for the duration of the flight if the flight goes beyond the scheduled time.

Turning to discussion of Congressional hearings, Dr. Knipmeyer said Dr. David Rall, Director of the National Institute of Environmental Health Sciences (NIEHS) would represent NIH at a May hearing on one of the animal welfare bills. The so-called Boxer bill would prohibit the Government from using lethality (LD_{50}) tests and addresses the entire issue of acute toxicity testing in animals. There is concern that enactment of this bill would have adverse repercussions on a wide range of research. A new bill, the Pet Theft Act, has been introduced in the Senate that requires pounds and shelters to maintain their animals for seven days, after which they can be sold to licensed dealers and provided to biomedical research facilities. This is in contrast to other bills that would make it difficult, if not impossible, to use pound or shelter animals in biomedical research.

Dr. Knipmeyer called attention to the Report on Animal Welfare Legislation provided to the Board and noted information on a petition to elevate the status of chimpanzees from "threatened" to "endangered" and on activities of the animal rights movement. Dr. Dorothy Canter noted that the Boxer bill would require non-animal toxicity tests unless the Federal department or agency head determines that non-animal tests would have less validity in specific instances. She said the bill has 105 sponsors in the House, and Dr. Rall is the only witness scheduled to testify in opposition to the bill. In response, Dr. Korn requested that a statement be drafted on the importance of appropriate, humane animal research for the Board's review.

VI. Black Leadership Initiative--Dr. Louis Sullivan

Dr. Louis Sullivan stated that this initiative had been undertaken as a result of a discussion at the September 1986 NCAB meeting, at which time it was noted that there was little visible participation among black leaders in helping to address the initiatives on reducing cancer morbidity and mortality by the year 2000. The initiative involves mobilizing black leaders to address the problem in six cities with large black populations. Hearings have been held in Atlanta and Los Angeles and are planned for Chicago, Washington, D.C., New York, and Houston. Dr. Sullivan acknowledged the assistance of Dr. Claudia Baquet, Chief of NCI's Special Populations Branch, and Mr. David Johnson of

Technical Resources, Inc. Also, the Association of Minority Health Professional Schools has endorsed the effort.

Dr. Sullivan said the second hearing, held in Los Angeles on March 10 and 11, was chaired by Dr. Walter Leavell, President of the Charles Drew Medical School, and Dr. Alfred Haynes, Principal Investigator of the cancer consortium of the Morehouse, Meharry, and Drew Medical Schools. Sessions were designed to bring together regional participants with state legislators and local elected officials. State and local proclamations were presented, and PSAs made by Diahann Carroll were viewed. Dr. Sullivan said that Marla Gibbs also taped four PSAs, and efforts are in progress to gain Bill Cosby's agreement to do additional announcements. These PSAs may be used at the discretion of the Black Leadership Initiative in all 50 states to spread the message about cancer prevention and early detection among black Americans.

Dr. Sullivan cited the central theme of the Los Angeles meeting as "Overcoming the Barriers to Cancer Prevention and Detection." Among those discussed were attitudinal, institutional, cultural, economic, and personal barriers. The identified strategies for intervention included communication, partnerships between professionals and lay persons, education, public policies for preventive medicine, and information dissemination.

The theme for the Chicago meeting, scheduled for May 16 and 17 and chaired by Dr. Clyde Phillips, is "Community Partnerships." This will be explored in the areas of policy, community institutions and organizations, service delivery, and education. The New York meeting, scheduled for June 23 and 24, will have as its theme "Accessibility." This will be discussed in terms of prevention awareness, early diagnosis, and treatment through community and national programs.

Dr. Sullivan said that the Washington, D.C., hearing on September 13 and 14 would immediately precede the annual meeting of the Congressional Black Caucus. The final hearing will be in Houston on September 29 and 30.

Following the Board review of videotaped PSAs by Diahann Carroll and Marla Gibbs, Dr. Sullivan noted a conference held in Washington, D.C., on March 28 and 29 on smoking behavior among blacks. Congressional support for action against smoking was expressed at that meeting.

In response to questions, Dr. Sullivan said efforts are under way to produce videos intended for the general public as well as for the black leadership. He also said that he was not aware of opposition to the Initiative in those states where the economy remains somewhat dependent on tobacco.

VII. Clinical Trials in Node-Negative Breast Cancer--Drs. Bernard Fisher and Robert Wittes

Dr. Fisher began his presentation by noting that most previous clinical studies of breast cancer had focused on Stage III node-positive breast cancer, and he reviewed early studies of node-negative breast cancer. In one of the first reports of breast cancer studies published in the 1960s, involvement of regional lymph nodes was used as a marker for patient outcome. This study showed that although patients with node-negative breast cancer have better disease-free survivals than those with positive nodes, the recurrence rate in node-negative breast cancer increases with time, and almost 4 out of 10 patients develop distant disease after surgery.

Dr. Fisher reported that his studies in the 1960s concerning the biology of tumor metastasis demonstrated that negative lymph nodes are not necessarily a marker of temporal events in the development of tumor spread because regional lymph nodes exhibit immunologic responses to tumor cells but do not necessarily destroy or act as a barrier to tumor cells, which can remain dormant in the nodes. He stated that these findings led to the hypothesis of positive nodes as an indicator of host-tumor relationships that permit development of metastases rather than as an instigator of distant disease; thus, it was hypothesized that the patient with negative nodes does better not necessarily because tumor cells have not broken off from the primary tumor and gone to the regional lymph nodes but because negative nodes are a marker for a host-tumor relationship that involves more than just mechanics.

Dr. Fisher stated that estrogen and progesterone receptors were then used as markers to differentiate which node-negative patients did well and which experienced treatment failure. He noted that while some studies reported that the presence of estrogen receptors (ER) was a good discriminator of outlook for node-negative patients, almost an equal number of investigators have demonstrated that ER was not a discriminator for outcome. However, this discrepancy could be attributed to low patient sample sizes, short followup time, and poor quality control of assay methods used in the studies. Further studies of the NSABP indeed demonstrated that ER-positive patients did better than ER-negative patients; however, the difference in disease-free survival, distant disease-free survival, or survival between the two groups was only 8 to 10 percent.

Dr. Fisher then reported that histologic tumor differentiation was found to be a better marker for outcome than the presence of ER or progesterone receptors (PR). He further stated that the level of ER--whether 100 or 10--did not affect disease-free survival. He also noted that patients in whom the tumor was too small to perform ER analysis do as well or even better than ER-positive patients relative to disease-free survival as well as to long-term survival. He emphasized that these findings support the concept that the fact that patients with small tumors have a better prognosis than those with large tumors is somehow related to the biologic rather than to the temporal characteristics of the tumor. In addition, evidence demonstrates that there is a higher degree of differentiation in small tumors than in large tumors.

On that background, in 1985 the NIH held a consensus conference on the treatment of breast cancer. The report from that conference stated that "the routine administration of adjuvant therapy in women with negative lymph nodes is not recommended at the present time." Dr. Fisher reviewed briefly the results of trials of node-negative patients that had been conducted prior to the conference and up until the last six months prior to this Board meeting. The NSABP trial published in the early 1960s demonstrated a benefit for the use of adjuvant chemotherapy in premenopausal women that was confined to node-positive patients. A Viennese trial and a trial in Southampton, England, concluded that adjuvant chemotherapy was effective in prolonging survival in both node-positive and node-negative patients. The trial that has created considerable attention is that conducted by Dr. J. Bonadonna in Milan, Italy, in which a striking difference in both event-free survival and survival was demonstrated for patients receiving CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) versus those not receiving adjuvant chemotherapy. The results of this trial became known immediately before the consensus conference in 1985 but were not taken into account in the consensus statement regarding the use of adjuvant therapy for node-negative patients. Dr. Fisher stressed that the patients in the control arm of the Milan trial were patients with a much poorer prognosis than those in the control group of the NSABP studies,

which could account for the finding that the survival rate for the Milan control group was only 50 percent whereas the survival rate in the control groups of the NSABP trials was approximately 70 percent.

Next, Dr. Fisher reported on two NSABP studies of node-negative breast cancer initiated in 1981 to 1982: one randomizing ER-negative patients to receive no adjuvant treatment or sequential methotrexate then 5-fluorouracil (MF) plus leucovorin; and one randomizing ER-positive patients to either a placebo or to tamoxifen treatment, an anti-estrogen demonstrated to be effective in node-positive patients, especially postmenopausal women. He stated that the MF combination was chosen because it had been used widely for treatment of solid tumors and had shown benefit in advanced breast and head and neck cancers. He noted that the two trials were stopped for ethical considerations because one cannot continue to put patients onto one arm of a trial when it has been demonstrated that the other arm is of benefit. The patients in the two arms of each study were similar in age, types of surgery, and tumor sizes. In the study of ER-negative breast cancer, the levels of ER were similar in both groups. Dr. Fisher emphasized the importance of reporting the methodology, including the method of statistical analysis, of all studies so that the credibility of studies can be assessed. He reviewed the statistical methods used in these NSABP trials, including life-table estimates computed by the actuarial method and multivariant analysis.

Dr. Fisher first presented the results of the study in patients with ER-negative tumors. There was a highly statistically significant benefit of M to F sequencing on disease-free survival for all patients on this arm of the study. This benefit was demonstrated both in patients under age 49 and in those over age 50. The sites of treatment failure were reduced for local, regional, and distant metastases. There were no life-threatening toxicities and only minimal toxicities (i.e., controllable nausea, vomiting, and diarrhea) associated with the MF therapy. No patient had developed a second malignancy.

Dr. Fisher emphasized that the NSABP positive findings substantiate the advantage obtained by CMF in the Milan trial as evidence of a chemotherapy effect. He stated, however, that the benefit observed in the NSABP study in patients over age 50 is inconsistent with the concept that chemotherapy is of little worth in postmenopausal node-positive breast cancer patients as reported in the consensus statement. He pointed out that previous studies in node-positive patients had always employed an alkylating agent (e.g., cyclophosphamide) and questioned whether the benefit seen in the NSABP study of node-negative patients, but not in previous studies of node-positive patients, might be related to the presence or absence of an alkylating agent. He commented that alkylating agents are known to be effective against undifferentiated tumors with a high growth fraction and hypothesized that antimetabolites might be more effective against differentiated tumors, which are commonly found in breast cancer patients over age 50. He further proposed that toxicity from alkylating agents results in dose reductions of all drugs in a regimen, impairing the effectiveness of the antimetabolites in the regimen.

Dr. Fisher then reported the results of the second trial using a placebo versus tamoxifen in ER-positive patients. He noted that there are approximately 3,000 patients in this trial because it was believed that the prognosis of these patients might be so good that a large number of patients would be needed to demonstrate any difference between outcome of the patients in the two arms. He stated that tamoxifen demonstrated a highly statistically significant benefit in patients under age 49 as well as in those over age 50. Metastases were eliminated in many different, but not all, sites.

An important finding was that tamoxifen alone reduced the chance of local recurrence following lumpectomy, adding more credibility to the use of lumpectomy for almost all patients with breast cancer. Tamoxifen therapy resulted in a reduction in regional recurrence and a reduction in skeletal recurrence but not in other distant sites, showing that there is some heterogeneity of the biological nature of the metastases in this group of patients.

Dr. Fisher also addressed the concept of the use of tamoxifen for chemoprevention, particularly to reduce the incidence of cancer recurrence in the opposite breast. He cautioned that although this NSABP study showed a benefit for tamoxifen in reducing the number of tumors in the opposite breast, this reduction does not necessarily indicate that tamoxifen prevents the occurrence of cancers of the opposite breast. Rather, because second breast cancers are more often present but undetectable at the time of diagnosis of the first breast cancer, tamoxifen is not actually preventing the second cancer but may be inhibiting the expression of the second breast cancer.

Returning to the results of the NSABP tamoxifen study, Dr. Fisher stated that the placebo tasted and looked like the tamoxifen pill and that the two groups of patients could be differentiated only by measuring for metabolites of tamoxifen in blood samples. In an equal number of patients from each arm of the study differentiated in this manner, thromboembolism occurred in 0.9 percent of patients receiving tamoxifen and in 0.2 percent of patients receiving placebo. While it is reported that tamoxifen causes hot flashes and increased vaginal discharge in over half of patients, 40 percent of the patients in the control group of this study experienced the same symptoms.

Dr. Fisher also pointed out that the fact that tamoxifen demonstrated benefit in patients under age 49 suggests that the effect of this therapy is not inhibited by increased ovarian production of estrogen. Because tamoxifen is an agonist it stimulates the ovaries and estrogen production. Thus, he questioned the hypothesis of some investigators that tamoxifen may be more beneficial in oophorectomized patients.

Dr. Fisher concluded by stating that although tamoxifen significantly improved disease-free survival in patients in this study, some patients did develop recurrences and that a subsequent trial will combine tamoxifen with other chemotherapy. He emphasized that both of the NSABP trials demonstrated a positive effect of adjuvant therapy in node-negative breast cancer but that neither had yet demonstrated a survival benefit.

To put the NSABP results in some perspective, Dr. Wittes then reviewed the results of several other randomized trials of adjuvant systemic therapy. A study known as the Scottish trial, which randomized more than 700 patients, including both ER-negative and ER-positive node-negative patients to five years of tamoxifen versus observation, showed after eight years' median followup a substantial improvement in disease-free survival of 74 percent with tamoxifen versus 57 percent without adjuvant therapy. Benefit was seen in ER-positive and ER-negative patients as well as in both pre- and postmenopausal patients. An overall survival advantage of 79 percent versus 74 percent was seen for tamoxifen. Another trial, known as the NATO (Nolvadex Adjuvant Therapy Organization) study, evaluated the effect of two years' tamoxifen therapy versus observation in approximately 600 postmenopausal ER-positive and ER-negative patients. At 45 months, there was 83 percent disease-free survival on the tamoxifen arm versus 76 percent on the observation arm. Survival benefit was also demonstrated by this trial. A third trial, initiated by the Eastern Cooperative Oncology Group and subsequently involving several other Cooperative Groups, evaluated a combination of cyclophosphamide, methotrexate,

5-fluorouracil, and prednisone versus no postoperative therapy in a total of 400 ER-negative and ER-positive patients with tumors larger than 3 cm. At three years, disease-free survival in the treatment group was 84 percent versus 67 percent in the observation group. Benefit was seen in both ER subsets and in postmenopausal patients. As with the NSABP studies, no differences in survival have yet been demonstrated.

Dr. Wittes concluded by emphasizing his belief that evidence overwhelmingly supports the benefits associated with adjuvant systemic therapy in node-negative breast cancer patients. He expressed the opinion that there is no longer any justification for including untreated control arms postoperatively in future adjuvant studies in breast cancer.

Points raised in discussion included the following:

- The fact that studies of adjuvant therapy in node-negative breast cancer patients have included different drug combinations given by different routes and sequencing of administration may influence results and requires further investigation.

- A previous NSABP study demonstrated a negative effect of tamoxifen given with chemotherapy in premenopausal patients. In postmenopausal women the combination was beneficial. Most current trials initiate chemotherapy first and tamoxifen later.

- Caution should be exercised in applying the therapies in these NSABP studies as state-of-the-art therapy until a clear survival benefit has been shown. However, it was emphasized that disease-free survival is a reasonable endpoint in the presence of relatively nontoxic and easily administered therapies such as tamoxifen.

- Every patient receiving tamoxifen on the NSABP trial is being randomized to either another five years of tamoxifen or a placebo because the ideal duration for tamoxifen therapy is as yet unknown.

- The importance of informing community physicians of the positive results of adjuvant systemic therapy in node-negative breast cancer was emphasized.

In conclusion, Dr. DeVita informed the Board that NCI staff members are planning a press announcement preceded by a mailing to the 12,000 physicians on PDQ about the evidence in favor of adjuvant therapy in node-negative breast cancer.

VIII. Health Effects of Radon Exposure--Dr. John Boice

Dr. John Boice, Chief of the Radiation Epidemiology Branch, Epidemiology and Biostatistics Program in the Division of Cancer Etiology, stated his presentation would include both a summary of the available information on health risk associated with radon exposure and an overview of the Program's activities in this area. He began by noting the irony of the fact that within the past few decades housing has become a hazard, and the accumulation of radon daughters in well-insulated and poorly ventilated homes may be a major contributor to lung cancer in the general population. Recent data also indicate that underground miners have an excess of lung cancer despite exposure levels only a

few times higher than those of the general population. Dr. Boice said there is concern that current standards may be too high.

Dr. Boice stated that radon is one of the world's most widely distributed natural carcinogens and may account for almost 50 percent of all radiation exposure from natural sources. Radon is a chemically inert gas produced by the decay of radium-226. It can diffuse through material in which it was formed, including uranium throughout the earth's crust, and eventually enter the atmosphere or be trapped inside homes. Radon itself gives off only a small radiation dose but decays into solid alpha-emitting daughters during the decay to stable lead. Dr. Boice identified the alpha particles as the cause of health hazards. When inhaled and deposited on the bronchial tree, the alpha-emitting radon daughters can deliver a dose of radiation that has been shown to be carcinogenic in miners.

Dr. Boice next reviewed the units used to describe radon exposure. A picocurie, which is commonly used to measure indoor radon, is a unit of activity or radioactive decay. One picocurie equals about two nuclear transformations in one minute. The working level (WL) was developed as a measure of radon daughter concentration, equal to about 130,000 million electron volts of potential alpha energy in a liter of air. One WL equals about 100 picocuries per liter of air if radon were present with equilibrium amounts of its daughters; one WL equals about 40 decays per second. The working level month (WLM) is a measure of cumulative exposure to radon of 1 WL for 170 hours, the average working month. Dr. Boice pointed out that these units only represent environmental conditions, i.e., the amount of radioactive gas in a volume of air, and that the conversion of these measures to actual radiation dose to the lung is extremely difficult. Occupational exposures to radon are 1 to 2 WLM per year, and the current mining standard in the United States is 4 WLM per year. Residential levels of radon have been estimated to be about .2 WL, on the average. A 70-year exposure to indoor radon would result in an exposure of about a 14 to 15 WLM.

Dr. Boice said the deleterious effects of radon on health were known even before radon was discovered in radium ores in 1900. Miners' deaths in Europe from "mountain disease" was described by Paracelsus as early as 1531. Three hundred years later, Harding and Hesse reported that 75 percent of deaths among miners were due to lung cancer, providing a clear record of an internal cancer being caused by an environmental exposure. In 1944, Lorenz stated that primary cancer of the lungs accounted for 50 percent of deaths among miners in the Black Forest region of Europe. Exposures were estimated to be on the order of 2,900 picocuries per liter or 15 WL. Lorenz suggested that other exposures in the mine, such as arsenic, or hereditary susceptibility might also contribute to lung cancer.

Referring to lung cancer risk, Dr. Boice said the many studies of metal and uranium miners indicate a clear correlation between cumulative exposures and WLM. All data on miners appear consistent with linearity over an extremely broad range of exposures, some of which are very high. In Colorado miners, no significant risk was observed for exposures under 120 WLM, and in a Swedish study, evidence for an effect at exposures under 50 WLM was very weak. Dr. Boice recalled that lifetime residential exposures to radon may be about 14 to 15 WLM, which would result in a relative risk of about 1.3 for lung cancer. However, higher exposures, e.g., at a level of 4 picocuries per liter, could result in a twofold increased risk for developing lung cancer based on current models of risk. Dr. Boice said the recent National Academy of Sciences BEIR IV Committee report estimated that about a 2.5 percent increase in the relative risk would follow an exposure

of about 1 WLM. Dr. Boice pointed out the serious limitations of miner studies which make extrapolation to residential situations very difficult: (1) There is great uncertainty about the estimates of the exposures of individual miners to radon; (2) limited followup restricts interpretation of the patterns of risk; and (3) risk could be influenced by smoking and non-radioactive air pollutants.

Dr. Boice noted that most data from miner studies strongly suggest that the combined effect of radon and cigarette smoking is multiplicative rather than additive. Data from the Colorado Plateau Miner Study indicate that the combined effect of heavy smoking and exposure to high levels of radon increased the risk of lung cancer almost 150-fold. Dr. Boice said the multiplicative model implies that the attributable risk of radon-induced lung cancer would be much greater in smokers than in nonsmokers. With respect to the mounting evidence that passive smoking may be a risk factor for lung cancer, Dr. Boice said it has been suggested that cigarette smoke can actually increase radon concentrations by increasing the number of aerosol particles in indoor air to which the radon daughters can attach. He said the implication is that radon and involuntary cigarette smoke may interact to cause lung cancer.

Next Dr. Boice described correlation or descriptive studies of residential radon exposure conducted in various countries. A correlation study of lung cancer deaths among persons residing in the Reading Prong, a region of high radon concentration in the United States, recently suggested an association with radon, identifying a need for further study. A study in China compared areas having both high and low background radiation. Although average exposures differed by a factor of 2, lung cancer rates were not different, and the authors concluded that there was no discernible excess of lung cancer following cumulative exposures of 15 WLM.

Dr. Boice also noted that some epidemiologic case control studies, mainly in Sweden, although positive are based on small numbers and limited exposure assessments. A recent study among long-term residents in Stockholm indicates a twofold risk associated with living close to the ground in areas with increased radon emanation. However, the population's attributable risk due to radon was estimated to be only 4 percent, and the authors concluded that radon was not a major health problem in Stockholm probably because most people live in highrise apartments.

In the United States, concern about elevated indoor concentrations of radon first arose in the late 1960s when homes in Colorado and other western states were found to have been built with materials contaminated by waste from uranium mines. High levels of radon were also found on reclaimed phosphate mine land used for residential and commercial development. Dr. Boice stated that he had been involved in studies of homes in Grand Junction, Colorado, that were found to have exposure levels several times higher than background. Extremely high levels of radon were rarely found, and when they were, they were usually related to other factors. The Surgeon General prepared guidelines for remedial action in Colorado, which was to be considered at 2 picocuries per liter above background, but mandatory at 10 picocuries per liter above background. The Environmental Protection Agency now recommends 4 picocuries per liter as the level for remedial action, and the National Council on Radiation Protection and Measurements recommends 8 to 10 picocuries per liter.

Dr. Boice said only recently has it been recognized that houses in various parts of the United States may have high indoor radon levels caused by natural deposits of uranium in the soil on which they were built. He recalled an incident in Pennsylvania

where an engineer set off radiation alarms in a nuclear power plant that had not yet begun operation. His home was found to have concentrations of radon of 2,700 picocuries per liter, or 14 WLM. This was a magnitude higher than any previously reported residential exposure and much higher than the levels allowed in mines today. However, Dr. Boice pointed out that homes on either side of the engineer's home had normal levels of radon, which illustrates the difficulty in making general estimates of residential exposures based on geographical characteristics or even from sample measurements. This incident led to the recognition of the Reading Prong, a bed of uranium-enriched soil through New Jersey, Pennsylvania, and New York where approximately 40 to 60 percent of the 600,000 homes may have levels of radon that exceed the Environmental Protection Agency (EPA) remedial action level of 4 picocuries per liter.

Next Dr. Boice explained how radon gets into homes. Because it is an inert gas that does not chemically interact, it can move through small spaces in the soil and rock on which homes are built. It can seep through dirt floors, cracks in concrete floors and walls, floor drains, sump pumps, and joints. Radon can also enter with natural gas used for heating and through water and be released in showers and other household uses of water. Some construction materials have high radon levels, but Dr. Boice said that housing materials are thought to contribute only a small fraction to total radon exposure. Primary contributors to high levels of radon are ground gas, lack of ventilation, and house pressure.

Dr. Boice noted that EPA has published guidelines on how to address the rapidly growing public concern about the health hazards of radon. EPA has also published several booklets: one for the public to explain what the radon problem is; one for householders to suggest what can be done about radon in homes; and a comprehensive reference manual. In addition, EPA has described the available types of radon detectors and their use. The charcoal cannister detector measures levels over a period of a week to obtain a quick and easy estimate of exposure. The alpha track detector can measure levels for up to a year to provide a complete integrated assessment of exposure. Dr. Boice said that if repeated and confirmed levels of 200 picocuries per liter or more are found, immediate action, including temporary relocation, should be taken. He said that while the EPA action levels seem reasonable, there is some controversy about lower levels that require remedial action.

Dr. Boice said although it appears that most homes have low levels of radon and only a small percentage have very high levels, data are incomplete and probably biased. Estimates suggest that 1 to 8 million homes, or from 1 to 12 percent, may exceed the 4 picocuries per liter action level. The high estimate implies that one in eight homes may have a radon problem. Applying underground miner estimates to expected population distributions of radon, estimated lifetime risks range from 0.1 to 0.8 percent. Dr. Boice said that EPA's estimate that 8 in 1,000 people may eventually die of lung cancer induced by residential radon may be somewhat high; the National Academy of Sciences' estimate is 5 per 1,000. By extrapolating data from miners to the general population and from mines to homes, then 4 to 23 percent of the 136,000 lung cancers per year in the United States may be due to residential radon. The average estimate is that about 10,000 deaths per year are possibly due to indoor radon exposure. The BEIR IV Committee suggested that risk decreases with time since exposure and with age at risk but is directly related to amount of exposure and cumulative WLM. The risk model proposed by the BEIR IV Committee estimates that 13,000 lung cancer deaths a year might be due to residential radon; 75 percent of this excess risk would occur among men because of higher

underlying background risk, and 87 percent would occur among smokers. Therefore, Dr. Boice stated, one of the most important things an individual can do to reduce the risk of radon-induced lung cancer is to stop smoking.

However, Dr. Boice also noted that if radon levels in all homes in the United States were reduced to below the 4 picocuries per liter remedial action level, the reduction in possible radon-induced lung cancer mortality would only be about 28 percent. Because most people live in homes with low levels of radon, they contribute more to the presumed lung cancer risk than the few individuals who live in homes with high levels. Dr. Boice cautioned that all these estimates be interpreted in the context of the many uncertainties involved. These uncertainties arise from the following problems: (1) The mine and home environments are very different; (2) there are no mining data on low dose exposures; (3) there is no information on radon risk in women or children; (4) most existing data are on male smokers; and (5) information is lacking on how to project lifetime risks based on limited followup periods. In addition, Dr. Boice said that even if measurements are made in the home, it is not known how to equate these values to actual WLM cumulative exposures, much less to actual dose to the lungs. Also, it is not known how to determine actual house exposure once an exposure measurement is made in the basement of a house. Finally, Dr. Boice explained that the actual dose of radon daughters to lung depends on many factors, including breathing patterns, whether the individual is a mouth or nose breather, thickness of the epithelium, presence of mucus, and the fraction of radon attached to aerosols.

In spite of these uncertainties, Dr. Boice said that the Epidemiology and Biostatistics Program believes that studies can be conducted that will yield useful information on radon risks as well as on the interaction of radon with smoking and on the temporal pattern of radon risk. He said that the Program has emphasized studies in areas of relatively high radon exposures and included radon studies in ongoing lung cancer investigations. Program staff have served on various committees assessing radon risk, including the BEIR IV Committee, and epidemiologic studies are in progress in China, New Jersey, Missouri, and Sweden. Dr. Boice summarized the studies as follows:

- Cohort study of 30,000 tin miners in collaboration with the China Cancer Institute and the Hunan Tin Corporation--includes details on smoking, radon exposure, arsenic exposure, and possibly childhood exposure; information on long-term followup should be available.

- Interview study of incident lung cancer patients in collaboration with the New Jersey Department of Health--800 women and 800 controls were available for evaluation; charcoal detectors and alpha track detectors were placed in homes including previous residences back to 1953. Recent measurements indicate that approximately 14 percent of basement readings exceeded 4 picocuries per liter.

- Missouri study of 350 non-smoking women and 700 controls--undertaken largely because of the stability of the population and likelihood that individuals have lived in the same home for extended periods. Approximately 15 percent of homes measured to date have radon levels above 4 picocuries per liter.

- Interview study of 200 women and 400 controls in collaboration with the Swedish Institute of Environmental Medicine--information obtained on risk factors such as passive smoking and diet in addition to residential histories.

- Study in Liaoning Province in China, where highest rates of male and female lung cancer in all of China are found; high levels of outdoor pollution from smelters and indoor pollution from coal stoves. Radon study includes 460 female lung cancer cases and an equivalent number of controls; radon measurements will be compared with interview data and other environmental measurements.

In conclusion, Dr. Boice recalled the nuclear reactor accident at Chernobyl. While the Swedish government recommended that farmers remain indoors because of contamination by cesium-137 and iodine-131 from the radioactive cloud, Swedish scientists felt that the recommendations increased the farmers' exposure to radiation because the indoor radon levels in homes were apparently much higher than the low amounts of fallout from the Chernobyl cloud in the fields.

IX. Colony-Stimulating Factor--Dr. Malcolm Moore

Dr. Malcolm Moore, head of the Laboratory for Developmental Hematopoiesis at the Memorial Sloan-Kettering Institute, described the colony stimulating factors (CSFs) and interleukins (ILs) as a family of very closely related small proteins or polypeptides. They are separate gene products but have substantial overlapping effects on the production of all types of blood cells, and some factors also affect the production of lymphocytes of T- and B-cell lineage. The CSFs were discovered because of their ability to stimulate progenitor or stem cells in the bone marrow. A single cell may give rise to a granulocyte, red cell, macrophage, or all those types of cells. In addition, the family of CSFs can selectively stimulate different subsets of early bone marrow progenitors that will comprise less than 1 percent of the total bone marrow.

At the time of his presentation, Dr. Moore said seven ILs were identified, but new factors are found every month. IL-1 has been found to affect the production of bone marrow stem cells and may have a major role in protecting against bone marrow failure associated with radiation exposure or chemotherapy. IL-3, which has been cloned and is in preclinical evaluation, can stimulate primitive stem cells and virtually all the blood-forming cells except the lymphoid series. Unlike IL-2, IL-3 seems to have no effect on lymphoid-type cells. IL-4 has effects on T cells and B cells, as well as certain bone marrow cells of the erythroid and myeloid series. IL-5 also affects certain lymphoid cells and certain cells of the eosinophil series. IL-6 appears to act on B cells, T cells, and possibly stem cells, and Il-7 affects very primitive B lymphocytes.

Dr. Moore said there was no reason to distinguish between the interleukins and CSFs. For ILs, the nomenclature was derived from the fact that they arise from and act upon cells of the leukocyte lineage. The CSF nomenclature was derived from the nature of the assay. MCSF stimulates monocyte and macrophage production; GCSF mostly neutrophil production; and GMCSF many types of cells. Erythropoietin acts on the late stages of the production of red cells, and another factor may stimulate the production of platelets. Dr. Moore suggested that there are so many factors with overlapping actions because blood cell formation is extraordinarily dynamic. The various cells have half-lives ranging from hours (neutrophils) to weeks (red blood cells), and the various populations of cells must be produced in balance and be able to respond to effects such as infections, hemorrhage, and exposure to myelosuppressive insults.

Dr. Moore reviewed the chronology of the development of human GCSF, at Memorial Sloan-Kettering, for use in clinical trials. The first requirement was the identification of a source of the activity, which was originally human peripheral blood leukocytes, a rather

poor source. A tumor cell line that produces large amounts of GCSF was subsequently identified. An assay system was developed using a leukemic cell line that was very sensitive to the differentiating effects of the activity in culture. Dr. Moore said that by 1984 the material had been purified to homogeneity, micro-sequenced, and cloned; cDNA was cloned in *E. coli* in 1985. Preclinical studies in mice, dogs, and monkeys were initiated in 1986, and in December 1986, the first Phase I/II clinical trial was undertaken in bladder cancer patients receiving high-dose chemotherapy.

Dr. Moore explained that CSFs of the G or GM type can induce a rapid dose-dependent increase in the production of the granulocytes in the peripheral blood. The CSFs also have a direct effect on the cells in circulation by improving their functional capacity: they enhance the capacity of the granulocytes to mediate chemotaxis and, in the case of GCSF, to migrate to sites of infection. They increase bactericidal capacity and the ability of the cells to kill tumor cells by an antibody-dependent mechanism. In addition, they bring about an increase in the production of granulocytes in the bone marrow and also in the spleen of rodents and increase the number of stem cells and progenitor cells of all of the different blood cell lineages in animals. Dr. Moore also noted a most valuable characteristic of GCSF--even with chronic treatment, all of the above-mentioned effects occur with minimal to no toxicity. The only observed toxicity has been mild bone pain. Other CSFs have somewhat greater toxicities, but none that would be contraindicative of use in conjunction with cancer chemotherapy.

Next Dr. Moore discussed the use of CSFs in conjunction with cancer chemotherapy, noting that the original purpose was to determine the safety, tolerance, and toxicity of multiple doses of recombinant GCSF, when administered daily by intravenous infusion. The bladder cancer patients chosen to receive CSFs were on the MVAC protocol (methotrexate, vinblastine, adriamycin, cisplatin), which is effective against bladder cancer, but with recurrent courses severe leukopenia occurs on day 14. Therefore, Dr. Moore said some patients were given GCSF one week before the initiation of the MVAC therapy, other patients were given GCSF after the initiation of chemotherapy, and other patients did not receive GCSF. At 14 days, the absolute neutrophil counts were determined to ascertain whether the patients would receive a second cycle of MVAC. With daily GCSF infusions of 1 μg/kg, the neutrophil count was approximately doubled and increased more with higher doses, up to a dose of 60 μg/kg with the white cell count approaching 100,000. Dr. Moore said no toxicity was observed except for some mild bone pain. All patients who received GCSF, even at the lowest dose, had neutrophil counts over 1,000, which made them eligible for a second course of MVAC.

Among the current clinical trials of GCSF and GMCSF, Dr. Moore identified the bone marrow suppression model in bladder cancer as initially the most exciting. He said a clinical trial in small cell lung cancer, using repeated courses of GCSF, is resulting in substantial reductions in episodes of hospitalization, infection, morbidity, and mortality. Other models have been proposed and initiated in breast cancer and acute nonlymphoblastic leukemia.

Dr. Moore said a second major area of CSF therapy is autologous bone marrow transplantation in cancer. Bone marrow is removed from patients, treated in some way, such as with very high doses of radiation or chemotherapy, and transplanted back into the patients. The rate of recovery of bone marrow function and peripheral blood parameters can be very slow, and the patient can be very immunocompromised during the recovery phase. Dr. Moore said that the administration of CSF could be expected to reduce the time until full engraftment. GCSF and GMCSF are also used to induce

leukemic cells to behave in certain ways. Another use is in patients who for genetic or other reasons cannot produce normal numbers of neutrophils and are chronically susceptible to infections. Finally, Dr. Moore said that CSFs are proving to be useful in treating radiation-induced bone marrow suppression, either pathologically or therapeutically induced.

Although the ability of CSF to stimulate the growth of blood cells and induce differentiation of leukemic cells are advantageous properties, Dr. Moore said it is possible that such factors may have a promoting effect on leukemia development in certain leukemias that are dependent on growth factors. According to the maturation theory, GCSFs can induce some leukemic cells to differentiate to apparently functionally normal cells, but Dr. Moore said the issue is whether this occurs with all cells. Using the PE-2 or recloning assay, it has been possible to demonstrate that with GCSF the leukemic process has been stopped.

Dr. Moore said a clinical trial will soon be initiated using CSFs to treat cyclic neutropenia, a recessive condition in humans and dogs. The purpose will be to determine whether recombinant GCSF or GMCSF could prevent the cycling. When GCSF was administered to dogs, the cycling was prevented but recurred when treatment was stopped. The same dose of GMCSF did not ablate the cycling. Dr. Moore said that humans and dogs with this condition do not lack GCSF but produce it only episodically in the serum. Therefore, it appears that the defect resides in the mechanism of control of the production of the growth factor. Dr. Moore described a patient who completely lacked neutrophil production for many years. When her bone marrow was placed in culture with GCSF, large numbers of mature, segmented neutrophils that were functionally normal were generated within two weeks. The patient was placed on GCSF therapy and had a very dramatic response in terms of producing high levels of normal neutrophils, which she had failed to do for 20 years.

Dr. Moore said another important observation is that IL-1 and CSF are synergistic and together potentiate the action of CSF, thereby indicating that factors should be combined to optimize the recovery of bone marrow from damage induced by high doses of certain types of chemotherapy. The combination of IL-1 and CSFs is expected to reduce the time needed for eventual recovery of normal bone marrow function and regain the normal numbers and functioning ability of cells in the peripheral blood. Dr. Moore said that in collaboration with Dr. Richard O'Reilly at Memorial Sloan-Kettering, the effects of combinations of irradiation and chemotherapy with biologicals are being studied in monkeys. Even two-day treatment with IL-1 beginning shortly after 5-fluorouracil treatment resulted in rapid recovery of platelets. Dr. Moore pointed out the importance of this result is that no hemopoietic growth factor generated by recombinant technology has yet been tested, either experimentally or in the clinic, that appears to cause recovery of platelets. Platelet depletion is a major complication of cancer therapy. Also in the trials with monkeys, administration of IL-2 for only two days, following treatment with 5-fluorouracil, reduces by half the time for neutrophils to return to levels above 500.

Dr. Moore reviewed animal model systems in which combination chemotherapy is being tested. He stated that each of the individual factors must be tested in an appropriate Phase I/II mode before combination trials can be initiated in humans. Using a spontaneous breast tumor model, mice were treated with 5-fluorouracil each week for three weeks and then given either IL-1 alone or in combination with GCSF or GMCSF. The addition of the hemopoietic growth factors protects against the bone marrow failure.

By the third week GCSF and GMCSF were no longer effective, but by combining the factors with IL-1, there were sustained high levels of production of neutrophils through multiple courses of chemotherapy. Dr. Moore said that in this study GCSF and GMCSF did not alter survival. All mice that received IL-1 survived, as did all mice that received IL-1 plus GMCSF. There was one mortality in mice that received IL-1 plus GCSF. Dr. Moore noted the preliminary nature of the study and said further studies would involve increasing the dosage of chemotherapy and increasing the number of courses of chemotherapy to determine whether the combination of chemotherapy and biotherapy will be effective in producing long-term remissions or possibly cures.

In response to a question about the importance of the sequence of the combination, Dr. Moore said that IL-1 acts on a very primitive stem cell that lacks the ability to respond directly to the other CSFs. It is thought IL-1 moves that cell to a point where it displays receptors for the CSFs and can respond to the CSFs by differentiation. Also, IL-1 induces the production of CSFs by an action on the T cells and on fibroblasts and endothelial cells. Dr. Moore said there is a sequential series of action in which cells at different degrees of maturity are first responsive only to IL-1, then at the second level become responsive to IL-3, then to GMCSF, and, finally, there is erythropoiety. Dr. Moore also said that if the CSFs or IL-3 are given at the same time as chemotherapy, the effect is counterproductive so it is very critical to work out the time period of administration of CSF. If the treatment is effective in obtaining rapid hemopoietic reconstitution, long-duration treatments with CSFs are not necessary.

Responding to a question about the differentiation response to the factors, Dr. Moore said that in a German study of pre-leukemic patients, patients began to show increased numbers of blast cells in their marrow with GMCSF therapy. Dr. Moore said these were not surprising because GMCSF is more likely to cause leukemia cell proliferation rather than differentiation. Approximately one-third of all acute non-lymphocytic leukemias have an autocrine production of GMCSF. Dr. Moore also suggested that the ability of the growth factors to stimulate leukemic blast cells could be used to cause dormant leukemic cells to begin to divide and become sensitive to chemotherapy. In response to other questions, Dr. Moore said that IL-3 appears to be a proliferative stimulant *in vitro*. While there is some question about identifying the best products, Dr. Moore said that to his knowledge, there are no production problems and the CSFs are widely available.

X. NIH Procedures Affecting the Awarding of Grants--Mrs. Barbara Bynum

Mrs. Barbara Bynum called Board members' attention to information in the Board book regarding NIH procedures affecting the awarding of grants and to a handout similarly titled. She pointed out that NCI is subject to NIH-wide policies and procedures and noted that the four procedures that she would discuss all require cognizance by advisory boards and councils.

● The first procedure discussed, the Accelerated Solicitation to Award Process (ASAP), was, Mrs. Bynum said, a followup to the Kennedy AIDS bill. The first reading of the legislation suggested that the time from the first publication of an RFA or RFP for AIDS-related research to the award by the Institute should not be longer than six months. NIH had initially interpreted the language to mean there could be six months from the time of receipt of applications or proposals until awards were made. The newest Senate version of the bill includes a total time period of seven months for announcement to award but, of this, allows the investigator-applicant three months for

preparation of the application or contract proposal. Therefore, NIH would have only four months to manage the review and award of AIDS applications and proposals that fit in this category.

Mrs. Bynum said that no matter which of the time frames is ultimately chosen, the review process will have to be severely compressed. She indicated that the Division of Research Grants (DRG) as well as NCI's Grants and Contracts Review Branches have proposed some time-saving steps but emphasized that, in any case, the concurrence of the NCAB must still be obtained prior to the award of any grants. Currently, 21 AIDS applications, scheduled for May 1988 NCAB review, are assigned solely or jointly to NCI. Most of these are R01 or single project investigator-initiated research grants, and most will be reviewed by DRG's Flexi Study Sections, which are large multidisciplinary groups assembled specifically to accommodate the AIDS grants.

Mrs. Bynum said that completed summary statements are expected from DRG in early June and that awards must be made by either August 1 or September 1. She requested the Board's agreement to the following: (1) that mail ballots be distributed to the NCAB during July to solicit concurrence with Study Section recommendations and (2) that responsibility for the resolution of problems or concerns about individual applications or summary statements be delegated to the AIDS Subcommittee of the Board. Because of questions about the second recommendation, an informal vote was taken resulting in the decision that the AIDS Subcommittee would first review all the applications and their recommendations would then be sent to the full Board along with the applications. This action is necessary to make grant awards in August, the only alternative being to hold a special Board meeting for the *en bloc* vote on these 21 applications. The Board then requested that to keep the procedure as similar to the normal process as possible, the AIDS Subcommittee should receive the complete summary statements and the rest of the Board only the face pages.

In response to a question, Mrs. Bynum acknowledged that this would be a recurrent situation because there are separate receipt deadlines for the AIDS-related applications. She said efforts will be made to improve procedures, but at the present the issue had to be dealt with on an *ad hoc* basis.

● The second procedure discussed was the triage of RFA-responsive applications. Mrs. Bynum said that unlike the ASAP, wherein expedited processing of AIDS grants and contracts is mandatory, the use of the triage procedure is optional but it has several potentially advantageous features that are clearly different from standard NIH operating procedures. Because of the large number of applications frequently received in response to RFAs, the triage procedure has been suggested as a way to reduce the number of applications requiring full peer review. Triage would involve (1) determination of responsiveness to an RFA, based on the referral guidelines from the announcement and made by the Institute program staff, and (2) determination of competitive status, based on scientific merit as judged by a committee of peer scientists. Those applications that are judged noncompetitive would be withdrawn from further consideration. The NCAB is not involved in the process at this stage. "Competitive" applications would be peer-reviewed as usual. Mrs. Bynum said that there is a strong legal basis for the triage process and that peer review is technically required only if there is an intention to award a grant. Although use of the triage process is optional, and NCI may not choose to use it, NIH has mandated that every RFA published include in the announcement language indicating that the triage process *may* be used.

In discussion, Board members questioned whether the triage process introduced an additional level of peer review and thus defeated the purpose of being work-saving. The question was also raised as to whether an applicant would be satisfied with a decision of noncompetitiveness without review of the application. Mrs. Bynum said the proponents of triage felt the decision would be acceptable because it involved peer reviewers and was a scientific judgment. It was pointed out that it takes a Study Section only a few minutes to identify a poor application, and it would not be fair to have a borderline application pre-reviewed by a group who may not be as expert as the Study Section. The sense of the Board was clearly to discourage use of triage by NCI.

● Mrs. Bynum next presented information on the use of percentile rankings on summary statements. NIH has proposed the general use of percentiles, rather than priority scores, in an attempt to improve the comparability of merit ratings assigned by numerous Study Sections. Mrs. Bynum said that the summary statements for DRG-reviewed, single-project research grant applications (ROIs and R29s) that Board members received for this meeting all contain a percentile ranking on the face page. During this transition period, some, but not all, of the summary statements on RFA-responsive applications have a percentile ranking. Where *ad hoc* review groups were used and there is no historical voting pattern against which to percentile the scores, a percentile ranking may appear on the summary statement, but it should be understood that DRG has chosen to use the entire universe of NIH grants as the base for calculation of those percentiles. Summary statements for other grant mechanisms, such as program projects, centers, cooperative agreements, training grants, etc., do *not* contain percentile rankings. The important point is that the NIH Director has determined that, for those categories of grants that are percentiled, the percentile ranking rather than the priority score is to be the primary determinant of the BID funding decision.

Mrs. Bynum suggested two possible advantages of this change: (1) it conserves, for use by Institute program staff (who have always had the option of using percentile rankings in funding decisions), numbers that make sense in the context of the DRG Study Sections; and (2) DRG has offered to work with the Institutes to develop internally consistent percentiling schemes for those grant mechanisms not currently included. The Institute's flexibility to recommend individual grants for exceptional funding will be maintained. The following points were raised in discussion by Board members:

- If the Board wanted to emphasize certain areas, they could suggest use of a greater percentile range so as to fund additional grants in those areas.

- The percentile is based on the review group and may therefore not be generalizable.

- Percentile normalization might result in reducing the number of grants that could be funded.

- Review staff will continue to emphasize to peer reviewers the necessity of separating scientific merit from considerations of funding.

It was noted finally that the use of percentile rankings would be adopted as an NIH-wide convention with the October round of reviews.

● As her final topic, Mrs. Bynum discussed the need for more effective implementation of the official NIH policy regarding recruitment of minority individuals

into NIH institutional training grants. There is concern that applicants for support under the institutional training grant (T32) mechanism seem not to be giving serious attention to addressing this issue at the institutional level. Mrs. Bynum reminded the NCAB that the NIH *Guide* announcement of this policy states that advisory Boards and NIH staff will be asked to consider information about recruitment of minority individuals in their review of T32 applications. It was then proposed that NCI staff provide Board members with quantitative and qualitative information from the Cancer Training Branch in DCPC and the Cancer Research Manpower Review Committee in DEA on the Institute's current activity involving institutional training grants with regard to the recruitment and retention of minorities. Starting in October, Mrs. Bynum said Board members will be asked to comment specifically on the T32 minority recruitment issue during the closed session of NCAB meetings. In preparation for these discussions she requested that Board members consider how concerns on this issue might be translated into a course of action for the Institute. Specifically, the Board should decide whether a more proactive approach to this problem is needed.

Dr. Korn suggested that at a future meeting the Board hear a presentation of the issues, including discussion of mechanisms that are in place and how they are working. It was agreed to schedule such a presentation and also to set aside some time in the Special Actions Subcommittee to discuss T32 grants that seem to be a problem.

XI. Closed Session

The second day of the meeting was closed to the public because it was devoted to the Board's review of grant applications. A total of 1,630 applications were reviewed, requesting support in the amount of $223,812,908. Of these, 1,327 were recommended for funding at a total cost of $171,489,664.

XII. Organ Systems Report--Dr. Brian Kimes

Dr. Kimes presented a brief overview of the background and previous operation of the Organ Systems Program (OSP), and he reviewed the significant changes in the OSP within the past 6 months. He outlined three recommendations from the February 3, 1988, meeting of the NCAB: (1) distribute the OSP portfolios to the divisional programs; (2) discontinue the outside Organ Systems Coordinating Center (OSCC) after July 1989; and (3) continue the working group component of the OSP.

Dr. Kimes reported that Dr. DeVita and the Executive Committee had created an NCI Organ Systems Committee (OSC) and appointed him chairman. He stated that the OSC will report directly to NCI's Executive Committee, and he briefly described the committee's charge. He added that the OSC members represent the Organ Systems Coordinators for each Division and other important areas within the Institute. He said that Dr. DeVita had sent a letter to the working group members, which described the changes recommended by the NCAB and informed them of the formation of the new committee. Dr. Kimes then described the individuals on the committee and their respective functions.

Dr. Kimes summarized the OSC's objectives as follows: develop a process for distributing the portfolios; recommend an organizational location for the OSP; establish guidelines to ensure staff attendance at working group meetings; and develop a plan for the production of OSP reports for the use of each working group. He reported that the new committee has met five times since February and has presented two reports to the

Executive Committee. He said that the OSC has made progress in three areas: administrative changes, transition operating guidelines, and policy recommendations.

Dr. Kimes outlined the following OSP administrative changes: distribute OSP portfolios (both active and unfunded/pending grant applications) to the divisional Programs; develop specific strategies for each initiative to ensure coordination among appropriate staff; and create a coding and tracking system for all unfunded and pending grant applications with an organ systems emphasis in FY 1989. He reported the following changes in the transition operating guidelines as follows: establish regular meetings with the OSCC staff; utilize conference calls to ensure cooperation among members of the OSP, the various Divisions, and the working groups on important issues; develop better agenda planning for meetings; utilize Division coordinators to establish better information flow between the OSCC and the Division staff; implement guidelines for the attendance of Division staff at working group meetings; require Division staff to present all concepts for review to the BSCs; utilize Division staff to prepare initiatives (PAs, RFAs, RFPs); and develop OSP reports across the Divisions at the operational level. In addition, he said that a policy recommendation had been made to locate the OSP in the Office of the Director or some other more appropriate organizational component.

Dr. Kimes next discussed some future issues and problems to be addressed by the OSP. He stated that the OSP will evaluate the following issues: formal chartering of the working groups versus maintaining an *ad hoc* structure; membership of the working groups; and NCI staffing requirements. In addition, a concept review of the current support contract and initiation/termination criteria for working groups will be presented for NCAB approval at the September meeting. Dr. Kimes said that the OSC has been very active and enthusiastic in pursuing its goals. He remarked that he has been impressed by the positive attitudes of the working group chairpersons, the OSCC staff, and the Division staff in relation to the restructuring of the OSP. He concluded that the committee has a unique opportunity to solicit ideas and suggestions over the next 14 months to make the OSP work in the most efficient and effective manner.

In response to questions, Dr. Kimes explained that the interdisciplinary aspect of the Institute will be preserved in the working groups; the OSP may be located in the Office of the Director, if Dr. DeVita and the Executive Committee approve of the OSC's recommendation, and the Institute is committed to maintaining regular meetings of the working groups. He added that he believes there is greater scientific flexibility in *ad hoc* working groups versus chartered working groups.

Dr. DeVita asked that the NCAB consider implementing a new working group to focus on skin cancer, particularly melanoma. He briefly discussed the morbidity and mortality associated with melanoma. Dr. Longmire asked if there would still be outside input on the selection of working group members. Dr. DeVita replied that the selection process will remain the same, except that instead of an outside Center there will be outside groups that focus on specific diseases. He stated that the NCAB will continue to work with the committee and the outside groups for the duration of the cooperative agreement. The NCI will select future working group members, and if the Board wishes, the proposed members will be presented to the NCAB for concurrence.

In response to a question about the continuity of the working groups, Dr. DeVita reviewed the advantages of chartered versus non-chartered working groups. He said that, in his opinion, non-chartered groups are superior because they allow for overlapping membership on other existing committees. Dr. DeVita then discussed the annual reports

that will be prepared for various organ systems and noted that he will be curious to see how they work out. He concluded that the new OSP should be considered an experiment that can be changed again, if it is not productive.

Dr. Lawrence said that Dr. Kimes and his staff should be complimented on their outstanding efforts to reorganize the OSP in the past few months. Dr. Korn and Dr. DeVita thanked Dr. Kimes for his recent efforts.

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

Dr. Roswell Boutwell, Chairman, reported that the Subcommittee on Environmental Carcinogenesis heard a review of programs within the Division of Cancer Etiology (DCE), beginning with a presentation by Dr. Bruce Wachholz, Chief, Radiation Effects Branch. This Branch administers a national extramural program of basic and applied research into the effects of radiation on biological organisms and systems, including three projects related to radioactive fallout. Research administered by this Branch is funded through grants, contracts, and interagency agreements, with the amount of grant funding showing a yearly increase since 1983, whereas the amount spent on contracts has decreased.

In the next presentation on the Epidemiology and Biostatistics Program (EBP) by Dr. Joseph Fraumeni, Associate Director, NCI, it was pointed out that the close organizational proximity of EBP, in the DCE, to the Biological Carcinogenesis and Chemical and Physical Carcinogenesis Programs has facilitated the creation of multidisciplinary studies that incorporate laboratory probes to clarify the risk factors and mechanisms of cancer development. The EBP collaborates extensively with the DCPC as well as extramural groups. Dr. Boutwell noted the broad range of research activities covered by the four Branches of the Epidemiology and Biostatistics Program. Future meetings might include presentations on research into the etiology of breast cancer and the potential carcinogenic effects of pesticides.

Dr. Boutwell moved for acceptance of the Subcommittee's report. Dr. Strong seconded the motion, and the report was accepted as presented.

XIV. Report of the Subcommittee for Review of Contracts and Budget--Dr. Roswell Boutwell for Dr. Phillip Frost

Dr. Boutwell reported that this Subcommittee, whose purpose is to review concepts emanating from the Office of the Director (OD), NCI, approved six proposed projects at the meeting on May 10. He noted the increased costs associated with the OD, some of which are attributable to actions of the NCAB (e.g., the public participation hearings), but emphasized the overall efficiency of the operation.

Dr. Boutwell noted that the Subcommittee has requested Mr. Phillip Amoruso and his staff to report on results and accomplishments of selected areas of the OD that are supported by contracts. In particular, the Subcommittee is interested in the effects of automation and the installation of hardware to computerize grant and contract reporting to the Board.

In the discussion, the following points were raised:

- Engaging an *ad hoc* expert in communications might be useful to provide verification of the technological advances in light of the professed inability of some Board members to advise in this technological area.

- The Information Systems Branch was created in NCI to facilitate work on automation from an institutional standpoint on cross-cutting issues.

- Outside experts have been utilized with varying degrees of success in the early stages of the automation process.

- Contract concepts presented to the Subcommittee for approval do not have the same type of scientific basis as do those presented to the divisional BSCs. The progress report in the fall, which will include demonstration outputs with regard to contracts as well as other types of reports generated by the system, should provide the Subcommittee with a better understanding of the program they are approving.

The report of the Subcommittee for Review of Contracts and Budget was accepted as presented.

XV. Report of the Subcommittee on AIDS--Dr. Gertrude Elion for Dr. Howard Temin

Dr. Gertrude Elion reported that subjects for discussion during the open session of the meeting included AIDS FTEs, the AIDS Vaccine Task Force, RFAs from the DCE, and an update on the status of Grant Referral Guidelines for AIDS grants. In the closed session, the Subcommittee heard a scientific presentation on data scheduled for publication in the June issue of *Annals of Internal Medicine.*

In summarizing for the committee the status of AIDS FTEs at the NCI, Mr. Donald Christoferson reported that approximately 143 FTEs will be dedicated to AIDS in FY 1989. Of these, approximately 60 occupy slots actually designated as AIDS FTEs received from NIH, and they are considered new positions because they were established at a time when Administration policy was decreasing the overall number of FTEs at NCI. In addition, Mr. Christoferson noted that a large number of FTEs occupying cancer slots are working on AIDS, creating a deficiency of FTEs of what should have been cancer slots. Dr. Temin asked if the approximate distribution of FTEs between professional and support staff could be estimated for the committee. The Subcommittee was informed that NCI plans to request additional AIDS FTEs from NIH in keeping with the actual AIDS work being done at NCI.

The Subcommittee next considered the earlier announcement by Dr. DeVita of the formation of an NCI AIDS Vaccine Task Force, chaired by Dr. Gallo and including representatives from other intramural and FCRF laboratories. Dr. Elion reported that the Subcommittee was generally in favor of consolidating this scientific effort within the Institute to identify research gaps more readily and provide needed support for experiments; however, they raised several points for consideration:

- How would this committee interact with NIAID and other NIH committees?

- This effort could be directed to develop vaccines against HTLV-I and HTLV-II as well as AIDS.

- The requirement for adequate peer review should be stringently adhered to.

The Subcommittee requested periodic updates on the activities of the NCI AIDS Vaccine Task Force.

In reporting to the Subcommittee on RFAs from the DCE, Dr. Iris Obrams noted that although no response to an RFA for AIDS-associated malignancies received a priority score within the funding cut-off, several will be considered for funding as exceptions. The suggestion by the reviewers that the RFA be reissued to give applicants more time to improve the quality of their applications elicited an expression of concern from the Subcommittee that this might be a repeated problem as rapid processing and review of AIDS grants receives wider implementation.

Dr. Jack Gruber then presented to the Subcommittee an update of the status of DCE's animal model RFA, the idea for which originated the previous year at a meeting of NCI, NIAID, and extramural experts in AIDS vaccine development. Following a presentation to the NIH AIDS Executive Committee, the RFA was concept reviewed and approved by the BSC, DCE, and is presently being circulated to other Institutes. Questions have been raised such as whether the RFA is duplication of effort within NIH and whether NCI should be involved. The committee noted that this issue brings to light an interesting issue: The NCI has historically been involved with retroviral research; however, now that retroviruses have been shown to cause an infectious disease, retroviral research would be in the province of a different Institute. While it could be argued that a transfer of program science might be necessary, Dr. Elion reported the Subcommittee's consensus that the price to pay in terms of disruption of science would be too great to make such an approach worthwhile. At this time, there was strong rationale for NCI to maintain its interest in animal models, both for purposes of drug development and vaccine work. The Subcommittee saw no reason why both NCI and NIAID should not continue to maintain their interests in developing an AIDS virus vaccine.

In reporting on the status of changes requested by NCI in NIH Grant Referral Guidelines for AIDS grants, Dr. Elion noted that action by NIH is still pending. She explained that NCI changes were submitted with the intent of being able to support a grants program in parallel with the intramural research interests of the Institute. She stated that the Subcommittee supported NCI's involvement in an extramural grant program but cautioned that the program should not become so large as to compete with NIAID and that NCI should not fund only grants originally referred to NIAID but not selected for payment by that Institute. A particular approach that the Subcommittee noted as worthwhile was the continued use of program-related RFAs.

In the discussion, the following points were raised:

- RFAs cannot be issued by a single Institute without NIH approval. They undergo a review process after their existence is made known. In the case of the animal model RFA, Dr. Anthony Fauci was acting in the dual positions of NIH AIDS Coordinator and Director of an Institute and therefore involved in the RFA approval process.

- NIAID concern over wording in the animal model RFA about understanding the pathogenesis of AIDS (a mission of NIAID) has been allayed by the explanation that the RFA's purpose is primarily animal model development for vaccine research; the RFA is cleared for release. Further clarification of extramural details is necessary before the RFA is issued.

- Subcommittee concern over the continuing shrinkage of cancer-related FTEs was reiterated, and the Board's endorsement of any effort that NCI can make to counteract the trend was stressed.

- NCI has never been fully reimbursed for cancer-related resources devoted to early AIDS research in its effort to respond to the AIDS emergency. It was estimated that years of delay would have resulted had NCI waited for specific AIDS FTEs and funding allocations before beginning research on retroviruses.

The report of the Subcommittee on AIDS was unanimously accepted as presented.

XVI. Report of the Subcommittee on Planning and Budget--Dr. Louise C. Strong

Dr. Louise Strong announced that the written minutes of the May 11 Subcommittee meeting would be distributed at the next NCAB meeting and proceeded with an oral report. As a first agenda item, Dr. DeVita reviewed for the Subcommittee the 1990 bypass budget, which was developed by NCI and presented to the President as part of the special NCI authorization. The budget represents the items necessary to achieve the goals of the NCI. The following are some of the assumptions upon which the 1990 bypass budget is based:

- Funding 50 percent of competing grants at their full recommended level (a 37.5 percent increase over the amount proposed in the President's FY 1989 budget).

- Expanding the number and role of cancer centers (increasing the number of centers from 60 to 90 by 1994 and funding 10 new centers beginning in 1990).

- Increasing by 60 percent the funding of clinical cooperative groups in a way that would double current patient accrual into clinical trials by 1992.

- Increasing prevention activities, largely through doubling the number of Community Clinical Oncology Programs (CCOPs) (a 70 percent increase over the amount proposed in the FY 1989 President's budget).

Additional items included in the bypass budget were an increase of 35 percent in the intramural research budget; an increase in the number of trainees (the Subcommittee recommended a 25 percent increase to 1,800); an innovative program of grants for small instrumentation needs in the extramural community (modified to approximately $20 million); funds for upgrading the supercomputer to increase its capacity and competitively award another to an extramural institution; and construction funds. The resulting bypass budget represented approximately a 50 percent increase over the FY 1989 President's budget for NCI, and the items included were considered by the Subcommittee to be critical to achieving the year 2000 goals.

As a second item of business, the Subcommittee reviewed the draft of the NCAB portion of NCI's Biennial Report and voted for approval after modifying the membership

list to include membership terms and to reflect the death of Dr. Tim Lee Carter during the 2-year reporting period. Dr. Strong noted that the biennial report provides NCAB members with an opportunity to identify items they consider vital to NCI activity as well as outstanding achievements and perceived problems.

The oral report of the Subcommittee on Planning and Budget was unanimously approved as presented by Dr. Strong.

XVII. Report of the Subcommittee on Cancer Centers--Dr. Enrico Mihich for Dr. John R. Durant

In the absence of Dr. John Durant, Chairman, Dr. Enrico Mihich presented summaries of two Subcommittee meetings held April 26 in Chicago and May 9 at NIH. He reported that the Subcommittee, including *ex officio* member Dr. Korn and NCI staff, met in Chicago on April 26 to consider the draft proposal concerning the definition of comprehensiveness as it applies to Cancer Centers. Dr. Mihich said the question of funding mechanisms was raised with the possibility that the P60 grant, a mechanism new to NCI, may be considered for funding the comprehensive centers after appropriate guidelines for the grants are developed by NCI, with input from the Subcommittee and the Board.

Dr. Mihich noted that the Subcommittee's proposal for criteria for Comprehensive Cancer Centers will be a subject for discussion at a July 21-22 workshop sponsored by the Subcommittee and will be presented for Board endorsement after modifications suggested by workshop participants have been incorporated.

Dr. Mihich said responses to the Subcommittee's request for comment and recommendations of the Association of American Cancer Institutes were considered in the formulation of the proposal. He pointed out that the issue of partnership with the NCI, both in identifying priorities and selecting approaches to implement them, surfaced at the Chicago meeting and again at the May 9 meeting, which resulted in a Subcommittee request that another pre-workshop meeting be held to work out details. Dr. Mihich noted that the Subcommittee also recommended development of appropriate guidelines for use of the P60 grant mechanism to avoid creating umbrella grants.

Next, Dr. Mihich presented an update on planning for the July 21-22 workshop, the purpose of which is to discuss a new direction for Cancer Centers. He noted that the draft agenda, which was distributed to Board members along with the May 9 meeting summary, included the following four topics for discussion: (1) the Subcommittee's proposal for criteria for Comprehensive Cancer Centers, (2) mechanisms for partnership in mutually identified high-priority issues, (3) major considerations in developing guidelines for P60 grants, and (4) resource requirements to meet the new criteria for Comprehensive Cancer Centers. Dr. Mihich reiterated the need for another pre-workshop Subcommittee meeting and a meeting following the workshop to incorporate resulting recommendations in the final proposal, which, he estimated, would be presented for Board endorsement in February 1989.

In response to a request, Dr. Mihich summarized the elements of the draft proposal on comprehensiveness as modified by the Subcommittee in Chicago. He stressed that the Board would have ample time to review the full document after further refinement by the Subcommittee and the incorporation of recommendations resulting from the workshop, to which all Board members were invited.

Responding to a question as to what is the potential for misuse of the P60 grant mechanism, Dr. Mihich compared provisions of the P30 mechanism, which is currently used as the core grant, with those of the P60 and noted that individual research project support prohibited by the P30 is considered an option under the P60. He expressed the concern that this option, if expanded, could become an umbrella of support for research within the centers. However, he said, the Institutes have the privilege and responsibility to define the guidelines for a particular instrument they are using, and the task ahead is to define them so that the intent in using the P60 mechanism is fully implemented and fulfilled. Dr. Korn announced that a listing of various NIH guidelines for P60s would be distributed to the Board for information purposes.

In response to a question, Dr. Mihich, assisted by Dr. DeVita and Ms. Judith Whalen, listed the following invitees to the July workshop: NCAB members, respondents to the Subcommittee's request for comment, center directors and administrators, and those people who call NCI in response to the *Cancer Letter* report on the Chicago meeting of the Subcommittee. Ms. Whalen noted that it is an open meeting. Dr. DeVita expressed the opinion that at least a half-day's discussion of the final draft would be required at a future Board meeting. He said a final decision would be postponed and further work done if the Board, at that time, could not endorse all of the elements. He stressed that the process cannot be hurried because it involves input from many institutions and people and impinges on the interests of the individual institutions.

There being no further discussion, the report of the Subcommittee on Cancer Centers was accepted as presented.

XVIII. New Business--Dr. David Korn and Mrs. Barbara Bynum

Before proceeding with new business, Dr. Korn asked for clarification of an action taken at the May 10 closed session. With the help of Mrs. Bynum and Dr. DeVita, it was clarified that the applicants under discussion would work with staff toward an October 1 submission of a revised application; that the proposed plan was accepted by all but with the proviso that the Board's involvement would be more direct; that a letter with an explicit set of instructions would be sent to the group (and copied to the Board) so that when the application is reviewed, the letter will provide, by inference, a series of evaluation criteria; that at the time of review and in addition to any action the review committee would take, the Board would receive a progress report; and that the group would be immediately disbanded and the Board informed of the action if, at the time of review--which precedes the next Board meeting in May, the group does not receive a fundable priority score.

National Cancer Advisory Board Resolution on the Use of Animals in Research

Dr. Korn presented a draft of this resolution for Board endorsement. Following discussion and revisions, Dr. Fisher moved that the Board approve the resolution for immediate distribution to Congress and widespread distribution nationwide. The motion was seconded, and the following resolution was unanimously approved as amended:

Whereas, progress in cancer prevention, diagnosis, and treatment depends on the humane and scientifically appropriate use of animals for research; and

Whereas, there is concern that the public is confused about the necessity to use animals in studying the causes, prevention, diagnosis, and treatment of cancer; and

Whereas, the Board finds that effective implementation and adherence to Federal statutes, regulations, and policies can ensure the appropriate use of animals in biomedical research; and

Whereas, the Board finds the misrepresentations endanger biomedical progress and blunt reactions to the illegal acts of vandalism, destruction of property, and theft that have occurred in many research institutions;

Be it, therefore, *resolved* that the National Cancer Advisory Board calls upon national, state and local legislators, health professionals, scientists, and others to support the humane use of animals in research to ensure continued progress against cancer. Furthermore, the Board affirms that further proscription or curtailment of the use of animals in research will seriously impair future progress against cancer and paralyze research on cancer prevention and treatment.

An additional paragraph will be included in the resolution indicating that there is a fundamental need for the use of animals in areas of cancer research for which there are no alternative methods.

Subcommittee Preferences for New Rosters

Dr. Korn requested that Board members convey their Subcommittee choices to Mrs. Bynum in the next few weeks so that assignments can be made and new rosters produced. Mrs. Bynum announced that she would revise the subcommittee choice statement and the functional statements to reflect the dissolution of the Subcommittee on Construction and the folding of the Cancer Information Subcommittee into the Subcommittee on Cancer Control for the Year 2000.

Proposed Formation of a Clinical Trials Subcommittee

Dr. Korn asked for a Board discussion on the need to form a subcommittee to deal specifically with the issues relating to clinical trials. In the discussion, the following points were raised:

- The BSC, Division of Cancer Treatment (DCT), is scheduled to discuss forming a committee at its May meeting to study the accrual issue and possible alternatives to the present structure of the cooperative group effort. DCT Director, Dr. Bruce Chabner, would report the result of these deliberations at the October NCAB meeting and at that time possibly ask for the participation of NCAB members who indicate an interest.

- Clinical trials issues will be a regular part of the report of the Director, NCI, to the Board.

- The DCPC is dealing with a parallel but somewhat different set of issues in its long-term prevention trials. There is a need for mechanisms to provide sufficient preliminary review and assure stability over the long process. Dr. Peter Greenwald, Director, DCPC, proposed exploring the issue at the divisional Board meetings and then bringing them to NCAB for discussion if needed.

- One possibility for addressing a serious impediment to clinical trials accrual, the public perception of clinical trials, might be to put the issue on the agenda at the public participation meetings around the country in the form of testimonies from people who have participated in clinical trials. This exercise could change the attitudes of people and their physicians as well as gather additional information on how the public perceives clinical trials.

- Another possibility for the public participation meetings is to visit one underserved area with a largely minority population and one major city that does not have active participation in clinical trials and find out what can be done to upgrade cancer care and access to trials in those areas.

Outstanding Investigator Grants

Mrs. Bynum called the Board's attention to the new brochure on the Outstanding Investigator grant (OIG) that has received widespread distribution. Applications for the current round of grants are due on June 15; 75 OIGs have been awarded to date.

Mrs. Bynum noted that DEA's experiment with the use of the mail ballot for review of this particular subset of grants has led other NIH peer review groups to do a comparative study of that process vis-a-vis more traditional methods. She said the Board would be apprised of the outcome of the study as well as receive DEA data on the use of the mechanism. Mrs. Bynum noted that in the next fiscal year, the earliest OIG awardees will be eligible for invitations to the second phase and it will be necessary for the Board and the President's Cancer Panel to decide how to structure that phase of the long-term support of outstanding investigators.

Future Agenda Items

For the benefit of the new Board members, Dr. Korn called attention to the list of future agenda items included in the Board book and invited members to suggest additional topics they would like to have discussed at future meetings. He asked that suggestions be sent either to himself or Mrs. Bynum. At Mrs. Bynum's request for suggestions as to items that can be removed from the list, the following items were recommended for deletion: Item 1--linkage of the year 2000 goals with the bypass budget; and Item 9--limitations and value of human subjects and animal welfare regulations. The timeliness of Item 7 (screening mammography) in relation to current events and the public participation hearings was emphasized.

The presentation on the Institute's Epidemiology Program, originally planned for the May 9 closed session, will be on the agenda of the October meeting closed session.

Regarding other NCAB business, Mrs. Bynum announced (1) that there will be a formal orientation session for new Board members in late summer and (2) called attention to the ballot for indicating grant program review choices, asking that each member indicate scientific program areas of the Institute for which he or she would like to have specific review responsibility.

Finally, the Board discussed the suggestion that NCAB meetings be reduced to two full days. Dr. Korn listed reasons for maintaining the 3-day meeting and noted the constant tradeoff between the third day and the comfort level and the breadth of activities that can be presented at a meeting. Mrs. Bynum added that the cyclical nature

of the grant load made it difficult to predict how many staff actions would be required each time. She pointed out for the benefit of new members that the May meeting included more free time than usual because many of the new members were unable to attend, requiring that certain substantive presentations be postponed. Alternative formats for two- and three-day meetings were explored as follows: (1) alternating three-day and two-day meetings; (2) regular two-day meetings with three-day meetings interspersed, as needed, to accommodate grant action loads; and (3) scheduling subcommittee meetings for the morning of the first day and beginning the open session after lunch, reserving day 2 for the closed session, and scheduling an all day open session on day 3. Dr. Korn promised to continue to seek a mutually acceptable solution to the problem and invited members to continue to express their preferences.

XIX. Adjournment

There being no further business, the 66th regular meeting of the National Cancer Advisory Board was adjourned at 10:50 a.m., May 11, 1988.

August 19, 1988
Date

David Korn, M.D.

THE NATIONAL CANCER ADVISORY BOARD RESOLUTION

ON THE USE OF ANIMALS IN RESEARCH

Whereas, progress in cancer research depends on the humane and scientifically appropriate use of animals for research; and

Whereas, there is concern that the public is confused about the necessity to use animals in studying the causes, prevention, diagnosis and treatment of cancer; and

Whereas, major advances in cancer research have depended on the use of animals, including the revelations of the most fundamental information about the development of cancer, and treatments for many previously incurable cancers; and

Whereas, the Board is aware of new research techniques that provide alternatives to the use of animals in specific circumstances, there are major areas of cancer research, including studies of causation, prevention and treatment, in which the continued use of animals is essential; and

Whereas, the Board finds that effective implementation and adherence to Federal statutes, regulations, and policies can ensure the appropriate use of animals in biomedical research; and

Whereas, the Board finds that misrepresentations endanger biomedical progress and blunt reactions to the illegal acts of vandalism, destruction of property and theft that have occurred in many research institutions;

Be it, therefore, resolved that the National Cancer Advisory Board calls upon national, state and local legislators, health professionals, scientists and others to support the humane use of animals in research to ensure continued progress against cancer. Furthermore, the Board affirms that further proscription or curtailment of the use of animals in research threatens to paralyze future progress against cancer.

May 11, 1988