DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

NATIONAL INSTITUTES OF HEALTH

NATIONAL CANCER INSTITUTE

NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
May 14-15, 1990

Building 31, Conference Room 10
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[1]
May 14-15, 1990

The National Cancer Advisory Board (NCAB) reconvened for its 74th regular meeting at 8:30 a.m., May 14, 1990, in Building 31, 6th floor, Conference Room 10, National Institutes of Health (NIH). Dr. David Korn, Chairman, presided.

NCAB Members

Dr. Erwin P. Bettinghaus
Dr. Roswell K. Boutwell
Dr. David G. Bragg
Mrs. Nancy G. Brinker
Mrs. Helene G. Brown
Dr. John R. Durant
Dr. Gertrude B. Elion
Dr. Bernard Fisher
Dr. Phillip Frost
Dr. David Korn
Dr. Walter Lawrence, Jr.
Dr. Enrico Mihich
Mrs. Irene S. Pollin
Dr. Louise C. Strong
Dr. Howard M. Temin
Dr. Samuel A. Wells (Absent)

President's Cancer Panel

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

***Ex Officio* Members**

Dr. Miriam Davis, NIEHS
Dr. William Farland, EPA (Absent)
Captain Bimal Ghosh, DOD
Dr. John R. Johnson, FDA
Dr. Richard Lemen, NIOSH
Dr. Rachel Levinson, OSTP
Mr. Theodore Lorei, DVA
Dr. William F. Raub, NIH
Mr. James S. Robertson, DOE
Dr. Louis W. Sullivan, DHHS (Absent)
Dr. Andrew Ulsamer, CPSC
Dr. Ralph E. Yodaiken, DOL

Members, Executive Committee, National Cancer Institute, NIH

Dr. Samuel Broder, Director, National Cancer Institute
Dr. Richard H. Adamson, Acting Deputy Director, National Cancer Institute and 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 and Development Center
Dr. Alan S. Rabson, Director, Division of Cancer Biology, Diagnosis, and Centers
Executive Secretary, Ms. Iris Schneider, Assistant Director for Program Operations and Planning

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[1]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. The procedure does not apply to en bloc actions.

Liaison Representatives

Dr. Eve Ida Barek, Associate Program Director for Cell Biology, National Science Foundation, Washington, D.C., representing the National Science foundation for Dr. Maryanna Henkart.

Dr. William Brown, National Medical Association, representing the National Medical Association for Dr. Vivian Pinn-Wiggins.

Dr. Clarence Ehrlich, President, Society of Gynecologic Oncologists, representing the Society of Gynecologic Oncologists.

Ms. Delores Esparza, President, Oncology Nursing Society, representing the Oncology Nursing Society.

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

Dr. Ed Gelmann, Professor of Medicine and Pharmacology, Georgetown University, Washington, D.C., representing the American Society of Clinical Oncology for Dr. Raymond E. Lenhard, Jr.

Dr. Thomas King, Lombardi Cancer Center, Georgetown University, representing the American Association for Cancer Research.

Dr. Elaine Locke, American College of Obstetricians and Gynecologists, Washington, D.C., representing the American College of Obstetricians and Gynecologists for Dr. Warren Pearse.

Mr. Alan Mills, Coordinator for Public Affairs, American Cancer Society, Washington, D.C., representing the American Cancer Society for Mr. Alan Davis.

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

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

In addition to NCI staff members, meeting participants, and guests, a total of 46 registered members of the public attended.

I. CALL TO ORDER, OPENING REMARKS, AND CONSIDERATION OF JANUARY 29-30, 1990, NCAB MEETING MINUTES--DR. DAVID KORN

Dr. Korn, Chairman, called the 74th meeting of the National Cancer Advisory Board (NCAB) 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 invited members of the public who wished to express their views on any part of the meeting to do so by writing to Mrs. Barbara Bynum, Director, Division of Extramural Activities (DEA), within 10 days of the meeting.

Approval of the January minutes was postponed until the following day's session.

II. FUTURE MEETING DATES

Dr. Korn called Board members' attention to the following confirmed meeting dates: October 1-2, 1990; December 3-4, 1990; February 4-6, 1991; May 6-8, 1991; September 23-25, 1991; and November 25-27, 1991. To be confirmed are the following dates: January 27-29, 1992; May 4-6, 1992; September 21-23, 1992; and November 30-December 2, 1992.

Dr. Korn noted that although 3-day meetings continue to be listed, the 2-day format will be used routinely or whenever possible.

III. REPORT OF THE PRESIDENT'S CANCER PANEL--DR. ARMAND HAMMER

Dr. Hammer greeted members of the Board on behalf of the Panel and expressed appreciation for those in attendance who were serving until new appointments are made by the President. He pointed out that the lack of a quorum on the Board could have serious consequences for NCI and its programs, and he said the Panel would assist in any way possible to encourage the White House to rectify the situation.

The first meeting for 1990 of the President's Cancer Panel took place on April 5 at Columbia University's Comprehensive Cancer Center. The meeting was held in the new state-of-the-art hospital building with the capacity to treat 750 patients that was built with funds from the Milstein family. Dr. Hammer said the Panel was struck by the fact that such new construction is increasingly dependent on the generosity of private individuals due to the lack of construction funds in the NCI budget. He expressed a need for the cancer community to find ways to convince the administration and Congress that new construction and renovation of existing and out-of-date facilities are crucial to the continued viability of the National Cancer Program.

Recalling a comprehensive study of construction needs of the cancer community in the United States, which was sponsored jointly by the Panel and the American Cancer Society in 1985, Dr. Hammer noted that the situation has not improved since then and may have deteriorated. He expressed the hope that the recent developments in Eastern Europe and agreements between the United States and U.S.S.R. will enable leaders to rethink U.S. priorities in terms of real human needs as compared to perceived political objectives.

The theme of the Panel meeting at Columbia was "Cancer Causation and Prevention: From Basic Research to Community Action." Included on the agenda were basic research presentations on oncogenes, suppressor genes, and gene knock-outs by Dr. Stephen Goff and on cervical cancer and human papillomavirus by Dr. Saul Silverstein. Dr. Frederica Perera spoke on research

programs at Columbia in molecular epidemiology, an interdisciplinary approach that attempts to bridge basic science and clinical efforts. Dr. Hammer commented that this developing field is worthy of expanded study because of its potential for cancer prevention in large segments of the population.

The Panel meeting ended with a presentation by Dr. Harold Freeman of Harlem Hospital on the human dimension of the cancer problem in which he made the following points: a black male growing up in Harlem has a lesser chance of reaching the age of 65 than does a male growing up in the Third World country of Bangladesh; cancer is the second leading cause of death in Harlem; and lung cancer accounts for the majority of cancer fatalities. Dr. Hammer pointed out the need to translate knowledge of prevention strategies (e.g., stopping smoking) into practical application for this segment of society. While acknowledging that these are socioeconomic problems on a national scale requiring attention by all segments of society, Dr. Hammer stated that steps can be taken and noted that NCI, with the full support of the Panel, is already initiating programs to address the problems. He cited the Summer Enrichment Science Program for disadvantaged youths as an example, and he called for a renewed sense of commitment, combined with sufficient funding, for the task of effectively translating discoveries made through NCI's basic research efforts into therapy that is available to all.

Dr. Hammer reported that the next three meetings of the Panel are in planning stages and will include a meeting at the Brown University Cancer Center in Rhode Island. The Panel also expects to receive the final report of the Lasagna Committee, which will be made public after it is submitted to President Bush.

Dr. Hammer then recalled that at the January NCAB meeting he had announced that a total of $25 million had been raised by *Stop Cancer*: $12.5 million from the private sector and $12.5 million by a congressional appropriation of matching funds. He stated that he would be sending NCI a check later in the day in the amount of $2 million and expected to send the balance of $7 million from the private sector by September 30. These monies, together with the matching appropriation, will be used to fund scientists whose programs have been approved by peer review but are not funded because of NCI budget constraints.

Finally, Dr. Hammer looked forward to savings in the budget that could result from the upcoming summit and recent happenings in Eastern Block countries and might very well mean a brighter future for cancer research. He quoted cancer statistics--500,000 deaths per year attributed to cancer, a disease that afflicts 1 out of every 3 or 4 persons and is overtaking heart disease as the leading cause of deaths--to indicate the scope of the task ahead of the cancer community.

IV. REPORT OF THE DIRECTOR, NATIONAL CANCER INSTITUTE-- DR. SAMUEL BRODER

Dr. Broder thanked Dr. Hammer for his efforts on behalf of the National Cancer Program and particularly for the good news of contributions *Stop Cancer* will make to the National Cancer Program at large. He added his thanks to those of Dr. Hammer and expressed gratitude to NCAB and Panel members who continue to serve until their successors are appointed.

Dr. Broder reported with sadness on the death on March 24 of Dr. Barney Lepovetsky, Director, Office of Technology Development. He noted Dr. Lepovetsky's career in many areas of

the National Cancer Program, most recently as an indispensable force in the implementation of the Federal Technology Transfer Act.

Dr. Broder then congratulated recipients of honors and awards as follows: Dr. Gertrude Elion, who was elected to the National Academy of Sciences, and the NCI Grants Administration Branch, headed by Mr. Leo Buscher, which received the Public Service Excellence Award from the Public Employees Roundtable. He announced the following staff changes: Dr. Marvin Kalt was appointed Deputy Director, DEA; Ms. Winnie Lumsden, NCI Committee Management Officer, DEA, is retiring; Mr. Kenneth Brow was appointed Chief of the Research Facilities Branch, Division of Cancer Biology, Diagnosis, and Centers (DCBDC); and Dr. Richard Ungerleider's appointment as chief of the Clinical Investigations Branch, Division of Cancer Treatment (DCT), is now permanent. He then announced that Dr. Hammer would be celebrating his ninety-second birthday on May 21, and he extended congratulations on behalf of all in the National Cancer Program. He acknowledged the debt of gratitude owed to Dr. Hammer for his ceaseless efforts for the Program as part of the President's Cancer Panel, and for taking NCI's case directly to the President.

As a followup to Dr. Hammer's comments on the Panel meeting at Columbia University's Comprehensive Cancer Center, Dr. Broder noted that the presentations, which spanned oncogene research to community outreach activities, highlighted NCI's commitment to the cycling of research from the laboratory to the clinic and back again.

Dr. Broder reported that the Summer Science Enrichment Program would begin its first season at Hood College from July 1 to August 10. He noted the enthusiastic response that was accorded this initiative to provide children of poor and underserved populations an opportunity to consider science careers; applications were received from many parts of the country. Approximately 100 young people will attend the first session. Dr. Broder thanked Dr. Claudia Baquet and her staff for developing the program in record time.

Turning next to an update on the research of Drs. Steven Rosenberg and R. Michael Blaese of the DCT and Dr. W. French Anderson of the National Heart, Lung, and Blood Institute (NHLBI), Dr. Broder recalled that these investigators had developed a number of adoptive immunotherapies for treatment of cancer. The adoptive transfer of lymphokine-activated killer (LAK) cells or tumor-infiltrating lymphocytes (TILs) has been shown to mediate the regression of established advanced malignancies in some patients. Investigators in the Surgery Branch of DCT have also developed certain of these therapies on an experimental basis; among them were the first gene transfer experiments ever conducted in humans. The first study used a potentially neutral gene, the neomycin-resistance gene, to trace TILs in the body to see if they targeted the tumor and survived long enough to have a therapeutic benefit. Permission was granted to treat 10 patients. The gene-engineered cells have been tracked in the circulatory systems and at the tumor sites of the 7 patients treated to date. All 7 patients have done well, with no side effects specifically attributable to the gene transfer experiment; the cells have persisted in the circulatory system for up to 200 days and have been found at the tumor site after 2 months in some patients; and there have been antitumor responses in about half of the patients, which would be consistent with previous experience using standard TIL therapy.

Dr. Broder stated that NIH, in the previous month, had lifted the restriction on the number of patients who could be treated under these experimental protocols. The next steps will include modifying cells with genes for a known antitumor substance, such as tumor necrosis factor. Dr. Broder pointed out that this historic work paves the way for the use of lymphocytes to fight

other diseases not necessarily connected with cancer, such as hemophilia or adenosine deaminase (ADA) deficiency, a genetically determined severe immune disorder. He noted that Drs. Rosenberg, Blaese, and Anderson, as the next phase in the gene transfer experiments, have requested permission from the NIH to begin gene therapy in children with ADA deficiency. Their proposal is to administer lymphocytes with a gene inserted to induce cells to produce ADA. If regulatory approvals are granted, this protocol is expected to begin in fall 1990.

Dr. Broder announced that Dr. Richard Adamson will be Acting Deputy Director, NCI, until a replacement is found for Dr. Maryann Roper. He thanked Dr. Adamson for assuming the role in addition to his duties as Director, Division of Cancer Etiology (DCE). He welcomed suggestions from the Board of candidates for the Deputy Director position, which is to be advertised about June 4 and for which applications will be accepted until about July 6. He emphasized that a broad-based search is to be conducted for a candidate with high professional qualifications and demonstrated abilities to originate, administer, and coordinate the programs of NCI. Search Committee members are Dr. Alan Rabson, chairperson, Dr. Jane Henney (Vice-Chancellor for Health Programs and Policy at the University of Kansas), Dr. Kenneth Olden (Director of the Howard University Cancer Center in Washington, D.C.), Dr. Adamson, and Dr. Vita Beaven (Assistant Director for Program Coordination in the Office of the Director, NIH).

Dr. Broder reviewed agenda items noting that Dr. William Raub, Acting Director of NIH, and Dr. Jarrett Clinton, Acting Administrator of the new Agency for Health Care Policy and Research (AHCPR) would address the Board, and Dr. Peter Greenwald, Director, and staff of the DCPC would present a briefing on the latest SEER data on cancer incidence and mortality to provide a perspective for future planning by NCI.

Dr. Broder reported that Dr. Raub had requested from NCI a funding plan for a portion of the monies appropriated to NIH and set aside for certain kinds of construction. Of the high-priority NCI construction projects proposed, Dr. Raub has concurred with the funding of the University of Southern California and University of Wisconsin proposals. Dr. Broder noted that the remaining funds will be competed for through an RFA that is under way now and that will include many different types of construction projects.

Turning next to a congressional update, Dr. Broder called attention to an April 30 hearing by a House of Representatives Subcommittee, headed by Representative John Dingell, on a conflict-of-interest and possible Title 18 violation in an NCI laboratory. General Accounting Office (GAO) investigators have provided sworn statements alleging possible violations of Federal law on the part of one NCI employee. Dr. Broder declined to comment further as the matter is currently before a Federal grand jury and personnel actions are in process. However, he said, public aspects of the information contained in GAO and NIH testimony before the committee would be made available to interested Board members and members of the public through NCI's Legislative Liaison, Ms. Dorothy Tisevich. Dr. Broder stated that NCI and NIH will continue to cooperate with the investigators in this matter, and he noted that NIH is instituting several changes in contracting and other procedures, some of which would be discussed later in the meeting by Dr. Raub.

Dr. Broder noted that he would testify on NCI's biomedical research contribution at the hearing on new research and progress on breast cancer to be held on May 16 by the House Select Committee on Aging (Representative Mary Rose Oakar, Chair). Others scheduled to testify include Mrs. Marilyn Quayle; Mrs. Nancy Brinker, as a representative of NCAB and of the Komen Foundation; Mr. Harvey Kushner; Ms. Isabel Hammond, Director of the American Italian

Foundation for Cancer Research; and Dr. Marc Lippman, head of the Lombardi Cancer Center at Georgetown University.

Continuing with the congressional update, Dr. Broder noted that the appropriations hearings before the House and Senate for fiscal year 1991 have been completed but information on the budget markup was not yet available. He indicated that a Gramm-Rudman-Hollings (GRH) sequestration could occur in fiscal year 1991 and if it does, NCI would be affected. As a point of information for grantees and recipients of NCI funds through other mechanisms, Dr. Broder stressed that the terms of a GRH sequestration, if implemented, are essentially nonnegotiable.

Noting the importance of consensus development conferences as a link in the transfer of research findings, Dr. Broder reviewed the conclusions of a consensus development conference on adjuvant treatment for patients with colon and rectal cancer, which was sponsored by NCI and NIH in April. The consensus development panel concluded that for colon cancer, future adjuvant clinical trials for stage III patients should no longer contain a surgery-only arm; optimal adjuvant therapy for stage II and III colon cancer has not been completely devised and continued clinical trials in this disease are essential to discover more effective adjuvant therapies; stage III patients who are unable to enter a clinical trial should be offered adjuvant 5-FU and levamisole as administered in the intergroup trials unless appropriate contraindications exist. Dr. Broder said that the panel did not recommend any specific adjuvant therapy at this time for stage II colon cancer patients outside of clinical trials.

For rectal cancer, the panel recommended that no adjuvant therapy should be undertaken for stage I patients but that stage II patients should receive adjuvant treatment that combined postoperative chemotherapy and radiotherapy. This combination of modalities has been shown to improve local control and survival. Dr. Broder pointed out that one of the most effective regimens was 5-FU combined with methyl-CCNU and high-dose pelvic radiation, although chronic toxicity considerations relating to methyl-CCNU remain an area for future research. He stated that the entry of stage II and III patients into clinical trials is encouraged because the trials are designed to improve the prognosis of patients with these stages of disease. Dr. Broder announced a consensus development conference on the treatment of early stage breast cancer to be held June 18 to 21, and he invited NCAB members to attend.

Turning next to the issue of clinical updates, Dr. Broder recalled that Dr. Korn had convened a meeting following the February NCAB meeting to discuss guidelines for the release of clinical research information. He thanked Dr. Korn and the members in attendance at that meeting for the draft guidelines they developed which Dr. Durant would present later in the meeting. He commented on the high degree of consensus among the group regarding the use of clinical updates or equivalent mechanisms for dealing with important information exchanges.

As a related issue, Dr. Broder reviewed the results of a survey conducted by the American College of Surgeons (ACS) following the NCI clinical update for adjuvant treatment of colon cancer issued in October 1989. The update was based on an intergroup study headed by Dr. Charles Moertel as part of the NCI Clinical Cooperative Group Program. The ACS survey showed that many surgeons who treat Dukes' C colon cancer have incorporated adjuvant therapy with levamisole and 5-FU in their treatment regimens. Of the 4,000 physicians who received the survey, nearly two-thirds responded: (1) 91 percent who received the update read it; (2) nearly three-fourths of those who read it reported changing their practice as a result; (3) the remainder did not change, but 17 percent reported that they were already using the recommended treatment, 10 percent were waiting for published information, and 5 percent were waiting for a consensus

development conference; and (4) 93 percent approved of using clinical updates to disseminate findings with major public health significance. Dr. Broder expressed satisfaction with these results and concluded that the clinical update clearly provides NCI an avenue for reaching physicians and surgeons quickly with research findings that promise to have a major impact on public health.

In concluding his remarks, Dr. Broder thanked Dr. Durant and the Subcommittee on Cancer Centers for comments and advice on the NCI Five-Year Plan for Cancer Centers under development, a second draft of which would be presented later in the meeting. He postponed his review of the NCI budget and draft of the 1992 bypass budget until the meeting of the Subcommittee on Planning and Budget.

V. LEGISLATIVE UPDATE--MS. DOROTHY TISEVICH

Ms. Tisevich referred Board members to the package that was distributed highlighting recent legislative activities of interest. She began with an update on NIH/NCI reauthorization, noting that preliminary indications are that Senate hearings on reauthorization for NIH programs are not being planned. Rather, it is expected that the Senate may introduce a bill reauthorizing existing authorities with few, if any, modifications. However, it is anticipated that House reauthorization hearings will be held in mid-to-late June. Potential topics for consideration in the House hearings include: the inclusion of women in clinical trials, prevention activities, minority and underserved populations, medical rehabilitation research, financial conflict of interest, fetal tissue transplantation research, laboratory break-ins, a senior health research service, and training issues. On the issue of the inclusion of women in clinical trials, Ms. Tisevich mentioned that recently the General Accounting Office concluded a review of NIH-funded clinical trials to determine the degree to which trials are designed to encourage the participation of women, as well as their actual participation. The results of the review, undertaken at the request of Representatives Snowe, Schroeder, and Waxman, are not yet available.

Next, Ms. Tisevich discussed the waiver from certain Government Printing Office (GPO) publication requirements granted to NIH in 1988, which allows NIH to contract for printing without GPO approval. Since then, several bills have been introduced prohibiting contracting with commercial vendors for publishing without prior GPO clearance. Legal counsel is being sought to determine how these provisions will affect NCI publishing activities. She also noted that in 1985, NCI authorities were extended for a 3-year period, but in 1988 the period was reduced to 2 years. This time, NCI is hoping for a longer authorization period. Also mentioned were recent demonstrations by animal rights groups on the NIH campus. This year the animal rights groups were joined by a group called Incurably Ill for Animal Research, which presented a proresearch message to media personnel covering the demonstration.

Ms. Tisevich called attention to statements by House members on breast cancer awareness that were included in the legislative package. Also included in the package were: a comparison of several mammography screening bills; reports of recent hearings at which NCI staff testified; and a comparison of bills establishing alternative pay systems for senior scientists.

Dr. Korn brought up his testimony before the Senate Appropriations Subcommittee in March on the NIH/NCI budget. He commented on the high level of congressional support for NIH. He observed, however, that some of the questions indicated a lack of understanding of the boundaries between basic research and how scientific discovery is moved along, when appropriate, into

commercial development. He also pointed out that the House Budget Committee report had set a mark for NIH considerably above the President's request.

VI. GUIDELINES ON REVIEW OF LARGE INVESTIGATOR-INITIATED GRANTS--MRS. BARBARA BYNUM

As requested by the Board at the January 1990 meeting, Mrs. Bynum reported on progress made on the development of guidelines for review of large investigator-initiated grants. She stated that the NCI supports the NIH policy that all grant applicants should consult with ICD staff about the appropriateness of any applications that are large, multi-institutional, or protracted in time before submitting the applications. She noted that NCI staff continue to inform Board members before review whenever any R01 applications in excess of $1 million have been accepted. However, she stated that the issue of developing a uniform policy for review of large grants that is acceptable to all ICDs has not yet been resolved and negotiations with NIH are continuing.

In discussion, Mrs. Bynum stated that it remains unclear whether or not the guidelines that are being developed will apply to all Institutes within NIH. She noted that questions are being raised about the appropriateness of various budget categories for clinical trials. She reiterated that the NCI staff will continue to bring all large grants to the Board's attention prior to establishing a policy.

VII. WORKSHOP ON CLINICAL TRIALS: INFORMATION DISSEMINATION AND PROPOSED GUIDELINES--DRS. DAVID KORN, MICHAEL FRIEDMAN, AND JOHN DURANT

Dr. Korn began by referring the Board to the summary of the workshop on clinical trials information dissemination prepared by Dr. Joyce O'Shaughnessy that was distributed to all Board members. He explained that Dr. Durant had agreed to report to the Board on the development of guidelines on the issuance of "clinical updates" and that Dr. Friedman had been instrumental in organizing the workshop. In Dr. Durant's absence, Dr. Korn briefly summarized the discussions at the workshop, noting that a majority of the workshop participants agreed that issuing updates was a valid means of disseminating information on clinical trials. The questions at the workshop focused on when, under what circumstances, and how the NCI should initiate the release of information on results from clinical trials. Concerns were raised about premature dissemination of results, the perception of NCI as a powerful participant in the field of cancer research and treatment issuing dogmatic statements, and issues of academic or professional freedom in deciding when and how to report results.

Dr. Korn then referred the Board to copies of the current working draft guidelines distributed to all members that Dr. Durant had prepared, based on discussions at the workshop. He pointed out that there is a continuing concern expressed in the draft that, to the maximum degree possible, signals should be built into protocols that will alert the participants to the appearance of results that would merit special consideration, and that participants, the sponsor, and the NCI should have agreed upon procedures to decide when and how release of information about such results should occur. He commented that the recent release of information from the National Institute of Neurological Disorders and Stroke on the results of a study that indicated that high-dose intravenous therapy with corticosteroids early after spinal cord injury may have a profound beneficial effect did not include adequate information to allow physicians to implement this therapy. He pointed to this as an example of the unresolved issue regarding the optimal

means of announcement and the amount of data that should be disseminated with an announcement to make the announcement useful.

Dr. Friedman concurred with Dr. Korn's summary of the workshop discussions, emphasizing the issues of having confidence in the data reported and in the procedures for disseminating the data. He stated that the draft guidelines stress collegiality, quality control and assurance aspects of studies, and mechanisms of information dissemination. He emphasized the importance of reporting clinical findings thoroughly and accurately so that such reports reflect scientific excellence in the conduct of clinical trials. He stated that the way to measure the success of an announcement of study results is based on assessments of accuracy and effectiveness. He referred to the two clinical announcements issued thus far by the NCI on breast and colon cancer study results, and reviewed the activities that led to the announcement of results from the colon cancer study with 5-FU and levamisole, which demonstrated the accuracy and validity of these data. He stated that the issue of whether the announcement of the colon cancer study results was effective in that it influenced practice in the community, accrual to clinical trials, and the cure rate, for example, was still unresolved. He concluded by emphasizing that such announcements are not Federal mandates, but rather announcements in the educational sense to promote better health. He welcomed comments from the Board members on the draft guidelines.

Dr. Durant reviewed the draft guidelines, first stating that a large majority, but not all, of the workshop participants agreed that issuing announcements concerning important clinical developments is a good idea. He noted that the guidelines reflect the feeling expressed at the workshop that as a general rule an announcement should be based on at least two studies, as was the case with the announcement after the colon cancer study, which was a confirmatory study. However, the guidelines left open the possibility that an announcement could be made on results from a single study showing a medically important benefit. Regarding publication of study results, Dr. Durant noted that some journals now have methods for making electronically available the text of clinical articles, and he stated that the workshop participants agreed that an article including the study results should be peer reviewed and accepted before an announcement is made. He pointed out that the guidelines do, however, include allowance for an exception for the NCI Director to waive this and other steps for developing announcements in the case of an unexpected and urgent need for information dissemination.

Dr. Durant pointed out that any announcement would be subject to agreement with the investigators and review by the Executive Committee of the NCI, the Chairman of the NCAB, the Chairman of the Board of Scientific Counselors (BSC) for the DCT, and the PDQ Editorial Board, which is an extramural group of clinical experts. The guidelines also address what factors in addition to increased survival would provoke an announcement; examples include the finding of an equally effective, but less expensive or less toxic treatment than the standard therapies.

The following points arose in discussion of the draft guidelines:

- A significant improvement in survival or some equivalent endpoint in a common clinical circumstance should form the basis for a clinical announcement. The specific number of cases that would be affected is intentionally not delineated in the guidelines.

- A clinical announcement could be based on studies other than a randomized trial, as for example, Phase II studies.

- An announcement could be justified prior to publication of the results in a peer-reviewed journal, particularly if the publication is inordinately delayed.

- The criterion for a lost to followup rate of 5 percent or less as delineated in the guidelines could prove unnecessarily restrictive in studies such as large, long-term trials.

- An overall purpose of such announcements is to address one of the primary responsibilities of the NCI--to ensure that its knowledge is disseminated equally to all of the public, that is, to create a "level playing field" for all patients and doctors by disseminating information on results of clinical trials.

- Ensuring the credibility of each announcement is crucial to the future effectiveness of this mechanism for disseminating information.

- Peer review of study results by the groups listed in the guidelines and including review by a data monitoring committee is essential before issuing an announcement based on the study results. Relevant extramural organizations (e.g., ASCO, American College of Surgeons, American Cancer Society) would also be offered an opportunity to review the draft announcement.

- The frequency of making clinical announcements is difficult to predict, but issuance of such announcements would probably be an unusual event. It was noted that two announcements had been made over the previous 3-year period.

- The public's expectations for access to information has increased considerably over the years. Thus, although such clinical announcements may not have been as necessary in previous years of clinical trials, they fill an important need in today's society.

- If the clinical announcements are to be drafted by a subcommittee of the DCT BSC and the NCAB, including skilled investigators and statisticians selected by the Director, NCI, and the study principal investigator, then subsequent review, as delineated in the draft guidelines, by the chairmen of the NCAB and the DCT BSC seems unnecessary. Dr. Durant will delete this review component from the guidelines.

- The therapy described in an announcement must be available to doctors before issuing an announcement.

Dr. Durant will revise the draft guidelines and mail copies to Board members for review, with a deadline for return of comments.

VIII. PROGRESS IN THE TREATMENT OF THE CHRONIC LEUKEMIAS--DRS. BRUCE CHABNER AND MICHAEL GREVER

Dr. Chabner introduced the presentation on progress in the treatment of the chronic leukemias by noting that the drugs that have been developed were studied in the NCI-sponsored drug development program under contract or in clinical trials and that Dr. Grever, in his previous position at Ohio State University, played a major role in the development of two of the new therapies.

After acknowledging the important contributions that Drs. Montgomery and Elion had made in the development of new treatments for chronic leukemias, Dr. Grever illustrated the classification of the various forms of the chronic B and T lymphoid leukemias. His presentation focused on chronic lymphocytic leukemia (CLL) and hairy cell leukemia (HCL).

Dr. Grever explained that early research on the mechanisms of lymphopenia in children with a complete absence of adenosine deaminase and severe combined immune deficiency disease led to research on adenosine deaminase inhibitors as a pharmacologic approach to the lymphoid malignancies. He illustrated the metabolic pathways in which adenosine deaminase is involved. Clinical studies in this area focused on deoxycoformycin (dCF, pentostatin), which is a potent inhibitor of adenosine deaminase, and is structurally similar to the natural substrates, adenosine and deoxyadenosine, for the enzyme.

Dr. Grever described studies conducted at Ohio State to determine the kinetics of enzyme inhibition after intravenous administration of dCF that showed that the inhibition of adenosine deaminase in the bone marrow and in circulating peripheral blood lymphocytes by dCF in leukemia patients was dependent both on the dose administered and on the patient's intrinsic cellular adenosine deaminase activity. He illustrated that in a group of patients with various forms of leukemia, those types of leukemias that are associated with a high proliferative index have relatively high adenosine deaminase activity compared to the more indolent forms of leukemia. High doses of dCF were required to produce complete inhibition of the enzyme in acute leukemias; however, because high doses of the drug caused severe and unacceptable toxicities (i.e., nephrotoxicity, CNS toxicity, end organ toxicity), its use in acute leukemias was not pursued. The low doses that were well-tolerated were pursued in the chronic leukemias. The toxicities that accompanied high doses of dCF were associated with a marked elevation of deoxyATP (dATP) and a marked decrease in ATP in the peripheral blood cells, but it remains unclear whether this is the mechanism of tumor cell cytotoxicity of dCF. Dr. Grever also noted the finding that dCF is excreted almost completely unchanged in the urine, and thus the pretreatment renal function of patients to be treated with dCF must be evaluated carefully.

Dr. Grever reported the results from the first publication from Ohio State on dCF trials showing a response rate of approximately 18 percent to dCF in a group of 28 heavily pretreated CLL patients. He added that this finding was confirmed by a multi-institutional Cancer and Leukemia Group B study, in which the response rate to dCF was about 26 percent. He illustrated several case records of patients treated with dCF, and commented that some dramatic responses have been seen in both T-cell and B-cell forms of CLL. However, he stated that dCF has had a major impact on clinical medicine because of the clinical results seen with HCL.

Dr. Grever presented the results from a general review published several years earlier in the *Annals of Internal Medicine*, in which Dr. Bruce Cheson compared the overall complete response rate of 10 percent with alpha-interferon to that of 60 to 90 percent with dCF in HCL. Dr. Grever summarized some of the larger studies of dCF in HCL that showed complete remissions (CRs) varying from 50 to 90 percent in the various studies. He noted that in studies in Canada and at Ohio State a higher CR rate was achieved using a lower total dose of the drug. One patient, who relapsed and was retreated with dCF a second time, responded, but it remains unknown whether or not resistance to dCF develops over time. Dr. Grever also noted that studies at Ohio State to determine the effect of dCF on the lymphocyte subpopulations of treated patients showed not only a reduction in the total number of lymphocytes but also a marked reduction in the CD4 subpopulation compared to the CD8 subpopulation. This reduction of CD4 to CD8 subpopulations

is comparable to that in AIDS patients, but a review of 218 treatment courses of HCL patients at Ohio State did not reveal an undue number of serious infections in patients treated with dCF.

Dr. Grever concluded his discussion of dCF studies by informing the Board that the data from an intergroup study of 356 patients of alpha-interferon versus dCF as initial treatment of HCL are being analyzed, and another study of dCF is ongoing in splenectomized HCL patients. He noted that a substantial partial remission (PR) had been seen in a patient with cutaneous T-cell lymphoma and that dCF clearly has activity in both B- and T-cell malignancies. The exact mechanism of activity of dCF, however, remains unknown.

Dr. Grever then turned to a description of studies of fludarabine, which has shown significant responses in patients with CLL and indolent forms of non-Hodgkins lymphoma. The dose-limiting toxicity of this compound is myelosuppression, and although low doses are relatively safe, large doses of the drug can cause unacceptable neurologic toxicity. In one study conducted by Dr. Grever within the Southwest Oncology Group of 32 heavily pretreated CLL patients, one patient achieved a CR and several other patients showed dramatic improvement. The response rate in another study at M.D. Anderson of 75 heavily pretreated CLL patients was approximately 50 percent. CRs were seen in about one-third of CLL patients in a group without prior therapy. Results in trials of non-Hodgkin's lymphomas showed a response rate of about 25 percent, with all of the responses occurring in an indolent form of non-Hodgkin's lymphoma. Dr. Grever noted that the NCI is organizing a series of pilot studies of combinations of fludarabine with other agents (e.g., chlorambucil) in preparation for conducting a prospective Phase III trial in CLL.

Turning to a description of studies of 2-chlorodeoxyadenosine (2-CDA), Dr. Grever first illustrated its structure, remarking on its striking similarity to other drugs previously found active in the indolent lymphomas. 2-CDA has been the subject of studies, mainly at the Scripps Institute, of CLL and HCL. In one study in CLL patients in which 2-CDA was given as a continuous infusion over 7 days in one to four courses, 10 of 18 patients showed some form of clinical improvement. Another recent study in HCL of one course of 2-CDA treatment over 7 days showed CRs in 11 of 12 patients and a PR in the remaining patient.

In closing, Dr. Chabner commented on the importance of advances in the treatment of CLL, which is the most common form of leukemia in older people (i.e., 10,000 cases/year), and in non-Hodgkin's lymphoma, which is becoming more common.

IX. SUPPORT OF FOREIGN GRANTS--MR. PHILIP D. AMORUSO

As requested by the Board, Mr. Amoruso reviewed the NCI grants portfolio as it relates to foreign grants, noting that the National Cancer Act requires the Director of the Institute to support research and training of foreign nationals. Guidelines for awarding foreign grants stipulate that the project (1) present some special opportunity, such as a highly talented scientist, an unusual population, or exceptional environmental conditions, either not available in the United States or augmenting existing U.S. research; (2) has specific relevance to the objectives of NCI and has the potential for promoting health sciences in the United States; and (3) is at or above the 50th percentile in the priority scores for approved applications at that review cycle.

Referring to the written report in the Board book, Mr. Amoruso pointed out that foreign grants constitute approximately 1 percent of all NCI grants and contracts and that this level of expenditure has remained stable for the past 3 years. He observed that funding for contracts increased by 1 percent from 1987 to 1988 but decreased a little between 1988 and 1989.

In response to a question about the nature of foreign contracts, Mr. Amoruso pointed out that many of them are awarded when the government needs to have a particular area investigated and foreign components can be found that are germane to the study, e.g., collection of natural products for the drug development program. To put into perspective the issue of distribution of NCI foreign contract funds, it was noted that Finland received 52 percent of current foreign contract funds to perform clinical trials sponsored by the Division of Cancer Prevention and Control (DCPC).

Finally, Mr. Amoruso noted that investigators in Canada lead in receipt of NCI grants and that NCI makes grants to international organizations based in other countries. For example, NCI makes grants to the World Health Organization and IARC in France, to the UICC in Switzerland, and to the EORTC in Belgium.

On behalf of the Board, Dr. Temin stated that the written report and presentation on foreign grants were very informative and helpful in dispelling concerns, particularly the fact that foreign applications must fall within the normally established payline for the fiscal year and constitute only 1 percent of the total grant portfolio.

X. REMARKS BY THE ACTING DIRECTOR, NATIONAL INSTITUTES OF HEALTH--DR. WILLIAM RAUB

As a followup to his discussion of the NIH draft conflict-of-interest guidelines at the January 1990 Board meeting, Dr. Raub explained that as a result of the issuance of the draft guidelines in 1989 and subsequent workshops and discussions, Dr. Sullivan has called for a carefully delineated notice of proposed rule making (NPRM) on this general topic. Dr. Raub explained that the NPRM is the first step toward development of a regulation and gives the interested public the opportunity for input before any final decision is made about a regulation. He noted that the DHHS General Counsel had also stressed a need for HHS action and leadership on this topic, and that the Office of Science and Technology Policy (OSTP), speaking for the White House, had urged that there be a particular focus on clinical trials. Members of Congress have reiterated their interest in the topic and indicated their plan for continuing oversight of the Executive Branch's effort. The NIH recently completed the analysis of the more than 700 public comments that were received on the draft guidelines.

Dr. Raub stated that in response to Dr. Mason's request that NIH, in conjunction with the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA), take the lead in responding with an appropriate draft NPRM, NIH has divided the issues into two categories: development and evaluation of commercial products, and management of awardee inventions. Dr. Raub noted that a draft NPRM on the development and evaluation of commercial products was being developed quickly along the lines of the instructions received from the Secretary and encouraged by OSTP. This NPRM will be provided to Dr. Mason and, if it proves acceptable, will be made available for comments from the affected scientific, business, and other communities.

Dr. Raub indicated that the second category, the management of awardee inventions, is a broader area about which there is considerable misunderstanding. He stated that much of the misunderstanding concerns the failure to distinguish between the rights of the individual scientists and the rights of the awardee institutions. For the purpose of an award, the NIH legally and administratively deals with the institution, and there are certain institutional rights that approximate, if not overlap, those traditionally perceived as the rights and intellectual property of individual scientists. Dr. Raub also drew attention to the fact that highly successful models of

productive and cooperative interactions between awardee institutions and private industry exist in effecting technology transfer, but that such interactions appear to be perceived as negative. Overall, he expressed the opinion that many issues associated with invention management are not truly conflict-of-interest issues and that the positive technology transfer interactions should be accentuated. He explained that the current NIH view is, therefore, that NIH should focus on developing the NPRM for the narrower sphere of development and testing of commercial products. Once that is accomplished, NIH will join with the research community, particularly universities, in identifying the issues around invention management, and promote and accentuate positive models to minimize, if not eliminate, the issues of conflict of interest.

In response to comments by Drs. Korn and Durant, Dr. Raub stated that it is likely that any new conflict-of-interest rules can be addressed within a traditional assurance framework rather than by additional reporting requirements for awardee institutions. For Dr. Mihich, Dr. Raub clarified the meaning of invention management by explaining the patent and trademark amendments of the early 1980s giving the first rights to an invention to the institution that receives a research award from a U.S. Government agency, that is, not only the opportunity, but also the obligation, to pursue all commercial outlets and seek patents and licensing agreements. He noted that the NIH is one of the funding agencies that retains the right of "march in" (i.e., to take back first rights) if commercial outlets for an invention with commercial promise are not being pursued, but that he was not aware that the DHHS had ever taken back an invention right. He stated that although issues have arisen at some institutions where the rights of the university have conflicted with those areas seen as exclusively the intellectual property of the involved scientist, many excellent models of cooperative management of invention rights exist. He referred to the Cooperative Research and Development Agreements (CRADA) being pursued by NIH to promote cooperative agreements between the NIH and private industry.

In response to a question from Dr. Korn on problems regarding the issue of data handling, Dr. Raub stated that NIH had traditionally promoted the policy that research results produced with public funding be made readily available to the public. He added that he did not foresee NIH issuing regulations on data records management (e.g., notebooks, printouts) for public-funded studies. He concluded by informing the Board that the intramural program had recently developed a statement of guidance to intramural scientists that delineates basic principles of good scientific practice but does not address specifications about the nature of data management. He assured Dr. Temin that this statement could be made available to Board members.

XI. CANCER STATISTICS REVIEW--DRS. PETER GREENWALD AND EDWARD SONDIK

Dr. Greenwald introduced the presentation on cancer statistics by emphasizing the importance of the cancer statistics and surveillance program as a fundamental component of the data systems that are used to manage NCI programs and to focus priorities. He outlined the organizational structure of the DCPC Surveillance Program, which was established by Dr. Sondik and is currently headed by Dr. Brenda Edwards, and explained that the Program includes three branches: Applied Research (Chief, Dr. Larry Kessler); Cancer Statistics (Chief, Dr. Benjamin F. Hankey), which includes the Surveillance, Epidemiology and End Results (SEER) Program; and Computer Systems (Chief, Dr. Thomas Marciniak).

Dr. Sondik provided an overview of the new annual statistics review, as published in the *Cancer Statistics Review 1973-1987* distributed to all Board members. Beginning with the sources of the data, Dr. Sondik explained that the cancer incidence data are provided by the SEER Program, the cancer mortality data from death certificates are from the National Center for

Health Statistics, and the population data are from the Bureau of Census. He illustrated the nine SEER Program geographic areas, which cover approximately 10 percent of the United States and include several metropolitan areas and entire states, ten rural counties, and the American Indians in Arizona. He reviewed several basic definitions underlying the statistics, as follows:

- incidence--annual new cancer cases per 100,000 persons
- mortality--cancer deaths per 100,000 persons
- observed survival--percentage of patients alive 5 years after diagnosis
- relative survival--percentage of patients who would be alive 5 years after diagnosis if cancer and associated diseases were the only causes of death.

Dr. Sondik pointed out that cancer is the second leading cause of death in the United States, accounting for 22 percent of all deaths, behind heart disease and ahead of cerebrovascular disease. He listed the four leading cancer sites in terms of both incidence and mortality as lung and colorectal cancers followed by breast and prostate, with bladder fifth in terms of incidence, pancreatic cancer fifth in terms of mortality, and non-Hodgkin's lymphoma sixth with 35,000 cases and 18,000 deaths; all other cancers account for 37 percent of cases and 37 percent of deaths. He noted that the American Cancer Society projects 1,040,000 cases and 510,000 deaths from cancer in 1990, and ACS data showed an increase in mortality rate of 44 percent between 1970 and 1990. Dr. Sondik explained that several factors form the basis of this increase: a 20 percent increase in the population; a 50 percent increase in the population over age 65; and a 90 percent increase in the population over age 85. Illustrating the age-adjusted mortality rates, accounting for the growth and aging of the population, he stated that the actual rate of increase in mortality is only approximately 5.4 percent. He compared this rate with an increasing incidence of approximately 14 percent between 1970 and 1987.

Turning to an analysis of the incidence of specific cancers from 1973 through 1987, Dr. Sondik pointed out increases of 83 percent in the incidence of melanoma, 51 percent in non-Hodgkin's lymphoma, and 46 percent in prostate cancer; incidence declined in relatively few cancers. He illustrated a decline in mortality from pancreatic (2 percent), colorectal (10 percent), and oral (16 percent) cancers, and increased mortality from lung cancer (34 percent), melanoma (29 percent), and non-Hodgkin's lymphoma (22 percent). He also compared changes in incidence versus mortality for specific cancer sites, explaining that the mortality from relatively few cancers (e.g., lung, melanoma, multiple myeloma) is increasing in the population under age 65, while significant decreases have been seen in several cancers (e.g., colorectal, oral, ovarian). He stated that overall the data show an actual 4.5 percent decrease in mortality in persons under age 65 and a 13 percent increase in those over age 65.

Next, Dr. Sondik gave the breakdown of statistics by race, which showed considerable disparity of the data for blacks versus whites. He noted that the overall mortality is 35 percent higher for blacks than whites, while the incidence is only 10 percent higher in blacks for cases diagnosed from 1983 to 1987. He pointed out that the survival rates for whites is 52 percent compared with 38 percent for blacks. He also illustrated a wide variation in incidence of specific cancers for blacks versus whites. He noted the important public health impact of the data showing that cancer mortality is 48 percent higher in black than white males and 20 percent higher in black than white females.

Describing trends in cancer incidence and mortality, Dr. Sondik indicated a 5 percent increase in mortality for whites versus a more than 10 percent increase for blacks over the period from the beginning of the SEER Program to the present. He compared the incidence and

mortality for a variety of races included in the SEER database, noting lower incidence and mortality rates for Hispanics versus whites but higher incidences of specific cancers (e.g., cervical, stomach) in Hispanics. The most recent survival rates drawn from the SEER Program show a 66 percent 5-year relative survival for white children ages 0 through 14, 52 percent for whites of all ages, and 38.2 percent for blacks.

Dr. Sondik commented on statistical trends for specific cancer sites, including:

- A higher increase in lung cancer incidence in females than in males, with the percentage of male smokers decreasing faster than that of female smokers.

- An overall increase in breast cancer incidence, which probably reflects earlier detection of existing cases due to the increase in breast cancer screening programs.

- Significantly higher incidence rates of non-Hodgkin's lymphomas.

- A 7 percent increase in incidence and a 10 percent decrease in mortality from colorectal cancer.

In conclusion, Dr. Sondik stated that the overall 5-year survival is increasing for whites but not for blacks and that the incidence continues to increase for many cancers. Overall mortality rates remain relatively constant, but the mortality rates in blacks are disproportionately high. Dr. Sondik expressed appreciation for the efforts of Brenda Edwards, Lynn Reese, Ben Hankey, and all of the SEER staff and contractors in compiling the data for the *Cancer Statistics Review 1973-1987*. He emphasized the importance of supporting programs on smoking, diet, screening, and state-of-the-art treatment to continue the fight against cancer.

The following points arose in discussion:

- Some differences in the data for blacks versus whites can be accounted for by adjusting the statistics for socioeconomic status, but methods of data collection make the calculations to adjust for such differences imprecise.

- The effect of air pollution in urban areas on the incidence of lung cancer is minimal compared to the effect of smoking.

- Another registry will be added to the SEER Program to increase the Hispanic population that is surveyed. Increased surveying of rural communities is also needed.

- The data included in the review are through 1987, not 1990; therefore, it is difficult to draw conclusions on the progress that has been made in the 5-year period since the goals for the year 2000 were set in 1985.

- Some areas of improved statistics in the population under age 65 should eventually translate into improvements in statistics in those over 65 and eventually all age groups.

- The SEER Program forms an important basis for setting Institute priorities and implementing policy.

XII. AN INTRODUCTION TO THE AGENCY FOR HEALTH CARE POLICY AND RESEARCH (AHCPR)--DR. J. JARRETT CLINTON

Dr. Broder welcomed Dr. Clinton to the NCI and briefly outlined his background in the area of public health, including his earlier service as Director, Bureau of Health Professions, Health Resources and Services Administration; Deputy Assistant Secretary of Defense for Professional Affairs and Quality Assurance in the Office of the Assistant Secretary of Defense for Health Affairs; and work in ADAMHA, the Agency for International Development, and the Peace Corps. Dr. Broder summarized the mission of AHCPR as enhancement of patient care services by researching society's health care needs and how to meet them, noting that this task will require promotion of improvements in clinical practice and patient outcome as well as improvements in financing, organization, and delivery of health care. He pointed out that NCI and AHCPR programs complement each other and stated that NCI would work closely with the new agency, beginning with an important collaborative initiative proposed by AHCPR that would be considered by the Subcommittee on Information and Cancer Control at its meeting the following day.

Dr. Clinton reviewed the events leading to the creation of the new agency in the Public Health Service (PHS), citing an article in the *New England Journal of Medicine* written by Dr. William Roper, then head of the Health Care Financing Administration (HCFA). Dr. Roper discussed the use of the HCFA database to begin to explore what works best in medicine by developing linkages with databases that exist in HCFA, Blue Cross/Blue Shield, and other insurance companies across the nation. He encouraged involvement by health care practitioners in discussion about clinical practice guidelines that might logically evolve from that research.

It was determined at the beginning of the Bush administration that the effort to bring science to bear on what works best for the furtherance of medical care in America should be located in the PHS. Dr. Louis Sullivan, Secretary, Health and Human Services (HHS), and Dr. James O. Mason, Assistant Secretary for Health, HHS, testified before Congress in support of the effort and to effect organizational changes in the PHS. AHCPR was established by Title IX of the Omnibus Budget Reconciliation Act of 1989 with the purpose of enhancing quality, appropriateness, and effectiveness of health care services and enhancing access to such services. Dr. Clinton stated that these goals are to be accomplished through a program of peer-reviewed scientific research modeled after those of other PHS organizations, particularly the NIH. AHCPR will promote improvements in primary care practice and the organization, financing, and delivery of health care services through intramural and extramural research, demonstration projects, evaluations, training, guideline and data development, and dissemination of information.

Dr. Clinton stated that the AHCPR will develop a process by which Federally facilitated guidelines for the clinical practice of medicine can be established in such a way as to gain the confidence of all who are affected by them, i.e., professional associations, health care providers, the scientific community, consumers, and insurance companies.

Among the general authorities of AHCPR is the emphasis on measurement of the effectiveness, efficiency, and quality of health care services. Groups such as the Joint Commission on Accreditation of Health Care Organizations or the Federation of State Medical Boards will participate in monitoring to ensure the quality of the provider, institution, or process. Dr. Clinton noted that the Office of Technology Assessment in the new agency will respond directly to requests from HCFA or CHAMPUS for assessments on health care technology on which to make reimbursement decisions. The agency's Center for General Health Services

Intramural Research deals with health care costs, health care utilization and long-term care, productivity, and market forces. This Center is conducting a national medical expenditure survey to determine the magnitude and demographic characteristics of the uninsured population. Some of the findings are that approximately 35 million people are uninsured; many of these are employed. Race differentials are striking, with two to three times more blacks and Hispanics than whites among the uninsured. The survey data base is being used to determine steps that can be taken to improve access to medical care, a high priority for Dr. Sullivan and this administration.

Next Dr. Clinton discussed the issue of medical liability, which, he said, has radically affected the delivery of health care. He cited the example of obstetrical care in rural communities where the high cost of liability insurance added to modest Medicaid charges and low salaries that prevail in those areas result in reduced access to obstetrical care as practitioners leave the area. Dr. Clinton noted that several strategies are being considered to deal with the problem of access to obstetrical care in rural communities, such as tort reforms by states and the alternative resolution processes being promulgated by the American Medical Association, PIAA, and others. He said AHCPR hopes to look systematically at determinants and distributions of liability.

Dr. Clinton noted that Congress has charged AHCPR specifically with focusing on health care services in rural and frontier areas (the latter defined as areas with very low population rates per square mile) and the health of low-income groups, minorities, and the elderly.

Dr. Clinton pointed out that AHCPR is a construct of both the Public Health Service Act and the Social Security Amendment, with monies both from budget authority and trust funds. He highlighted distinctions between the primary charge of NCI, which is to focus on what works in a "controlled" population, and that of AHCPR, which is to assess the effectiveness of those therapies when delivered to the general population. To illustrate the types of projects being funded by AHCPR, Dr. Clinton listed the following: management of low back pain (University of Washington), management of benign prostatic hypertrophy (Jack Wennberg and the American Urological Association), management of myocardial infarctions (Harvard), management of total knee replacements (University of Indiana).

Research priorities of the new agency include (1) areas in which large numbers of people are affected and could be benefited if the best among alternative plans of management is determined, e.g., breast cancer; (2) areas where variations in practice are prominent, e.g., benign prostatic hypertrophy; and (3) areas where the cost of care is of particular import, e.g., management of cataracts. The objective is to bring greater uniformity to health care provision and improved quality, thereby reducing the health care cost by reducing inappropriate care. Dr. Clinton stated that the FY89 and FY90 budgets of $50 million and $100 million, respectively, will enable AHCPR to fund some research directly and some through collaborations with other departmental components, including NIH, Centers for Disease Control, Indian Health Service, and HCFA.

In response to questions, Dr. Clinton provided the following additional information:

- Research priorities will be determined (1) with the help of a 17-member multidisciplinary national advisory council appointed by the Secretary; (2) by topics resulting from Institute of Medicine consensus conferences; and (3) in response to requests for assistance from HCFA.

- An Intradepartmental Committee, comprised of the Assistant Secretary for Health, the Administrator of HCFA, the Assistant Secretary for Management and Budget, the Assistant Secretary for Planning and Evaluation, and the Administrator, AHCPR, meet regularly to review programmatic issues such as research priorities and guidelines development.

- Guidelines development is envisioned as a dynamic and continuous process similar to that in use by PDQ; the process may provide direction and a pragmatic focus to investigator-initiated clinical research but will not curtail it.

- AHCPR will work through its Center for Research Dissemination and Liaison in communicating research results to the practicing community. Strategies will include working with local organizations such as county medical societies, evaluating and making use of PDQ, implementing public information programs, influencing reimbursement policies, and involving primary care physicians as well as health care researchers in the guideline development process.

- AHCPR has not yet resolved the issue of how to avoid duplication of effort. Responsibility for research that theoretically falls within the authority of more than one PHS agency will be decided through continuing communication between those organizations.

XIII. CLOSED SESSION

A portion of the second day of meeting was closed to the public because it was devoted to the Board's review of grant applications. A total of 1,308 applications were received, requesting support in the amount of $249,010,703. Of these, 1,239 were recommended for funding at a total cost of $205,219,996.

XIV. SUBCOMMITTEE REPORTS

SUBCOMMITTEE ON CANCER CENTERS--DR. JOHN DURANT

Dr. Durant reminded Board members that the Subcommittee on Cancer Centers has been working on NCI's Five-Year Plan for Cancer Centers, which the Institute of Medicine recommended in its study that was undertaken at the request of Congress. He reported that the subcommittee's initial draft of the plan was revised at meetings with the ad hoc Cancer Center Director Consultants Group over the past several months, with Dr. Albert Owens of Johns Hopkins University acting as chairman of the group. A new draft was then reviewed and revised by NCI staff for presentation to the Subcommittee. Dr. Durant said the new draft, which the subcommittee titled the NCI's Strategic Plan for Cancer Centers, will be presented to the cancer center directors at their workshop in June before a final plan is made available to the NCAB.

Dr. Durant said the plan states clearly that there are goals in discovery, education, and cancer control and prevention. It discusses the need for a broader geographic representation and suggests the need for an implementation plan based on the strategic plan. The plan centers on the role of cancer centers in the bypass budget. It also indicates that more leadership is needed to establish relationships with the various state and city agencies that are responsible for the delivery of public health programs.

Dr. Durant said the subcommittee has unanimously recommended the plan's approval and that Dr. Broder has also indicated that the current plan is suitable for NCI's purposes. There is now a charge to NCI staff, with input from the center directors and with the oversight of the Subcommittee and the DCBDC Board of Scientific Counselors, to develop an implementation plan for the cancer centers based on the NCI's Strategic Plan for Cancer Centers.

SUBCOMMITTEE ON PLANNING AND BUDGET--DR. DAVID BRAGG

Dr. Bragg presented a report by the Subcommittee on Planning and Budget that summarized the 1991 President's budget in comparison with the 1990 operating budget. The report also described the NCI's 1992 By-Pass Budget. Dr. Bragg noted that the 1991 congressional hearings were positive and very supportive of the NCI. Issues raised at these hearings included information transfer, clinical trials, proton beam therapy, cancer vaccine research, cancer statistics, screening activities for breast and cervical cancer, and efforts directed toward minorities and the underserved.

Dr. Bragg pointed out that the 1991 budget projects a slight increase in the number of competing grant awards from the 1990 budget, but that there will be a downward negotiation of approximately 20 percent in grant budgets. He also said the By-Pass Budget is significantly increased from the 1991 President's Budget, with two of the largest increases being for the grants pool and funding for the Cancer Prevention and Control Program. Dr. Bragg suggested that in the future this subcommittee might provide assistance in development of the By-Pass Budget.

Dr. Broder commented that the Congress is showing an increasing interest in and support of the By-Pass Budget and at least one member of the Appropriations Committee, Representative Boxer, has endorsed the By-Pass Budget. Questions to Dr. Broder at the congressional hearings on the By-Pass Budget led directly to questions to Dr. Raub about the professional needs budget of the entire NIH. He said that the By-Pass Budget might not only serve the needs of NCI but also help direct attention to the total professional needs of the NIH.

SUBCOMMITTEE ON AIDS--DR. GERTRUDE ELION FOR DR. HOWARD TEMIN

Dr. Elion began the report of the Subcommittee on AIDS with a summary of a paper by Mitchell H. Gail, Philip S. Rosenberg, and James J. Goedert that was published in the *Journal of Acquired Immune Deficiency Syndromes*. Dr. Gail, of the NCI Epidemiology and Biostatistics Program in the Division of Cancer Etiology, had reviewed the data and conclusions in this paper at the subcommittee meeting.

Since the middle of 1987, fewer cases of AIDS have been reported than were expected from previous projections among homosexual and bisexual men in the United States. Dr. Gail presents evidence that this "AIDS deficit" may be largely accounted for by the introduction of effective medical care, primarily AZT and possibly pentamidine, into these subpopulations of HIV-seropositive individuals. The AIDS deficit was greatest among homosexual and bisexual men in New York City, San Francisco, and Los Angeles. Deficits were virtually absent among intravenous drug users.

Zidovudine (AZT) was approved by the Food and Drug Administration in March 1987. Dr. Gail's review of treatment patterns suggests that possibly one-half of the AZT administered in 1987 was given to patients with AIDS-related complex, thereby prolonging the HIV incubation period and delaying or preventing the diagnosis of AIDS. Three independent sources of data

(placebo-controlled trials, pharmaceutical company reports, and the San Francisco Men's Health Study) were used to estimate the number of patients receiving AZT from 1987 to 1989 and to demonstrate that the amounts of AZT given prophylactically to those at highest risk of AIDS since March 1987 have been sufficient to account for most of the observed AIDS deficit. The incidence of AIDS cases is now at a plateau rather than increasing every year, as it had been previously.

The AIDS deficit that began in mid-1987 was greatest in groups expected to have the best access to medical care. The deficits increased over time from mid-1987 through the end of 1988, as increasing numbers of patients began treatment. No deficits were found in 1987 for non-homosexual intravenous drug users, heterosexuals, or Haitian immigrants and only very small deficits were noted by the end of 1988 in these groups. These groups are less likely to be able to obtain good medical care, either because they are unaware of AIDS risks or for economic reasons.

Dr. Elion said that important implications follow from the hypothesis of this study. The first is that treatment is reducing the national AIDS incidence rate; therefore, these treatment effects must be kept in mind while interpreting current AIDS incidence trends. Dr. Gail presented data showing that if these treatment effects are ignored, the number of patients previously infected will be seriously underestimated, leading to an overly optimistic estimate of future AIDS incidence. In years to come the incidence of AIDS may increase if current treatments have simply delayed the development of AIDS in these patients.

Dr. Elion said the second policy implication of this study is that the data suggest the need to provide better access to treatment for those subgroups that are not showing an AIDS deficit. She emphasized that Dr. Temin and other NCAB members believe Dr. Gail's analysis that medical therapies are changing the natural history of AIDS is a very positive note in the AIDS epidemic. However, she cautioned that one should not be too sanguine about the decrease in incidence, and she reminded the board members that HIV prevention strategies are needed as the final solution to control the disease.

SUBCOMMITTEE ON INFORMATION AND CANCER CONTROL FOR THE YEAR 2000--MRS. HELENE BROWN

Mrs. Brown began by saying the NCAB Subcommittee on Information and Cancer Control had reviewed a proposed Interagency Agreement between the NCI and the Public Health Service's Agency for Health Care Policy and Research (AHCPR). Under the agreement, NCI would contract for an assessment of the PDQ model as a system to disseminate information to health-care providers, at an estimated cost of $750,000 a year. Mrs. Brown said AHCPR would provide $500,000 a year for 3 years and NCI will pay one-third of the costs, or $250,000 per year, for the 3-year period of performance of the contract. The project would be conducted and monitored by NCI. Mrs. Brown said this review will answer a number of questions about the effect of the PDQ system on physician treatment practices. PDQ currently provides guidelines for cancer care; the central question is whether these guidelines have an impact on the practicing physicians.

Mrs. Brown reported that PDQ's monthly usage has gone from less than 600 to nearly 1,200 "connect hours" since 1987. Approximately one-half of that usage is by CIS offices, although it is presumed that the information from many of these searches eventually reaches physicians. Direct physician usage has also increased. Mrs. Brown reported that the subcommittee voted unanimously to approve and fund the project.

Dr. Bettinghaus commented that a PDQ appraisal was supposed to have been done for NCI a number of years ago, but the contractors reported at that time, in essence, that there was not enough usage to justify the evaluation. PDQ usage has now increased to a level to justify evaluation.

Dr. Korn questioned whether AHCPR is sensitive to the function of NCI guidelines for physicians, namely that the guidelines are only recommendations for practice, not mandatory standards for physicians. He recalled a GAO report issued 2 to 3 years ago that severely criticized NCI for not ensuring that state-of-the-art therapies and medical breakthroughs become standard practices in the medical community. He stressed that when the efficacy of PDQ is tested and evaluated, the AHCPR and the study contractor should make no presumptions that every practice in PDQ should be adopted by physicians.

Dr. Broder agreed with this point, saying that NCI is not a regulatory agency. NCI's primary mission is to generate and provide knowledge and to teach the medical community how to implement the knowledge with the appropriate peer-review processes. He said it is not NCI's mission to dictate what a physician does or to establish absolute standards. This NCI mission should be clarified to the study contractor and whenever else it is appropriate.

XV. NEW BUSINESS AND ADJOURNMENT--DR. KORN AND MRS. BYNUM

Mrs. Bynum informed the Board members that in addition to receiving the mail ballot on construction grant applications, they will also receive a mail ballot concerning an RFA for proton beam therapy. She said this is a late set-aside activity and a mail review is needed to make an award in Fiscal Year 1990. Dr. Broder told the Board that NCI is responsible for awarding planning grant(s) for proton beam therapy because it was specifically written into the Institute's budget.

Mrs. Bynum brought up the issue of a new subcommittee on OD contracts. The Board agreed to postpone consideration of the matter pending the appointment of the new Board members and a chairperson.

Mrs. Brinker said that a concept for a follow-up summit to the one held last fall or breast cancer treatment related topics is being developed and will be presented at a later Board meeting.

There being no further business, the 74th meeting of the National Cancer Advisory Board was adjourned at 1:44 p.m., May 15, 1990.

9/21/90
Date

David Korn
Dr. David Korn, Chairman