Department of Health and Human Services

Public Health Service

National Cancer Institute

National Cancer Advisory Board

Summary of Meeting
February 3-5, 1986
Building 31, Conference Room 6
National Institutes of Health
Bethesda, Maryland

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

Summary of Meeting*
February 3-5, 1986

The National Cancer Advisory Board (NCAB) convened for its 57th regular meeting at 8:30 a.m., February 3, 1986, in Building 31, 6th Floor, Conference Room 6, National Institutes of Health (NIH), Bethesda, Maryland. Dr. David Korn, Chairman, presided.

Board Members Present

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

President's Cancer Panel

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

Ex Officio Members

Dr. Hollis Boren, VA
Dr. Lois Beaver, FDA
Dr. Dorothy Canter, NIEHS
Dr. Lakshmi Mishra, CPSC
Dr. Robert Rabin, OSTP
Captain Steven R. Veach, DOD
Dr. Ralph E. Yodaiken, DOL

Absent

Mrs. Barbara Shook

* 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

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

Dr. Judi Johnson, Cancer Services Coordinator, North Memorial Medical Center, Robbinsdale, Minnesota, representing the Oncology Nursing Society.

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

Dr. George Hill, Chief of the Division of Surgical Oncology, University of Medicine and Dentistry, Newark, New Jersey, representing the Association of the American Cancer Institutes.

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

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

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

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

Members, Executive Committee, National Cancer Institute

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

In addition to NCI staff members, meeting participants, and guests, a total of 18 registered members of the public attended the meeting.

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

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

The minutes of the December 2-4, 1985, meeting were unanimously approved, with the following change on page 22:

- The length of time from concept initiation in the Working Groups to grant award was of concern to Board Members (2 years for Flow Cytometry in Bladder Cancer). The delay was eventuated by personnel vacancies at the NCI, specifically the lack of an Executive Secretary to deal with this project. The Board expressed the hope that this time period would be greatly reduced in the future.

II. Future Board Meeting Dates

Future meeting dates were confirmed as follows: May 19-21, 1986; October 6-8, 1986; December 8-10, 1986; February 2-4, 1987; May 26-28, 1987; September 28-30, 1987; and November 16-18, 1987.

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

Dr. Hammer noted that the first meeting of the NCAB in 1986 came at a time of great opportunity in cancer research and a time of great uncertainty about adequate funding for the maximum realization of opportunities. He expressed the hope that the President's Cancer Panel (PCP) and the Board can work together to support the NCI as it deals with required cuts in the budget.

The Panel met on January 30, immediately following the luncheon ceremony in Los Angeles at which Dr. Steven Rosenberg of NCI and Dr. Tadatsuga Taniguchi of Osaka University were awarded the Fourth Annual Hammer Cancer Prize. The topic for the Panel meeting, "Innovations in Cancer Therapy," evolved from the workshop Dr. Hammer supported on biological approaches to cancer therapy held in September 1985 at the Jonas Salk Institute, La Jolla, California. The participants in the January meeting included Dr. Emil Frei, Dana Farber Cancer Institute; Dr. Sidney Golub, University of California at Los Angeles (UCLA); Dr. Jordan Gutterman, M.D. Anderson Hospital and Tumor Institute; Dr. Carmack Holmes, UCLA; Dr. Ronald Mertelsman, Memorial Sloan-Kettering; Dr. Lloyd Old, Memorial Sloan-Kettering; Dr. Judith Gasson, UCLA; Dr. Donald Morton, UCLA; and Dr. Rosenberg.

Dr. Hammer shared some of the promising approaches discussed at the meeting: granulocyte macrophage colony stimulating factor; effective use of

alpha interferon in early stages of leukemia (favorable results also in some kidney cancer cases); use of monoclonal antibodies combined with interferon; and tumor necrosis factor (TNF) and interaction of the TNF with interleukin-2 (IL-2). He noted especially Dr. Rosenberg's work using lymphokine-activated killer (LAK) cells and IL-2. Fifteen successes (at least 50 percent reduction in tumor burden) have been achieved, with 100 percent success in six renal cell cancers. A new focus of research in Dr. Rosenberg's laboratory is the development of tumor-infiltrating lymphocytes with specific activity against tumors from which they are derived. In experiments with mice, tumor-infiltrating lymphocytes appeared to be 50 to 100 times more potent than killer cells in destroying tumor cells. Dr. Hammer expressed confidence that Dr. Rosenberg would be able to adapt this technology for treating humans. He announced that awards have been made to six institutions for trials of the NCI LAK cell-IL-2 protocol.

A May workshop and a September symposium are planned to continue the exchange of information on various innovations in cancer therapy, information of value to cancer researchers and therapists. Recognizing that the subjects discussed at these workshops and meetings do not constitute the only innovations in cancer therapy, the Panel hopes to cover others at subsequent meetings.

Dr. Hammer expressed confidence that 1986 would be a good year despite budgetary restrictions and said the Panel is committed to helping the NCI convince those responsible for allocating funds that a breakthrough in cancer research and therapy is imminent. Ideas that would help move the National Cancer Program toward the goal of cancer eradication were solicited from the Board.

In the discussion, the suggestion was made that the outgoing members of the NCAB meet with the Panel to present ideas, concepts, and recommendations resulting from their cumulative experience on the Board. Dr. Hammer said these members would be welcome at the next PCP meeting.

Outgoing members expressed appreciation for the outstanding leadership provided by Dr. Hammer, Dr. Longmire, and Dr. Montgomery and for their many contributions to the National Cancer Program.

IV. Director's Report, National Cancer Institute--Dr. Vincent T. DeVita

Dr. DeVita thanked Dr. Hammer for his optimistic report. He expressed gratitude for the outstanding efforts of Dr. Hickey, Dr. Katterhagen, Mrs. Kushner, Ms. Landers, Dr. Leffall, and Dr. Powers, members whose terms expire before the next meeting, and presented each with a certificate of appreciation. Appointments to replace these members will be made before the May Board meeting. Mrs. Barbara Ingalls Shook will replace the late Mrs. Angel Bradley on the Board. Mrs. Shook served on the Board of Directors of the Southern Research Institute in Birmingham and on the Board of Trustees at the University of Alabama. Staff appointments announced were Dr. Paul Rambaut, Deputy Director of the Division of Extramural Activities (DEA); Mr. Lawrence Ray, Administrative Officer of DEA; and Dr. Robert Browning, Chief of the Grants Review Branch, DEA.

Dr. DeVita did not discuss the budget because the President would not be submitting it to Congress until February 4, and it would not become public until February 5. Instead, the effects of the Gramm-Rudman-Hollings Act were to be discussed at a closed session of the Budget Subcommittee.

Follow-up Items

Low-Fat Trials in Breast Cancer

As requested by the Board, a summary of the status of the low-fat studies in breast cancer was presented during this meeting (see Section VII).

Cancer Centers Program

Specific grants relating to the Cancer Centers Program were presented to the Board in closed session. Funds for a grant for the Mary Babb Randolph Center in West Virginia have been transferred to the Office of the Secretary as directed by Congress. NCI staff will provide technical assistance to the Department in making this award.

Summer Program for Students

Because of the shortage of full-time equivalent positions (FTEs), the NCI will not have a summer program for students. It will utilize donations to the Gift Fund to provide student stipends for summer training placements as it did last year. Dr. DeVita again expressed appreciation for the individual and corporate donations that have enabled the Institute to do this.

Smokeless Tobacco

The Consensus Development Conference on the Health Effects of Smokeless Tobacco in January concluded that human evidence for cancer developing at the site of the placement of chewing tobacco and snuff is sufficient to issue a warning to people who use these products.

Prevention Awareness Program for Black Americans

A progress report for the Prevention Awareness Program for Black Americans was distributed.

AIDS Drug Development Program

Progress in the NCI and National Institute of Allergy and Infectious Diseases (NIAID) AIDS drug development program was reported. Five drugs have high priority for clinical trials: azidothymidine, ribavirin, foscarnet, HPA-23, and suramin. Phase I trials have been completed with suramin and azidothymidine, with the latter being much less toxic than any other drug. Two compounds, 2'3'-dideoxycytidine and 2'3'-dideoxyadenosine, are in full-scale preclinical development, and 11 other compounds are being considered for clinical trials. In addition, trimetrexate has been used successfully against *Pneumocystis carinii*, a major killer of AIDS patients.

Physicians Data Query (PDQ)

Dr. Robert C. Young, Chief of the Medicine Branch of the Clinical Oncology Program, Division of Cancer Treatment, will replace Dr. Daniel Ihde as Editor-in-Chief of the PDQ Editorial Board; several members of the Board have rotated off and new members have been named.

Dr. DeVita summarized the publicity PDQ has been given at medical meetings, in hospitals, and in medical journals. It was suggested that changes made to PDQ state-of-the-art statements at closed meetings of the Editorial Board be summarized in press releases for science writers to enhance publicity for PDQ.

LAK Cell Project

Dr. DeVita reported the chronology of the events leading to the publication in the New England Journal of Medicine of Dr. Rosenberg's paper on the LAK cell project, which included 11 responders of 25 patients. At present, there are 15 responders of 41 patients, including 6 of 6 renal cell cancers, 3 of 14 colorectal cancers, and 5 of 10 melanomas. There has been one death attributed to LAK cells and IL-2, and one serious complication related to arterial catheter insertion. Dr. Rosenberg has also begun to use IL-2 alone in doses of 300,000 units/kg 3 times a day.

Six institutions have been funded to reproduce the LAK study extramurally: Tufts University in Boston, the University of California in San Francisco, Loyola University in Chicago, City of Hope National Medical Center in Los Angeles, Montefiore Medical Center in New York, and the University of Texas in San Antonio. The total funding is $2.5 million, with Cetus Corporation supplying all of the IL-2.

Discussion about the LAK extramural program clarified the following:

- At present, the program plan includes Phase II testing against renal cell carcinoma, melanoma, and a few other tumor types and adjuvant studies in Stage II melanoma and colon cancer.

- The selection process involved invitations to the clinical cooperative groups and cancer centers and review of the 45 proposals received by the DCT Cancer Therapy Evaluation Program. From the six selected, one of the investigators received support through additional funding in a grant, and five of the investigators received support through additional funding in cooperative agreements.

- Because IL-2 and LAK cells have proven highly successful in renal cell carcinoma and melanoma, the treatment will be used as first-line therapy in these tumors.

- Intra-arterial administration of LAK cells will continue to be used in the extramural protocol, as the single complication arising from this method of administration resulted from an anatomical anomaly in the patient's arterial system.

The importance of repeating Dr. Rosenberg's study design precisely as reported was emphasized.

New Items

A site visit to the new super-computer facility at the Frederick Cancer Research Facility (FCRF), which will be operational in May, was proposed.

It has been decided that the revised in vitro cell line screening program for new agents will be housed at FCRF, under the direction of Dr. Michael Boyd, Associate Director of the Developmental Therapeutics Program, Division of Cancer Treatment (DCT).

Two new types of grants established by NIH were described:

- MERIT Awards--which have some similarity to the Outstanding Investigator Grants and allow a 3- to 5-year extension of a competitive renewal without further review.

- FIRST Awards--which replace the New Investigator Awards and provide up to a 5-year award to investigators who have not had an R01 grant. The upper limit is $350,000 over 5 years. There are no age limits for applicants.

Dr. DeVita announced that the NCI Executive Committee met in January to set priorities and will meet again in July to verify program details. In addition, the NCI Forward Plan review has been completed with the NIH Office of the Director. The appropriations hearings in the House have been scheduled for March 11.

The Health Research Extension Act was passed by Congress, and NIH has established a committee to examine the impact of the Act on all of the Institutes within NIH.

The following points were raised in discussion:

- The in vitro screening will be phased in gradually to enable identification of any problems that may arise if in vitro screening alone is used in drug development.

- The new FIRST Award is an NIH-wide grant mechanism.

- There may be problems in peer review of a new investigator for a 5-year grant.

- Interferon is the treatment of choice for hairy cell leukemia, a rare tumor, and has been somewhat effective against melanoma and some other solid tumors. Experimental studies using pure gamma interferon with LAK cells and TNF are showing some promise.

- Passive smoking is an important area of study in terms of risk of cancer.

Revision of the National Cancer Act--Dr. Mary Knipmeyer

Dr. Knipmeyer presented a summary of the revision of the National Cancer Act (P.L. 99-158), which became law as part of the Health Research Extension Act of 1985 on November 20, 1985. A copy of Dr. Knipmeyer's report and of the new law itself were distributed to the Board. A full understanding requires study of sections other than just the cancer section of the Act.

Two new information dissemination mandates are included in the cancer section of the Act:

- To emphasize information dissemination on the continuing care (i.e., rehabilitation) of cancer patients and their families

- To target much of the NCI information to students of the health professions.

Other changes include:

- An increase from $35,000 to $50,000 for the ceiling of projects that need not be approved by the Board before funding

- A new statutory requirement that intramural programs be peer reviewed (NCI's system will not need to be changed)

- The NCAB annual report to become part of a new biennial report by the NIH Director

- The report of the President's Cancer Panel to be transmitted to the Secretary of Health and Human Services and to Congress, as well as to the President

- The addition of the new position of Associate Director for Prevention to be added to several Institutes, including the NCI.

The following points were raised in discussion:

- The bypass budget for NCI is retained and has a narrative section that is distinct from the NCAB annual report

- An action by NCI to stop a grant because of noncompliance with the Animal Welfare Act can be appealed and funds restored if the problems are remedied.

V. The Balanced Budget and Emergency Deficit Control Act of 1985 (Gramm-Rudman-Hollings)--Mr. Philip D. Amoruso

Mr. Amoruso summarized the principles of the Gramm-Rudman-Hollings Act, drawing on published data from the January 15 Federal Register, including a report of the Office of Management and Budget (OMB) and the Congressional Budget Office (CBO). It was emphasized that the Act would go into effect only if all other measures are insufficient to meet the deficit targets.

The purpose of the Act is to reduce the budget deficit to zero by FY 91. Reductions will be split equally between defense and non-defense categories of the budget. The application of reductions to non-defense areas involves the following:

- National debt and Social Security are exempted from sequestration
- Eight low-income programs (e.g., supplementary security income) are exempted
- Special rules exist for certain automatic spending programs (e.g., unemployment programs)
- Some programs (e.g., Medicare) have percentage limits on reductions--1 percent in FY 86 and 2 percent in subsequent years.

Mr. Amoruso discussed Constitutional issues related to the Act. CBO and the Government Accounting Office (GAO) are agents of Congress, but the Act may give the Congress functions reserved for the Executive Branch, such as a role in calculating budget estimates to trigger the Deficit Control Act and empowering GAO to verify reductions proposed for defense contracts.

Economic conditions can also influence the Act. The House and Senate would consider suspension of the Act if 1) CBO or OMB forecasts or estimates economic growth to be less than zero in two consecutive quarters; or 2) the Department of Commerce reports real economic growth to be less than 1 percent for two consecutive quarters.

Mr. Amoruso then provided deficit targets defined by the Act from FY 86 to FY 91. The FY 86 projected deficit reduction is $11.7 billion, split equally between defense and non-defense categories. In summarizing the 1986 proposed reductions to health programs, Mr. Amoruso noted that NCI budget authority would be reduced by $53.8 million, thereby causing estimated outlays to be reduced by $26.5 million.

A calendar of trigger mechanisms for deficit reduction under the Act was provided, noting particularly that the President's sequester order takes effect unless Congress passes alternative legislation within 1 month (i.e., between February 1 and March 1 for FY 86 and between September 1 and October 1 for FY 87 to FY 91). Revisions to the budget process timetable 1987 to 1991 were also presented, noting past budget schedules.

The following points were raised in discussion:

- Gramm-Rudman-Hollings does not allow much leeway to Agencies in how budgets are cut
- Several Constitutional issues have been raised, including the contention that the Act gives the Executive Branch powers reserved to Congress
- For FY 86, $109.3 billion out of $272.8 billion and $114.8 billion out of $723.7 billion for defense and non-defense programs, respectively, are subject to full cuts.

VI. The Basis of Broad-Spectrum Drug Resistance to Cancer Chemotherapy--Dr. Charles E. Myers

Dr. Myers based his discussion of broad-spectrum drug resistance on an analogy between the development of resistance to the cytotoxicity of multiple carcinogens and the development of multi- or pleiotropic drug resistance. Using a group of five natural products (Adriamycin, actinomycin-D, VP-16, vinblastine, and vincristine) as an example, he showed that tumors exposed to a single agent (e.g., Adriamycin) develop resistance to many drugs that have no chemical similarity or common mechanism of action. Analogously, the body develops resistance to a wide variety of toxins via a common, two-phase mechanism that converts the toxins to water-soluble compounds that can be rapidly cleared from the body. Phase I involves attaching a reactive group to the toxin, and Phase II involves conjugating that compound with sulfate, glucuronic acid, or glutathione. If this system fails, an alternate response is activated. This response involves the following: 1) the uptake of the toxin is decreased; 2) P450 isoenzymes that are responsible for Phase I activation are no longer expressed and can no longer be induced by toxins; and 3) the expression of Phase II enzymes responsible for conjugation is dramatically enhanced.

Dr. Myers expanded on his discussion of this alternate response by explaining the "resistant hepatocyte model" of chemical carcinogenesis, developed by Emmanuel Farber in Toronto in the early 1970s. This model describes the development of resistance to a wide range of toxins after a 2-week exposure to a single carcinogen. The liver is damaged partially through the process and then regenerates. After 2 weeks, exposure to the carcinogen is stopped, and abnormal hyperplastic nodules appear on the liver. These nodules are resistant to a wide range of carcinogens that are unrelated to the original, single carcinogen.

This pattern is similar to that seen in pleiotropic drug resistance. For example, biochemical testing shows that drug-resistant cell lines fail to respond when the conjugating enzyme, glutathione transferase, is overexpressed. Resistant cell lines also exhibit decreased net accumulation of drugs, which is analogous to the hepatocyte model where the nodules show decreased accumulation of toxins. Dr. Myers also described a study of transient overexpression of glutathione transferase after treatment with ara-C or radiation in leukemias.

- Expanding the PDQ capsule summaries would make the system more useful to patients and lay people. The PDQ Editorial Board will be asked about translating some file information into lay language.

- The suggestion that any physician may be listed within the PDQ directory will be considered by the PDQ Editorial Board.

The Board approved a motion that any restrictions that the NCAB placed on the NCI in the dissemination of PDQ be removed (one abstention).

Ms. Brown showed the Board a model of the poster on unproven methods of cancer therapy to be distributed to post offices nationwide. For further information, the poster lists the Cancer Information Service number and the NCI, American Cancer Society, Food and Drug Administration, Better Business Bureau, and U.S. Postal Service.

The Board approved the distribution of the poster to post offices nationwide.

Subcommittee on Organ Systems--Dr. Robert C. Hickey

Dr. Hickey distributed the report of the Organ Systems Program Subcommittee, which met on February 2. Dr. Hickey provided an historical overview of the program and summarized the annual report presented to the NCAB at the December 1985 meeting (see Summary of the December 2-4, 1985, meeting).

The Subcommittee recommended that

- The Organ Systems Program be continued and recommendations of prior group reviews be recognized

- The Organ Systems Coordinating Center as a single headquarters be continued, have periodic reviews, and recompetition

- A grant review process (i.e., of Requests for Applications, Requests for Proposals, and Program Announcements) be structured as recommended in the Brown report, "relevant to the program and not necessarily to cancer in general"

- The Subcommittee have the privilege of recommending funding to the NCAB Planning and Budget Committee

- The time flow be studied to shorten the interval between concept initiation and activation

- Neuro-oncology and Upper Aerodigestive Systems Working Groups, with appropriate funding recommendations, be added to the program.

The report included an amendment adopted by the Subcommittee which read as follows:

> The Organ Systems Program should be recognized and operated as a special program of the NCI equivalent to the Centers Program, the Clinical Trials Program, and the Training Program, including but not limited to:
>
> - A chartered review group within the NCI for review of Organ Systems Program grants (until such time as a committee is established, there could be an ad hoc review mechanism, for example).
>
> - Funds be set aside for the Organ Systems Program to fund relevant applications similar to the funds set aside for the Centers Program, Clinical Trials Program, and Training Program.
>
> - Develop the relation of the Organ Systems Program to a Board of Scientific Counselors, BSC, similar to that for the Centers Program, Clinical Trials Program, and Training Program in which the general concept rather than specific contents of proposals be reviewed, or, if necessary, develop a Board of Scientific Counselors representing the several Divisions of the NCI that the Organ Systems Program reflects.

The discussion following Dr. Hickey's report focused on whether the amendment should be accepted and whether the Neuro-oncology and Upper Aerodigestive Systems Working Groups should be added at this time. Dr. Powers, who had offered the amendment in the Subcommittee, moved acceptance of the report with the exception of the amendment, which he recommended be struck from the report. He did, however, express the view that the actions directed by the amendment would prove to be necessary for the success of the OSP.

The Board voted to accept the report without the amendment. The entire Organ Systems Program, including the new Neuro-oncology and Aerodigestive Systems Working Groups, will be reviewed by the Board at the December meeting.

Subcommittee on Innovations in Surgical Oncology--Dr. Ed L. Calhoon

Dr. Calhoon presented the report of the Subcommittee's February 4 meeting. The seven funded T32s and seven funded KO8s were noted and discussed. Other discussion focused on current interest in central nervous system tumors, chemotherapy and surgical oncology, Dr. Rosenberg's research, laser surgery as an acceptable modality, and use of monoclonal antibodies in the evaluation of axillary spread in breast cancer.

The report, with minor editorial corrections, was approved by the Board.

Suggestions for speakers and topics for future Board meetings raised by the Subcommittee are included in the Future Agenda Items noted below.

Based on documentation of and probes for these biochemical changes, the goals of Dr. Myers's research are to continue investigation into the ability to predict the development of drug resistance and ultimately to prevent or abrogate this series of biochemical changes. The following points were raised in discussion:

- The hypothesis that the capacity to inhibit glutathione transferase may inhibit the development of drug resistance should be further investigated.
- The effect of carcinogens (e.g., those in cigarette smoke) on response to anticancer therapy should be further investigated, as these carcinogens are postulated to induce the same enzyme systems that cause pleiotropic drug resistance.
- The duration of pleiotropic drug resistance may have important clinical implications, especially in persons who were treated for childhood leukemia and subsequently develop a second (resistant) malignancy as adults.
- The effects on the immune system of anticancer drugs and the consequent biochemical changes described by Dr. Myers are unclear.
- The P170 membrane marker found in a variety of human cell lines in culture may represent glutathione transferase associated with the cell membrane or in complex with another compound or by itself. However, no clinical correlation has been established between P170 and pleiotropic drug resistance.

VII. Low-Fat Trials in Preventing or Retarding Breast Cancer--Drs. Peter Greenwald, Maureen Henderson, William Insull, Jr., Ross Prentice, and Sherwood Gorbach

Dr. Greenwald opened the discussion of the low-fat trials in preventing or retarding breast cancer by distinguishing the two independent trials:

- The Nutrition Adjuvant Study--a study to determine whether a low-fat diet will reduce the recurrence rate in women with Stage II breast cancer, limited to the breast and adjacent lymph nodes
- The Women's Health Trial--a study to determine whether a low-fat diet will decrease the incidence of breast cancer in women at high risk.

The Policy Advisory Committee (a subcommittee of the Division of Cancer Prevention and Control's [DCPC] Board of Scientific Counselors), the Steering Committee made up of investigators of the Nutrition Adjuvant Study, and the NCI Executive Committee have recommended closing the Nutrition Adjuvant Study. This recommendation was based mainly on the fact that only 11 patients had been randomized to the trial by the end of January, and it does not appear feasible for the investigators, as presently organized, to reach their

projected 250 on schedule. During the discussion, it was noted that the decision of whether or not women in the trial should be given chemotherapy awaited recommendations from the NIH Consensus Development Conference in early September 1985, thus delaying accrual to the trial by several months.

A report on the Women's Health Trial followed. Dr. Greenwald and Dr. Insull, Chair of the Steering Committee of Investigators, presented an overview of the objectives and progress of the trial, reporting that the feasibility phase has been successfully completed and that enthusiastic support for the full-scale trial has been given by the DCPC Board of Scientific Counselors. NCAB approval to progress to the expanded, full-scale trial was requested.

Dr. Prentice, head of the Statistical Coordinating Unit for the trial, summarized the goals and results of the feasibility study as follows:

- 303 women, aged 45-69, were randomized to the feasibility study, with a ratio of 3:2 of intervention to control. The three clinics in operation are located at the University of Cincinnati, Baylor College of Medicine, and the Fred Hutchinson Cancer Research Center at the University of Washington at Seattle.

- The intervention women began an intensive program of dietary counseling with a goal of reducing percent calories from fat from the customary 40 percent down to 20 percent, while control women were asked to stay on their usual diet. Both groups underwent medical screening, including a mammogram and breast physical examination, as well as breast self-examination instruction.

- After 6 months, the intervention women had reduced the percent calories from fat from the original 39 percent down to 20.8 percent. This included a reduction of an average 425 calories/day, which was reflected in an average weight loss of 7.3 pounds. A modest, but significant reduction in total serum cholesterol was also seen in this group.

Based on the result of the feasibility phase, a full-scale trial involving the randomization of 30,000 women--12,000 in intervention and 18,000 in control--meeting the same eligibility criteria as in the feasibility phase was recommended. These criteria and sample size will allow an 80 percent probability of detecting an overall 18 percent reduction in breast cancer incidence in the intervention compared to the control group. Although the proposal covers a total 10-year study period, the NCAB was asked to support only the first 18 months due to uncertainty over identification of funds in future years.

The following comments and details of the study were discussed:

- One of the following risk factors must be present for eligibility: family history of breast cancer in a first-degree relative; nulliparous or age at first pregnancy 25 years or over; two or more benign breast biopsies; atypical hyperplasia or fibroadenoma diagnosed after age 45 years.

- The chosen age range of 45-69 years was debated. No attempt will be made to exclude premenopausal women. (In the feasibility trial, 80 percent were postmenopausal and 14 percent were premenopausal.)

- Subjects will not be stratified by risk factors, but rather on the basis of clinic and age. Race will not be considered.

- In the feasibility trial, the ratio of polyunsaturated to saturated fat in the diet was not changed, although the decrease in total fat consumption was dramatic.

- The rationale behind changing the ratio of intervention to control subjects from 3:2 in the feasibility trial to 2:3 in the full-scale trial was based mainly on cost effectiveness.

- The effects of any "drift" of the control group or of partners of women in the intervention group to a low-fat diet should be monitored. The fat intake of the control group will be monitored using a 4-day diet record every 2 years; 10 percent of these records will be analyzed for efficiency.

- Although analysis of the effect of the low-fat diet on other diseases, such as colon cancer, heart disease, and stroke, is not specifically planned at present, all mortality will be monitored and studied, possibly in conjunction with other Institutes such as the National Heart, Lung, and Blood Institute.

- Stopping the trial before the 10-year projected period would cause a reduction in the probability of detecting an overall reduction in breast cancer incidence.

Dr. Henderson then outlined the operation and costs of the trial. The three currently active sites would go into full operation in the first year (1986), 10 already selected sites in the second year, and another 10 to 17 sites in the third year. This would include randomization of 1,000 women in the first year, 15,000 by the end of the second, and 30,000 by the end of the third. Thus, the workload and costs will be extensive during this period and peak in the fourth year, with an estimated budget of $14.7 million, or approximately $490/randomized subject in the peak year. Women in the intervention group attend 16 group sessions in nutrition counseling in the first year, 9 in the second, 3 to 4 in the third and fourth years, and eventually 1 to 2 per year at the subject's request.

The following points were clarified in discussion:

- The total cost of the 10-year trial will be $98.7 million in direct costs and $20-30 million in indirect costs

- Many women in the feasibility phase took the program as an opportunity to lose weight, but they will reach a stable weight during the subsequent study phase

- As the trial itself provides medical screening, but not medical care, the majority of the participants will be middle to upper middle class women who have their own arrangements for medical care.

A motion to proceed with the full-scale Women's Health Trial was unanimously approved by the Board.

In the subsequent general discussion, several further points were raised about the accrual failure of the Nutrition Adjuvant Study. Mrs. Kushner felt that possible contributing factors were an NCI staff problem, lack of consultation with the Breast Cancer Task Force in writing the RFA, and coordination problems among the investigators. It was suggested that the feasibility of this trial be re-evaluated after the first year and a half of the Women's Health Trial (i.e., mid-FY 87), but the possibility of losing momentum, contingent on the current high level of public interest in the trial, was raised. The Chairman suggested that Mrs. Kushner prepare a brief statement to present to the Board (see Section IX. New Business).

VIII. Subcommittee Reports

Subcommittee on Cancer Information--Mr. Richard Bloch, Ms. Susan Hubbard, and Ms. Helene Brown

Mr. Bloch distributed the minutes of the February 2 meeting of the Subcommittee and introduced Ms. Hubbard's presentation on PDQ to the Board. The main concern of the Subcommittee regarding PDQ is the restriction on access, limiting codes only to physicians. This limitation on access is inhibiting both the dissemination of PDQ information as well as adequate promotion of the data base to the entire medical community. Ms. Hubbard indicated that Dr. Donald A. Lindberg the Director of the National Library of Medicine, would like to make PDQ available to all MEDLARS code holders. Commercial vendors have found that restricting PDQ access to physicians curtails their ability to promote PDQ and also requires expensive software to differentiate types of users. In addition, many health care organizations and science writers are currently denied access to PDQ.

The following points were raised in discussion:

- The AMA's position is that PDQ is a physician-oriented system and should remain as such.

- The NCI is proposing a pilot study at 20 medical schools to introduce PDQ into the curricula.

- Removing restrictions on access would allow many paramedical personnel, nurses, physicians' assistants, secretaries, and science writers to access PDQ and thus make promotion of the system easier.

- Allowing more users to access the data base would have no impact on cost.

IX. New Business

Ms. Brown poetically thanked the outgoing members of the Board for their time and effort in Board activities and presented each with a gift on behalf of the other members of the NCAB.

Nutrition Adjuvant Study--Mrs. Rose Kushner

Mrs. Kushner distributed her written recommendations that the concept of the Nutrition Adjuvant Study be approved by the Board and be resubmitted for development by the Breast Cancer Working Group of the Organ Systems Program. The following points were raised in discussion:

- The effects of a low-fat diet on recurrence rates in this very high risk group could be discovered much more quickly than in the Women's Health Trial, with fewer women and less expense to the NCI.

- Two investigators have expressed interest in developing a grant application and submitting it through peer review, but it was felt that the RFA mechanism should be continued.

- The design of the study should be re-evaluated, with particular consideration of a new design including Stage I breast cancer patients and the effect of a low-fat diet on recurrence in the contralateral breast.

- It is expected that 330 breast cancers will be diagnosed in the 12,000 study subjects in the Women's Health Trial. A study of the effect on therapy of continuing the low-fat diet in this group could be considered.

Mrs. Kushner's recommendation regarding the Nutrition Adjuvant Study was approved unanimously by the Board.

Future Agenda Items--Dr. David Korn

In addition to the distributed list of proposed NCAB agenda items, the following were suggested:

- Dr. Patrick Walsh, Chairman of Urology at the Johns Hopkins Medical School, should be invited to speak on the nerve-saving radical prostatectomy technique in prostate cancer

- A presentation on breast biopsies using laser surgery

- Drs. Jeffrey Schlom and Steve Larson, both at NCI, should be invited to speak on their research involving monoclonal antibodies to avoid surgical removal of the axillary lymph nodes

- A presentation on the issue of DRGs and prospective payment.

It was also suggested that orientation for new Board members should include a clear explanation of government funding mechanisms (e.g., RFA vs. RFP), and that future presentations be organized into shorter programs.

Finally, it was suggested that synopses of the minutes of Boards of Scientific Counselors be prepared for the information of NCAB members.

X. Closed Session

The second day of the meeting, February 4, 1986, was closed to the public as it was devoted to the Board's review of grant applications. Of the $174,795,590 requested, the NCAB approved $118,076,637.

XI. Adjournment

The 57th meeting of the NCAB was adjourned at 9:38 a.m., Wednesday, February 5, 1986.

5/8/86
Date

David Korn, M.D.