DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

NATIONAL INSTITUTES OF HEALTH

NATIONAL CANCER INSTITUTE

NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
October 1-2, 1990

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[1]
October 1-2, 1990

The National Cancer Advisory Board (NCAB) reconvened for its 75th regular meeting at 8:00 a.m., October 1, 1990, in Building 31, 6th floor, Conference Room 6, 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 (Absent)
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

President's Cancer Panel

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

***Ex Officio* Members**

Dr. Miriam Davis, NIEHS
Captain Bimal Ghosh, DOD
Dr. Richard Greene, DVA
Dr. John R. Johnson, FDA
Dr. Rachel Levinson, OSTP
Dr. Hugh McKinnon, EPA
Dr. Lakshmi C. Mishra, CPSC
Dr. William F. Raub, NIH
Mr. James S. Robertson, DOE
Dr. Louis W. Sullivan, DHHS (Absent)
Mr. John J. Whalen, NIOSH
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 Barak, Associate Program Director for Cell Biology, Division of Cellular Biosciences, National Science Foundation, Washington, D.C., representing the National Science Foundation for Dr. Maryanna Henkart.

Ms. Barbara Britt, President, Oncology Nursing Society, South Pasadena, California, representing the Oncology Nursing Society.

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

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

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

Dr. Charles Johnson, President, National Medical Association, Durham, North Carolina, representing the National Medical Association.

Dr. Thomas J. King, Treasurer, Vincent T. Lombardi Cancer Research Center, Georgetown University Medical School, Washington, D.C., representing the American Association for Cancer Research.

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

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

Dr. John F. Potter, Professor of Surgery, Vincent T. Lombardi Cancer Research Center, Georgetown University Medical School, Washington, D.C., representing 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 MAY 14-15, 1990, NCAB MEETING MINUTES--DR. DAVID KORN

Dr. Korn, Chairman, called the 75th 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 May 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: December 3-5, 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 whenever possible.

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

Dr. Hammer began with a review of his meeting with President Bush on August 15, at which time he presented the President's Cancer Panel 1989 Report to the President and the Final Report of the National Committee to Review Current Procedures for Approval of New Drugs for Cancer and AIDS, known informally as the Lasagna Committee. He noted that Dr. Samuel Broder and the Department of Health and Human Services (DHHS) Secretary, Dr. Louis Sullivan, were present at the meeting, as well as the President's personal physician, Dr. Burton Lee.

Dr. Hammer reported that the President expressed interest in both reports and said he would study the recommendations of the Lasagna Committee. Dr. Hammer mentioned that he also handed President Bush the executive summary of the FY 1992 By-Pass Budget, pointing out that it was strongly endorsed by the Panel. The President indicated he would look carefully at the recommendations of the By-Pass Budget. Dr. Hammer noted that the length and timing of the meeting demonstrated the President's interest in cancer research and treatment programs.

When submitting the Cancer Panel Report, Dr. Hammer said he conveyed to President Bush the Panel's consensus that NCI's programs are well established and productive and that major treatment advances have evolved from NCI-funded intramural and extramural programs, citing the gene transfer research of Dr. Steven Rosenberg and his colleagues at NIH. On behalf of the Panel, Dr. Hammer extended congratulations to Dr. Rosenberg on being selected Scientist of the Year by *R&D Magazine*. Dr. Hammer said he also commented to the President on a renewed sense of urgency to redouble efforts to ensure that all Americans share equally in the benefits to be derived from the latest advances in cancer prevention, pointing to funding requirements in the By-Pass Budget that will provide the ability to markedly reduce the incidence of cancer mortality within this decade.

In presenting the Lasagna Committee Report to the President, Dr. Hammer said he noted that the Committee had been established by the Panel in response to a request made by President Bush when he was Vice President. Dr. Hammer then expressed the appreciation of the Panel to the Committee and its Executive Secretary, Dr. Elliott Stonehill, for the final report, which he has transmitted to the Secretary of Health and Human Services and the Acting Commissioner of the Food and Drug Administration (FDA). He expressed hope that the recommendations will be considered carefully and will be useful in reducing the delays in marketing new drugs for the benefit of AIDS and cancer patients. Dr. Hammer added that the Panel recognizes that FDA is not solely responsible for the problems in the drug approval process, noting that the report recommends that FDA resources and staff be expanded to enable the agency to better carry out its responsibilities.

Shortly after his meeting with the President, Dr. Hammer said that Dr. Broder wrote him to notify the Panel of the possibility of a 31.9 percent budget sequestration facing the NCI as a result of the Gramm-Rudman-Hollings legislation and noting that such a reduction would have catastrophic effects. In response, Dr. Hammer sent a letter to the President stating that the advances alluded to at their meeting would be severely threatened, pointing out the devastating impact on major medical centers in the United States and on the intramural research program of NIH, and urging the President to avoid the consequences of sequestration. Dr. Hammer noted that the situation has since been resolved.

Next Dr. Hammer briefly reviewed upcoming meetings in 1990. An October 22 meeting will be held at the Roger Williams Medical Center in Providence, Rhode Island. One of the topics will be international information exchange, and speakers will include the Director of the Hungarian National Cancer Center at Budapest and Senator Claiborne Pell, who has an interest in this topic. A Panel meeting will be held at NCI on November 16 to receive reports from the various NCI Divisions on programs and plans for the future. The final meeting for the year is scheduled for December in San Francisco.

Dr. Hammer reported that the *Stop Cancer* Program continues to make progress and noted that some runners in the November 4 New York Marathon will be running for the program. A major gala will be held early in 1991 in Los Angeles that will be broadcast on cable TV, and various other *Stop Cancer* projects are being developed. Dr. Hammer said he felt it was important to extend even greater efforts to make *Stop Cancer* a success in view of the uncertain budgetary situation NCI is facing. He pointed out that *Stop Cancer* funds go exclusively to the NCI and are used largely to fund immunological projects recommended after peer review. He then quoted from a letter received from President Bush after the Health Retreat Summit thanking Dr. Hammer for his work in the fight against cancer and expressing his appreciation for the work performed by the President's Cancer Panel as well as for the Report of the National Committee to Review Current Procedures for Approval of New Drugs for Cancer and AIDS. In his letter, the President mentioned that the report will be reviewed by Secretary Sullivan in conjunction with a committee chaired by the Vice President and that it "will be a valuable catalyst . . . to help speed up the safe approval of new drugs, continuing a process that is already underway at the FDA."

Dr. Hammer noted with satisfaction that the Administration appears ready to appoint a new Director of NIH (Dr. Bernadine Healy) and a new Commissioner of FDA (Dr. David Kessler).

In conclusion, Dr. Hammer pointed out that the volatile situation in the Persian Gulf has jeopardized the peace dividend expected from the improved East/West political climate that it was hoped could be applied to domestic needs, such as improved health care. As a result, he called for

a redoubling of efforts to secure support for the National Cancer Program in order to achieve the goals for this decade.

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

Dr. Broder began with brief comments on the budget, explaining that a continuing resolution through October 5 had been passed and that the 1991 budget would probably be prorated as $1.634 billion, based on the FY 1990 rate. He expressed his opinion that if the Congress did not approve a budget plan to achieve the budget deficit reduction by October 5, an extension of the continuing resolution was likely.

Dr. Broder acknowledged the hard work of all staff who had monitored the 1990 NCI budget successfully. He gave special recognition to Mr. John Hartinger, Ms. Mary Cushing, Mr. Leo Buscher, Mr. Jack Campbell, and all of the Division administrative officers.

Dr. Broder provided a brief update on the gene therapy protocols and congratulated the principal investigators involved in the protocols, Drs. Steven Rosenberg, R. Michael Blaese, W. French Anderson, Kenneth Culver, and Attan Kasid. He noted that a presentation on the protocols would be given later in the meeting (see below).

Dr. Broder then announced the following honors and awards, and staff changes: Drs. Emil Frei and Emil Freireich, who received a new NIH award for distinguished alumni at a symposium entitled "Leukemia: 25 Years Later"; Dr. Judy Karp, who is on interagency personnel agreement loan from Johns Hopkins and is serving as a special assistant to Dr. Broder; Dr. Thomas Mays, who has joined NCI as the Director of the Office of Technology Development; Dr. Gisele Sarosy, who was promoted to Chief of the International Cancer Research Data Bank Branch in the International Cancer Information Center; Ms. Julianne Chappell, who was appointed Chief of the Scientific Publications Branch of the International Cancer Information Center; Ms. Iris Schneider, who will serve as Acting Deputy Director of the new NIH Office of Research on Women's Health; Ms. Susan Connors, who received an EEO Special Achievement Award; Dr. Charles Grieshaber, who left his position as Chief of the Toxicology Branch, Developmental Therapeutics Programs (DTP), DCT, to join the FDA staff; Dr. Charles Myers, who has been appointed Chief of the Clinical Pharmacology Branch, Clinical Oncology Program (COP), DCT; Dr. Robert Wittes, who has returned to the NCI as Chief of the Medicine Branch, COP, DCT; Dr. John Bader, who was appointed Chief of the new Antiviral Evaluations Branch, DTP, DCT, which was established on August 8; Drs. Charles Myers, Ilan Kirsch, and James Mulshine, who received the PHS Outstanding Service Medal; Dr. Jeffrey Norton, who received the NIH Director's Award; Dr. Richard B. Alexander, who received the AACR/Upjohn Young Investigator Award; Dr. Harvey Pass, who received the President's Award from the Southern Thoracic Society; Dr. Douglas Schwartzentruber, who received the ASCO/Upjohn Award; Dr. Katherine Marconi, who was appointed Chief of the Cancer Control Applications Branch, Division of Cancer Prevention and Control (DCPC); Dr. Paulette Gray, who received the NIH Director's Award; Ms. Rosemary Cuddy, who received the NIH Merit Award; Ms. Carole Frank, who was appointed the NCI's new Committee Management Officer; Dr. John Cooper, Chief of the Extramural Programs Branch, Division of Cancer Etiology (DCE), who retired on August 1; Dr. G. Iris Obrams, who replaced Dr. Cooper; Dr. Robert Gallo, Chief of the Laboratory of Tumor Cell Biology, DCE, who was honored by the American Association for Clinical Chemistry; Dr. William Blattner, who received the NIH Director's Award; Dr. Jerry Rice, who received the Outstanding Service Medal; Dr. Louise Brinton, who received the PHS Special Recognition Award; Dr. Robert

Hoover, who received the Distinguished Service Medal; Drs. Mitchell Gail and Margaret Tucker, who received the Meritorious Service Medal; and Dr. Neal Copeland, who received the Elliott Osserman Award of the Israel Cancer Research Fund for distinguished service in support of cancer research. Dr. Broder then congratulated Board member Mrs. Nancy Brinker, whose book entitled *The Race Is Run One Step At a Time* was published recently.

Turning next to an update on recent important developments, Dr. Broder outlined an important clinical study in chemoprevention that was published recently in the *New England Journal of Medicine*. He stated that the study, which evaluated the positive role of 13-cis-retinoic acid in preventing new head and neck tumors, represents a milestone for scientifically based preventive oncology research.

Dr. Broder reported that NCI had held a successful 6-week Summer Enrichment Program at Hood College in Frederick, Maryland. Some 107 ninth-grade students attended this intensive science and math program. Students were recruited from underrepresented minorities and underserved youth in 25 states and the District of Columbia. Dr. Broder noted that this program was put into action as one part of NCI's commitment to finding ways to encourage minority and disadvantaged students to prepare for and choose careers in health care and biomedical research. Dr. Claudia Baquet spoke about the program later in the meeting (see below).

Dr. Broder then announced that a lecture dedicated to the memory of Mr. Lou Carese would be held at NCI on October 18. Mr. Carese was NCI's first Associate Director for Program Planning and Analysis, and he helped develop the National Cancer Plan in the early 1970s, following the mandates of the National Cancer Act.

Dr. Broder stated that the Report of the National Committee to Review Current Procedures for Approval of New Drugs for Cancer and AIDS, which was presented to President Bush on August 15, is available for review. He acknowledged the commitment and effort of Dr. Louis Lasagna and the members of the Committee, and commended Dr. Stonehill on a fine job as Executive Secretary of the Committee. Dr. Broder explained that he and Dr. Hammer met with President Bush in the Oval Office at the White House to present the Report, and at the same time Dr. Hammer presented the executive summary of the FY 1992 By-Pass Budget. Dr. Broder noted that the Strategic Plan for Cancer Centers, which was developed in consultation with the NCAB Subcommittee on Cancer Centers and the ad hoc Cancer Center Directors' Consultants Group, is included in the By-Pass Budget.

Dr. Broder then reported that he met with the Subcommittee on Human Drugs and Biologics of the Advisory Committee on the FDA, which was appointed by Dr. Sullivan to examine the agency's mission, responsibilities, and structure. He expressed the opinion that the oversight provided by the Committee will have a broad impact on the leadership, management systems, and resources of the FDA. The Advisory Committee on the FDA is composed of 16 experts from the private sector and is chaired by Dr. Charles C. Edwards, President and Chief Executive Officer of the Scripps Clinic and Research Foundation in La Jolla, California, and a former FDA Commissioner. The Committee will prepare a progress report and then a final report by May 1991. Dr. Broder stressed that while issues of disagreement remain, NCI and FDA are enjoying an unprecedented degree of communication and effective interactions.

Turning to Congressional issues to be discussed in further detail by Ms. Dorothy Tisevich, Legislative Liaison, NCI, later in the meeting, Dr. Broder informed the Board that on September 19, the Office of Technology Assessment (OTA) released a report entitled *Unconventional Cancer*

Treatments. This report was undertaken by OTA following a request from Congress to review the issues surrounding unconventional treatments. As part of the overall study, OTA was asked specifically to evaluate immunoaugmentative therapy and to design a clinical trial protocol for its evaluation.

Dr. Broder listed other congressional hearings and meetings held recently, including:

- Testimony on colorectal cancer screening by Dr. Peter Greenwald, Director, DCPC, before the House Ways and Means Subcommittee on Health.

- The appearance of Dr. Sheila Zahm, Occupations Studies Section, DCE, as an expert witness on the toxicological effects of Agent Orange and other herbicides before the House Government Operations Committee's Subcommittee on Human Resources and Intergovernmental Relations.

- Testimony by Dr. Philip Pizzo, Chief of the Pediatrics Branch and Head of the Infectious Diseases Section, DCT, before the House Government Operations Subcommittee on Human Resources and Intergovernmental Relations on drugs for opportunistic infections in persons with HIV disease.

- Issues related to the health of women

  -- Testimony by Dr. Broder before the House Committee on Health and Long-Term Care, Select Committee on Aging on breast cancer research.

  -- Testimony by Dr. Richard Adamson, Acting Deputy Director, NCI, before the House Energy and Commerce Subcommittee on Health and the Environment on the reauthorization of the National Institutes of Health, at which the primary focus was the inclusion of women in NIH clinical trials.

  -- A meeting of senior staff at NIH with Representatives Connie Morella and Pat Schroeder and Senator Barbara Mikulski to discuss the status of women in NIH research.

Dr. Broder reported that subsequent to these hearings and meetings on issues related to women's health, on September 10, Dr. William F. Raub, Acting Director, NIH, announced the establishment of an Office of Research on Women's Health within the Office of Director, NIH. Dr. Raub appointed Dr. Ruth Kirschstein, Director of the National Institute of General Medical Sciences, to head the office as Acting Associate Director on Women's Health. Dr. Broder explained that the Office of Research on Women's Health is charged with assuring that research conducted and supported by NIH appropriately addresses issues regarding women's health and that there is appropriate participation by women in clinical research, especially in clinical trials. Dr. Broder assured the Board that NCI has reviewed its clinical research and has found that women participate in every phase of NCI-sponsored investigative activity. He stated that NCI has proportional representation of women in its clinical trials programs and will continue this policy in the future. For example, in clinical treatment trials sponsored by NCI, at least 50 percent of patients enrolled are women; in 1989 alone, 14,594 or 56 percent of the 25,064 patients enrolled in the NCI-sponsored cooperative group trials were women. In addition, NCI's multifaceted research in breast cancer and lung cancer--two leading causes of cancer deaths of women--has received a high priority.

Also on the subject of women's health, Dr. Broder added that on June 8, Surgeon General Antonia Novello, Marilyn Quayle, Marie Mason (wife of Dr. James Mason, Assistant Secretary for Health), and Ginger Sullivan (wife of Dr. Sullivan) participated in mammography screening at NIH. He noted that these individuals have been active in supporting NCI's program to encourage screening for breast cancer and in promoting the NCI guidelines. In addition, Dr. Broder noted a study by NCI and the Jacobs Institute that found more American women over 40 are participating in mammography screening: 64 percent (up from a previous figure of 37 percent). However, only 31 percent of the women followed the guidelines for ongoing mammography. Almost 75 percent of those who had mammograms did so because it was recommended by their physicians.

Turning to a review of recent NCI-sponsored conferences and workshops, Dr. Broder mentioned a consensus conference on treatment of early-stage breast cancer held in June and a consensus conference on adjuvant therapy for patients with colon and rectal cancer held in April. He announced that the complete consensus conference reports are available.

Emphasizing that progress toward curative and preventive approaches is predicated on fostering and supporting innovative clinical studies, which in turn depends on a continuous pool of individuals trained in clinical research, Dr. Broder stated that on September 12, 1990, a workshop was held on the training and retention of clinical oncology investigators. Dr. Freireich, who has played an important role in this area, conducted a 6-month study for the NCI on the current status of clinical cancer research. He visited 20 training programs, including those at 11 comprehensive cancer centers, and conducted many interviews in the process of his study. The purpose of the workshop was to clarify issues and policies that affect the recruitment, training, and retention of young physicians in clinical oncology research, as well as the allocation of resources to support clinical investigations from both NCI and the academic institutions. The final report from this workshop is forthcoming.

In addition, Dr. Broder stated that NCI had sponsored a workshop on cancer pain on September 14 and 15. Three working groups were convened to survey the research needs in this area. About 80 individuals from Federal and private agencies attended. A summary report is in preparation.

Dr. Broder also announced that on October 29-30, NCI will hold a workshop on cancer vaccines, at which current knowledge will be assessed and suggestions gathered for accelerating the development of vaccines. He noted that for some cancers in which a viral disease plays a role, a conventional vaccine may be viable. However, for tumors of nonviral etiology, the problems are more difficult. He stated that recent work on tumor-infiltrating lymphocytes (TILs) is presenting a possible approach for developing vaccines against these more common tumors, in particular by answering the question of whether it is possible to identify antigens that specifically induce cytotoxic T cells in patients.

Dr. Broder then referred to NCI's September 19 release of a report on its study on cancer in populations living near nuclear facilities. He stated that briefings were held for Federal agencies involved with nuclear facilities and with Congress, and noted that Dr. Adamson would be discussing the study later in the meeting (see below).

Dr. Broder also noted FDA activity on a number of cancer drugs: the approvals of both Levamisole and Idarubicin, and favorable consideration by FDA's Oncologic Drug Advisory Committee of two other drugs, Fludarabine--a unique advance in the treatment of chronic lymphocytic leukemia and other B-cell malignancies--and Hexamethylmelamine.

Dr. Broder reminded the Board that during the fall of 1989 NCI had collaborated with the D.C. Commission of Public Health and the Washington Bullets basketball team to produce an antismoking television public service announcement--"You Can't Miss!"--featuring Bullets' head coach Wes Unseld. Dr. Broder acknowledged Board member Mrs. Irene Pollin's instrumental role in arranging for Coach Unseld's appearance. He stated that NCI's broadcast tracking reports showed that D.C. stations aired the announcement extensively and that Baltimore and Richmond stations also used this public service announcement. He reported that it won a Silver Reel Award, the top award for TV public service announcements, at the International Television Association's 22nd Annual Video Festival in June, and that NCI is now working to extend the campaign to other National Basketball Association cities.

Before dealing directly with the NCI budget, Dr. Broder reviewed the language in the House Appropriations Report on the House markup for the FY91 budget, which has major implications if retained in the bill that is signed into law. He quoted exact language regarding NIH, as follows:

> NIH is directed to provide necessary cost control on the research grant system by ensuring that the average length of a grant not exceed approximately 4.0 years and that the average cost of a grant not increase faster than the biomedical research deflator index. This can be accomplished by specific cost management strategies or by factoring cost into the grant selection process, or both.
>
> The total cost of a grant, including indirect costs, should be considered at all stages of the grant review process.
>
> The practice of downward negotiation should be eliminated. Grants should be approved at the most economical level compatible with the science being proposed and then the average cost should be controlled through which grants are actually chosen for funding. The Institutes, through their study sections and advisory councils, should aggressively eliminate any costs which they believe are unnecessary. Once this is done, a grant should be funded at the full level without arbitrary reductions. This system would apply to both project grants and centers beginning with new grant awards in 1991.
>
> NIH is encouraged to modify the peer review system to require that "approval" reflect a decision by a study section about whether a project merits funding based on its inherent value to biomedical research as well as meeting technical standards. This would eliminate the situation where 95 percent of applications are approved, of which only half are really considered as deserving of support.
>
> The number of center grants should not exceed approximately 640 (15 more than the FY90 level) with new center grants to be funded in future years by turnover within this base number.
>
> The NIH Director should control an allocation system for centers with as many as 10 to 15 center slots reallocated each year. The overall budget for centers should be increased each year to reflect inflation. If center costs increase faster than inflation, the number of center grants should be reduced in order to adequately fund those which remain.

Requesting that discussion of specific budget figures and complete budget status be reserved for the meeting of the Board's Subcommittee on Planning and Budget later in the day, Dr. Broder

stated that the estimated obligation for FY90 was $1,634,332, noting the start of a new Federal fiscal year on October 1. He provided an update on the construction money that NIH had received, recalling that as part of the FY90 Appropriation, Congress provided nearly $15 million in construction funds to the NIH Director for transfer to the Institutes. Dr. Broder stated that NIH had made the final allocation decisions the previous week and transferred funds to NCI for grant awards to Jackson Laboratories ($9.5 million for animal production facilities), the University of Michigan ($1.045 million), and Purdue University ($1.538 million). Earlier in the year NIH had given NCI funds to award construction grants to the University of Southern California ($1.2 million) and the University of Wisconsin ($0.4 million). In summary, of the $14.8 million available to NIH, $13.5 million was transferred into the NCI budget. The remaining $1.3 million was awarded by the National Heart, Lung, and Blood Institute and National Eye Institute. Noting the need to address some fundamental construction issues, Dr. Broder pointed out that Congress in its House Report has language that would permit NCI to reprogram up to $7 million from other sources to fund meritorious construction projects.

Dr. Broder closed his report with comments on the status of the FY 1992 By-Pass Budget of $2.612 billion. He reminded the Board that NCI had submitted the By-Pass Budget to the Office of Management and Budget (OMB) and the President, with a copy to each Board member. Dr. Broder emphasized the important role of the By-pass Budget and its use to formulate policy.

The following points were made in discussion of Dr. Broder's presentation:

- Dr. Korn, from his interaction with the House Subcommittee on Appropriations, also noted specific language in its Report that identified (1) low numbers of new grants, (2) high levels of downward negotiation, and (3) general lack of stability of Government support for the biomedical sciences as problems that must be addressed. He asked that the complete Report be distributed to Board members.

- Dr. Broder noted that the language of the Report reflected an expert knowledge of the NCI review process and award rate, and he stressed the need to address the points made in the Report with an informed response.

- It was pointed out that a previous NIH policy had instructed study sections to use the full scoring range, while the language in this Report stressed the desirability of being much more stringent in the designation of approval.

- The average length of an NCI grant is currently 4.1 years. A maximally extended MERIT award is counted as two 5-year awards, not as a single 10-year grant.

- The distribution of 640 centers over the NIH Institutes is not specified in the Report. It was emphasized that the Cancer Centers Program is vital to NCI's program of basic research and clinical trials.

- The proscription against downward negotiation will be difficult to implement in FY91 because the fiscal year has already begun; NCI will attempt to negotiate a phase-in period on this point.

- The language in the Report calling for renewed leadership at the NIH seems to reflect the perceived need to develop a long-term biomedical strategy that deals realistically with future economic climates.

- The issue raised in the Report about considering indirect costs in the grant review process is complex and sensitive. Indirect costs, which are averaged across each institution and include such services as utilities and adequate police and fire services, are audited annually on an institution-wide basis and cannot be negotiated piecemeal, on a project-by-project basis. Moreover, assessment of the components of indirect costs cannot be done from review of the content of any individual grant application. Considering these costs in a review of institutions will affect particularly those in high-cost areas.

V. GENE THERAPY UPDATE--DRS. BRUCE CHABNER, STEVEN ROSENBERG, W. FRENCH ANDERSON, AND R. MICHAEL BLAESE

Dr. Chabner introduced the presentation on the gene therapy research and clinical trials and noted that this has been an ongoing collaborative project in the Clinical Center, NCI, and the National Heart, Lung, and Blood Institute (NHLBI) as well as other Institutes.

Dr. Blaese (Deputy Chief, Metabolism Branch, DCBDC) provided background on the gene therapy research, explaining that much of the initial work was directed toward bone marrow gene therapy to treat various hemoglobinopathies. He stated that because hemoglobinopathies were proving to be a difficult problem, adenosine deaminase (ADA) deficiency, a pediatric disease characterized by profound defects in both the T and B lymphocytes, was chosen as one of the initial candidates for gene therapy. ADA deficiency Severe Combined Immune Deficiency (SCID) is inherited as an autosomal recessive with an incidence of less than 1:100,000; the gene, which consists of 12 exons spanning 32,000 base pairs on chromosome 20, encodes a single-chain protein enzyme of 36,000 daltons. As well as having the important property of being a single-chain protein, all the clinical manifestations of ADA deficiency SCID are cured by bone marrow transplantation. Thus, it was postulated that the disease could also be cured by inserting corrected genes into the bone marrow stem cells and giving patients their own marrow back. In addition, this disease was a particularly attractive candidate because ADA enzyme concentrations from one-tenth of normal to as much as 50 times the normal concentration can be found in individuals with normal immune function, allowing a broad latitude in which to cure enzyme deficiency by gene reinsertion.

Dr. Blaese outlined the method for gene transfer using retroviruses. For the ADA deficiency gene transfer experiments, a murine leukemia virus, the Molony virus (MoMuLV), was used; this virus was modified to be non-infectious and contained a bacterial gene for neomycin resistance (NeoR) instead to permit selection of stable transductants. In the initial experiments a vector called SAX was used to transfer the human adenosine deaminase gene into the clinical construct, thus including a bacterial gene, a viral promoter, and a human ADA gene.

Dr. Blaese explained that, based on the fact that ADA-deficient cells are inhibited by a 50-fold lower concentration of deoxyadenosine than normal cells, ADA-deficient T cells were infected with the SAX retrovirus construct and exposed to increasing concentrations of deoxyadenosine to determine whether the gene transfer was successfully accomplished. This cell population demonstrated acquired resistance to deoxyadenosine and also to the neomycin analog G418, due to the successful transfer of the human ADA gene and the second functional gene, NeoR, in the construct. Dr. Blaese also provided data from subsequent experiments in primates showing successful gene transfer of human ADA; however, the effect was transient, lasting less than 6 months.

In providing a summary of the problems of the bone marrow gene transfer experiments and other potential approaches to gene transfer, Dr. Blaese explained experiments using lymphocytes as potential cells to modify by gene insertion. Lymphocytes have several characteristics that make them attractive for gene transfer, particularly the capacity to culture these cells for long time periods, permitting attempts at serial gene insertion. Also, the antigen receptors on lymphocytes may permit targeting of the gene-modified cells to a site of antigen in the body such as deposits of tumor cells. Dr. Blaese described early experiments in nude mice showing successful transfer of human ADA after infusion of mice with lymphocytes expressing human ADA.

Dr. Blaese also outlined two other approaches to gene transfer, which Dr. Rosenberg described in more detail (see below): the use of gene transfer to characterize and optimize standard therapy with tumor-infiltrating lymphocytes (TILs) by using a marker gene for trafficking studies; and the use of gene therapy for treatment of cancer by introducing genes to enhance TIL cell function or to target a therapeutic product directly to tumor sites.

In closing, Dr. Blaese described the gene transfer protocol for ADA deficiency, in which the first child was treated in mid-September 1990. The protocol consists of induction of peripheral blood T cells from the patients to proliferate in culture by stimulation with the anti-T cell receptor monoclonal antibody in IL-2, then transduction of these proliferating T cells with normal ADA gene using the retrovirus, and infusion of the patient with the gene-corrected T cells. The process will be repeated over several months so that the patients receive a broad spectrum of T-cell specificity.

Dr. Rosenberg (Chief, Surgery Branch, COP, DCT) summarized the gene therapy research involving the insertion of genes into lymphocytes that are used as a component of anticancer therapy. He noted that this approach represents an extension of his previous work to develop adoptive cell transfer therapies for cancer (i.e., adoptive immunotherapy). He first provided some background by reviewing the results of his group's initial adoptive immunotherapy trials with lymphokine-activated killer (LAK) cells and the cytokine, interleukin-2 (IL-2). He stated that as of March 1990, 178 evaluable patients had been treated with the LAK plus IL-2 therapy. Most of the patients treated had either advanced kidney cancer or melanoma, the two cancers that responded to the therapy in early trials. Approximately 10 percent of all patients had a complete regression (CR), and another 10 percent of melanoma patients and 25 percent of patients with kidney cancer had an objective partial response (PR). Patients with other cancers (e.g., colorectal and non-Hodgkin's lymphoma) also showed some response, but fewer than 10 patients with other cancers were treated.

The next attempt to improve this type of therapy involved the use of TILs. Dr. Rosenberg explained that clinical trials with these cells began in May 1990 after extensive preliminary laboratory research. He stated that although the TILs used in the initial trial of 50 patients were grown in high-dose IL-2, ongoing research had shown that TILs grown in low-dose IL-2 and TILs administered with IL-2 and α-interferon were more effective in experimental animals. He reported that the first 50 patients who received treatment with TILs grown in high-dose IL-2 had a 38 percent response rate, compared with the 20 percent response rate to LAK plus IL-2 in earlier studies.

Dr. Rosenberg emphasized that one important characteristic of TILs is their tendency to traffic to and accumulate in tumor deposits. This observation, illustrated with indium-111 labeling of TILs, led to the conceptualization that TILs could be used as vehicles to deliver to tumor sites molecules that would accrue anticancer activity or have anticancer activity of their

own. Thus, the goal of future studies was to insert genes into TILs that would improve their anticancer activity.

In collaboration with Drs. Blaese and Anderson, Dr. Rosenberg's group developed modified TILs including the NeoR gene (to allow study of long-term distribution of the modified TILs) and a modified MoMuLV. Dr. Rosenberg emphasized that the first gene transfer protocol had undergone extensive review beginning in June 1988, and that it had been demonstrated that the NeoR-marked TILs could be detected in animal models and that there was low risk to patients and no risk to the public from the use of the retroviral vector. He stated that the FDA had approved treatment with the gene-modified TILs of 10 patients who had life expectancies of 90 days or less. Thus far, nine melanoma patients with disease in multiple organ systems have received the treatment, and the results in the first five patients were reported in the *New England Journal of Medicine* in August 1990.

Dr. Rosenberg reviewed the results in these five patients, noting first that no safety problems or side effects were seen due to the introduction of the gene-modified TILs. All patients survived at least 3 to 4 weeks after treatment, when IL-2 was administered to help keep the gene-modified TILs alive. The presence and expression of the NeoR gene were demonstrated in TILs from all the patients by using Southern blot analysis and the enzymatic assay for the neomycin phosphotransferase coded by the bacterial gene. Continued survival of the cells was seen at 189 days in one patient and at tumor deposits at 64 days in another patient, showing that the cells can survive a considerable length of time and can traffic directly to tumor sites. Three of the patients in the trial showed evidence of antitumor effects; two achieved at least an objective regression, including one who achieved a CR of all metastatic cancer and remains in CR now after 16 months.

Dr. Rosenberg restated that the ultimate goal of these studies was to insert genes to improve the therapeutic potency of TILs. For this purpose, the gene for tumor necrosis factor (TNF) was chosen. While humans can tolerate only a many-fold lower dose of TNF than mice (i.e., 8 μg/kg vs 400 μg/kg), it was postulated that TILs could be used to deliver the TNF directly to tumor-specific sites, thus avoiding the toxicity of TNF to normals cells. Dr. Rosenberg reported that it was then shown that by inserting the TNF gene into the modified TILs, sufficient concentrations of TNF beyond 400 μg/kg can be administered to humans. In subsequent experiments, a retroviral construct including two separate genes--the TNF gene promoted by the retroviral LTR and the NeoR promoted by SV40--were used. In five patients, stable expression of this TNF gene in TILs has been demonstrated. Initiation of trials with this construct awaits FDA approval.

In closing, Dr. Rosenberg emphasized the implications of these studies: that gene modification may be used to design TILs with properties that increase their therapeutic effectiveness; and that lymphocytes, in the absence of currently being able to perform successful gene-modified bone marrow transplants, may be suitable vehicles for introducing genes to treat a variety of diseases such as hemophilia and ADA deficiency SCID as well as cancer.

On the same subject, Dr. Anderson (Chief, Molecular Hematology Branch, NHLBI) reviewed the potential uses of gene transfer therapy in cancer and genetic, viral, and cardiovascular diseases.

Dr. Anderson first briefly reviewed the potential use of gene therapy in the two types of diseases already mentioned by Drs. Blaese and Rosenberg: genetic diseases and cancer. Regarding genetic diseases, he listed sickle cell anemia, hemophilia, β-thalassemia, and cystic fibrosis in addition to ADA deficiency as potential candidates for gene therapy. He also mentioned several

approaches other than using TNF gene-modified TILs to treat cancers, including TILs modified with α-interferon, IL-2, tumor-suppressor genes, and other antimetastasis genes.

Next, Dr. Anderson summarized potential gene therapies in viral diseases, specifically AIDS. He outlined two types of approaches:

- Direct delivery of therapy, such as anti-*tat* and anti-*rev*, to the cells to target HIV-infected cells and block the HIV pathway.
- Continuous production of antivirals by introducing a biologic molecule (e.g., soluble CD4) that would result in an ongoing production of the biologic in the patient's body.

Dr. Anderson explained that in order to investigate how to reintroduce the patient's own gene-engineered cells back into the body, a "neo-organ" was developed and evaluated in animal models. Such neo-organ implants, which include cells natural to the body (e.g., fibroblasts, endothelial cells) that have been shown to be accepted as natural tissue and become part of the physiology of the animals, may be incorporated with gene-engineered cells as another potential approach to gene therapy. Thus far, the results of this approach of including gene-engineered cells on implanted neo-organs for secretion of a product have not been reproducible, but research in this area is ongoing.

As an example of gene transfer for cardiovascular diseases, Dr. Anderson cited research involving gene-modified cells for the secretion of t-PA from vascular endothelial cells to prevent clotting *in situ* at vascular grafts.

In conclusion, Dr. Anderson listed the current gene therapy protocols in ADA deficiency SCID and TNF gene-modified TILs in cancer (to be approved). A third protocol, pending further development and approval, will be a protocol for AIDS using a construct on a vascular implant to secret an antiviral. Dr. Anderson closed by expressing his optimism and the hope that other investigators are developing protocols in the field of gene transfer therapy.

In discussion, in response to a question about long-term survival of gene-modified TILs after IL-2 administration ceases, Dr. Rosenberg stated that it appears that the level of TILs decreases rapidly after IL-2 administration ceases. Investigations continue as to whether the effect of the TNF gene-modified TILs is maintained for a period sufficient to achieve a CR. He stated that gene-modified TILs proliferate in animals, but that this has not yet been demonstrated in humans.

Dr. Anderson acknowledged Dr. Temin's critical role as a reviewer of the gene therapy protocols.

VI. STUDIES OF CANCER IN POPULATIONS LIVING NEAR NUCLEAR FACILITIES IN THE UNITED STATES--DR. JOHN BOICE AND MR. SEYMOUR JABLON

Dr. Adamson introduced the next presentation by relating that four scientists from the Radiation Epidemiology Branch, DCE--Drs. Boice, B.J. Stone, and Z. Hrubec, and Mr. Jablon--have been conducting epidemiologic studies of cancer and the environment near 62 nuclear facilities in the United States. These facilities included 52 commercial power plants that began operating prior to 1982, 9 Department of Energy (DOE) laboratories, and 1 commercial fuel reprocessing plant. Dr. Adamson noted that the studies, which were carried out both for scientific

reasons and because of American public health concerns, received guidance from an extramural committee, including members of the DCE Board of Scientific Counselors and Dr. Roswell Boutwell from the NCAB.

Dr. Boice (Chief, Radiation Epidemiology Branch, DCE) began with an overview of the investigation, which was initiated in 1987 after reports from the United Kingdom suggested elevated rates of childhood leukemia in areas around certain nuclear installations. He mentioned that the advisory committee for the NCI study, composed of seven scientists from outside the U.S. government with expertise in radiation epidemiology, met three times between 1989 and 1990 and that a three-volume, 1,700-page report was recently published by the Government Printing Office. Dr. Boice added that the charge of the advisory committee was to provide guidance, assist in interpretation, and suggest areas for future study.

Dr. Boice then reviewed the 1987 U.K. survey of cancer risks in the vicinity of nuclear installations that reported significant excesses of childhood leukemia in areas around defense facilities and fuel reprocessing plants. He reported that this investigation prompted the initiation of a similar survey based on routinely collected vital statistics in the United States. The U.S. study of county death rates used methods similar to those in the United Kingdom.

Dr. Boice pointed out that the excess of childhood leukemia in the United Kingdom was particularly noted around the Sellafield nuclear reprocessing plant, with little evidence of excess risk around nuclear power plants that generated electricity. Most recently, the Sellafield excess was thought to be related to occupational exposure of the father prior to conception.

In the United States, 107 counties with, or adjacent to, nuclear installations were selected for analysis along with 292 control counties. Dr. Boice pointed out that the study of cancer deaths at the county level has been used effectively by NCI in the past. He presented a map from NCI's *Cancer Atlas* showing that although lung cancer rates vary across the more than 3,000 counties in the United States, the highest rates are found in the South Atlantic and Gulf coasts. He stated that subsequent studies have linked this excess to asbestos exposure in shipyards. He also reviewed other studies of cancer deaths at the county level that have been valuable in identifying environmental factors responsible for geographic patterns of cancer.

To give an idea of the numbers involved in the NCI survey, Dr. Boice stated that approximately 19 million people resided in the 107 counties near nuclear facilities and that approximately 900,000 cancer deaths occurred between 1950 through 1984. Thirty-three million people resided in the 292 control counties, and there were approximately 1.8 million cancer deaths in this 35-year period. In the study, cancer death rates for persons living in counties near nuclear facilities were compared to control counties for 16 different kinds of cancer.

Dr. Boice then turned the presentation over to Mr. Seymour Jablon, the principal investigator, to discuss the study in greater detail. Mr. Jablon reviewed the history of the NCI study, beginning with the 1983 British television documentary indicating excessive mortality from leukemia among young people living near the Sellafield nuclear processing plant. As a result of the program, a Ministry of Health committee was formed to investigate the situation. Mr. Jablon related that in the next year, 1984, the committee reported that although there were only a few cases of leukemia in young persons, the number was excessive compared to national leukemia mortality rates. Mr. Jablon then reviewed the results of other studies conducted on areas around individual nuclear plants in Great Britain. In 1987 the British Office of Population Censuses and

Surveys published a massive study of populations living near nuclear facilities in the United Kingdom, and this stimulated NCI to mount a parallel study in the United States.

Next Mr. Jablon reviewed the county data available to the DCE team, which included counts of the numbers of deaths each year in each county as well as population data needed to calculate rates. He mentioned that overall incidence data, i.e., the number of cases of disease diagnosed, existed for only a few states and cities, while mortality data were available for every county in the United States for each year from 1950 on and included cause of death, age, sex, and race. He pointed out that the U.K. findings were also largely based on mortality data.

Mr. Jablon then described the facilities that were in the study. Every commercial nuclear electric generating plant in the United States that went into service before 1982 was included, in addition to a lone commercial fuel processing plant and nine DOE nuclear facilities, which included nuclear reprocessing plants and nuclear weapons manufacturing plants. He noted that the plants that went into service prior to 1970 have much lower power levels than the later plants, but they have been active long enough that if their emissions were responsible for the induction of leukemia or other cancers, the increase would be reflected in mortality data through 1984. Mr. Jablon pointed out that the minimum time for the development of radiation-induced leukemia is thought to be about 2 years, while other forms of radiation-induced cancer generally take 10 years or more to develop. Thus, for facilities that started service in 1975 or later, associated cancers other than leukemia would not be reflected in the mortality data through 1984.

Moving on to a discussion of the 107 study counties, Mr. Jablon noted that they either contain or are adjacent to one of the facilities and account for 20 percent or more of the area within 10 miles of the facility. Three control or comparison counties were chosen for each study county, and an attempt was made to find a match on several characteristics that are important for mortality rates (e.g., mean family income, migration rates, infant death rate, race, education, employment).

Mr. Jablon stated that data were presented as observed deaths, number expected at concurrent national rates, and standardized mortality rates, which were calculated as the number of observed deaths divided by the expected number. Standardized registration ratios, relative risk measures, and statistical tests of significance were also calculated. The study compared the frequency of disease in counties with nuclear facilities with the frequency in control counties and compared the amount of disease before a facility went into service with the amount afterwards. Sixteen kinds of cancer were examined, including leukemias, all other cancers combined, and particular forms of cancer known to be sensitive to induction by radiation.

To illustrate the types of data and forms of analysis employed in reporting study results, Mr. Jablon reviewed a table comparing data on childhood leukemia for all facilities. He demonstrated the design of the table and showed how data were analyzed to come to the conclusion that in both study and comparison areas, the risk of death before age 10 from childhood leukemia went down after plant startup.

Mr. Jablon described the three-volume report of the NCI study as voluminous, with tabulated data in volume one for all facilities combined, as well as for certain groups of facilities such as DOE, electric, early, and late plants. The second and third volumes contain detailed data on individual facilities before and after startup and by 5-year time periods, permitting an assessment of whether cancer rates in those facilities are increasing, decreasing, or unchanged relative to the United States.

Pointing out that childhood leukemia is considered by some to be a bellwether of radiation carcinogenesis, Mr. Jablon than reviewed a table with data showing the number of deaths before age 10 in the study and control areas and the relative risk ratios for the periods both before and after startup. He pointed out that the relative risks, which measure the excess or deficit of disease in one group compared with another, were never significantly different before and after startup and that it was presumably a coincidence that the relative risks before startup are larger than those after startup. In reviewing the data for all cancer except leukemia for all of the facilities and all age groups, he pointed out that the overall relative risk ratios were 1 before startup and only 1.01 after startup.

Dr. Jablon reviewed the overall findings comparing all facilities for leukemia and other cancers before and after startup. For childhood leukemia, the relative risks were larger than 1 both before and after startup, but actually a little larger before startup than after. Similarly, for all ages combined, the leukemia relative risk went down after startup to a value less than 1. For other cancers, the relative risks for children were both less than 1, while there was only a 1 percent increase for all ages.

In reviewing a graph showing the distribution of the ratios of relative risks of childhood leukemia before and after startup, Mr. Jablon pointed out that if there were increases in childhood leukemia after startup, the ratios for more of the facilities would be larger than 1. In fact, the distribution before and after startup was approximately symmetrical and, in fact, 17 of the ratios were less than 1 and only 15 were larger. He stated that the investigators searched for every significant statistical test of relative risk of leukemia that was different from 1 after startup for any facility and any age group and found only 18, which, he stated, was close to the number that chance alone would have produced. Of the 18 significant comparisons, 14 were below relative risks while only 4 were high. He noted that only one of the significant comparisons was for children under 10 and there were three significantly lower comparisons for children 10 to 19 years of age, despite the findings in the U.K. study that showed excesses in childhood leukemia.

Dr. Jablon showed incidence data that were available for study and comparison counties for four commercial nuclear electric generating stations in Iowa and Connecticut. He pointed out that the relative risks after startup in the three counties in Iowa were not significant. For Millstone, New London County, Connecticut, however, the standardized registration ratio (SRR) after startup was a significantly high 1.55 compared with only 1.19 before startup. Mr. Jablon stated that the ratio for mortality was smaller than the incidence ratio (1.45 compared to 1.55 or 17 deaths in 44 incidents), noting that the raised SRR near Millstone may be a chance finding or caused by some other characteristics of New London County, since the SRR was somewhat high before startup. He noted that a 1987 Connecticut Department of Health Services study found no association between the cancer and leukemia rates and proximity to the Millstone electricity-generating plant. Mr. Jablon stated that his research group has just become aware of an investigation of a leukemia cluster in New London County by the CDC in 1972, the year Millstone began operation. The CDC was unable to determine any reason for the cluster. He reported that the high rates of childhood leukemia have continued in New London County from 1972 through 1984, and discussions are underway with the Connecticut State Department of Health concerning further investigations.

In summarizing the NCI findings for all the counties, he related that there is little indication of an increase in risk in the study counties after the facilities went into service. He quoted the advisory committee as concluding that "even the highest relative risks of individual facilities were compatible with the general level of variations seen."

Mr. Jablon listed the following as limitations of the study: (1) the fact that so many comparisons were made that some "significant" differences must have resulted from chance; (2) the variation in the size of the counties; i.e., some counties are very large and contain large cities far away from the nuclear facilities, yet the whole county is included in the study; (3) the fact that many of the facilities began operating in recent years and not enough time may have passed to permit the detection of cancers associated with their operation; and (4) the availability of mortality data only for most of the facilities studied; incidence data, which are needed for the study of some cancers, were available for only four facilities.

Mr. Jablon listed the following as the considerable strengths of the NCI study: (1) the availability of data for each study area over a span of 35 years, which allowed for a comparison between cancer risks before and after the nuclear facility began operation; (2) the large number of facilities in the United States, which provided ample opportunities for expressing risk; and (3) the identification of county data in previous studies that successfully demonstrated the lung cancer risks associated with asbestos exposures in shipyards and with arsenic air pollution from the smelting of nonferrous ores.

In closing, Mr. Jablon reviewed conclusions of the study: No evidence was found that the operation of any of the nuclear facilities that were studied caused excess deaths from childhood leukemia or from other cancers in the counties in which they are located; the increases in childhood leukemia seen in the United Kingdom occurred near reprocessing and weapons plants, but no parallel increases near such plants are apparent in the United States. He added that the study provides general background information that can help guide future studies of areas around nuclear facilities.

Dr. Boice concluded the presentation with a review of the advisory committee's conclusions with regard to the study. The committee concluded that the survey provided no evidence of an excess occurrence of cancer resulting from living near nuclear facilities. Further, measurements of radioactive releases near nuclear facilities indicate that the dose from routine operations is generally much below that from natural background radiation and, hence, unlikely to produce observable effects on the health of surrounding populations. The committee did note, however, that there have been releases from some facilities that have been high, such as at Hanford, Washington. Because there is continued widespread public concern, in part raised by the U.K. findings, the committee recommended further investigations and monitoring, including surveys of smaller population groups, continued monitoring of mortality data, and exploration of the use of cancer incidence data. The committee also recommended that case control studies or analytic studies in small areas around nuclear facilities, though potentially informative, should be undertaken only after careful consideration.

In addition, the committee felt that a study based on linking rosters of records together might be feasible in the future, as well as a study similar to the U.K. study that was conducted around the Sellafield nuclear fuel reprocessing plant. In this regard, Dr. Boice mentioned that scientists at the Pacific Northwest Laboratory in Washington State have initiated a study of areas around the Hanford site to determine if childhood leukemia could possibly be linked to occupational exposures of the parents. In addition, NCI is conducting a collaborative study of 2,000 children with leukemia to evaluate the risk of preconception radiation.

A final recommendation of the committee related to cooperation with others conducting similar types of research. Dr. Boice pointed to DCE investigators' efforts to maintain contact with their counterparts at DOE and CDC. He added the DCE has been interested in studying the

workers at nuclear power stations for several years and, with the Nuclear Regulatory Commission, has recommended making changes in reporting requirements so that occupational doses and personal identifiers can be reported annually. He stated that these changes have been approved and will be published in the Federal Register in the near future.

Dr. Boice concluded that the overall findings are reassuring but pointed out that some of the counties may be too large to detect any risk that may be present in limited areas around some of the plants. He pointed out that while no study can prove the negative, if any excess cancer risk due to radiation pollution is present in counties with nuclear facilities, the risk was too small to be detected by the methods employed. He stressed that the NCI study should not be considered a definitive one but rather a first step in providing background information to help guide further studies.

In response to Dr. Temin's question, Dr. Boice stated that it is not clear whether the U.K. findings of excess cancers in Sellafield could be attributed to chance on the basis of the U.S. data or to factors that are not yet known. He noted that a case control study around the Sellafield processing plant linked the excess in childhood leukemia to the occupational exposures of the parents. This hypothesis is going to be tested further in both the United Kingdom and the United States. He added that a number of other hypotheses are being explored including the hypothesis that the childhood leukemia may be a response of the host population to a viral infection when populations are migrating into rural areas. He also described a U.K. study of potential sites for nuclear plants that had never been built that found the same results of excessive childhood leukemia and Hodgkin's disease that they found in areas around nuclear facilities. Thus it was concluded that there may be something operating in the U.K. environment other than radiation pollution. Dr. Boice was also asked if the variation in prevailing winds was considered in choosing the counties for the study. He noted that was a concern but was not an issue that could be looked at comprehensively for all the sites.

Speaking as a member of the ad hoc advisory committee, Dr. Boutwell commented on the careful design and thoroughness of the study and commended Mr. Jablon for his work in heading the study. He noted Mr. Jablon's long experience as an epidemiologist in the followup studies on the atom bomb and service as administrator for that program before he come to NCI.

VII. CLOSED SESSION

A portion of the second day of the meeting was closed to the public because it was devoted to the Board's review of grant applications. A total of 1,226 applications were received, requesting support in the amount of $270,371,594. Of these, 1,162 were recommended for funding at a total cost of $231,487,213.

VIII. UPDATE ON THE CENTERS, TRAINING, AND RESOURCES PROGRAM-- DR. BRIAN KIMES

Dr. Kimes reminded the Board that the reorganization of the Division of Cancer Biology and Diagnosis involved the creation of the Centers, Training, and Resources Program (CTRP) in November and a change in name to the Division of Cancer Biology, Diagnosis, and Centers (DCBDC). Recruitments to the new Program include Dr. Margaret Holmes as Chief of the Cancer Centers Branch, Dr. Andrew Chiarodo as Chief of the Organ Systems Coordinating Branch, Dr. Ken Brow as Chief of the Research Facilities Branch, and Dr. Vincent Cairoli as Chief of the

Cancer Training Branch. He noted that with the reorganization, all research programs of the Institute have been placed under one administrative aegis.

Following comments on the unique role of CTRP as a linkage for communication between NCI research programs, and on CTRP's commitment to represent equally the interests of programs within every Division of NCI, Dr. Kimes brought Board members up to date on the accomplishments of the four CTRP branches.

The Organs Systems Coordinating Branch held major workshops on prostate and breast cancers. Smaller workshops included "Multiple Myeloma and Black/White Risk Factors," as an add-on to the workshop sponsored by the Laboratory of Genetics, and "Workshop on Levamisole: Mechanism of Tumor Action" in conjunction with DCT. The Branch is planning workshops on lung, colon, and rectal cancers for the next year. In addition, the Branch is working to initiate R13 grants for conferences on organ cancer site topics, this year in the area of ovarian cancer and next year in upper digestive tract cancer, renal cancer, and melanoma. Dr. Kimes emphasized and commended the Branch's more comprehensive focus following the recent restructuring and the importance of its function in linking scientists in basic and clinical areas across operational levels of the Institute.

Dr. Kimes pointed out that the Research Facilities Branch of CTRP administers NCI's construction program, which is the only active peer-reviewed construction program at NIH; the only construction grants currently being funded are to NCI-supported cancer centers with P30 grants. The Branch acts as a resource for inquiries from other Institutes about the peer review and award of construction grants, and is currently handling the review of the Jackson Laboratories grant for NIH. In addition, the Branch has updated a construction handbook that will serve as a guide for all of NIH and is studying the construction projects of the past 20 years to see if the goals of the NCI construction program have been maintained.

In speaking of the current work of the Cancer Centers Branch, Dr. Kimes first reviewed the purposes of a cancer center support (core) grant, also called a P30 grant. He emphasized that core grants are not merely administrative grants; rather, they are important components of Cancer Centers in that they sustain and enhance a cancer focus, support interdisciplinary collaboration on cancer research, provide cost-effective access to new technologies and critical services, and help build new programs by providing development funds to take advantage of research opportunities. Dr. Kimes noted further that the core grant is only one funding mechanism for Cancer Centers; other funding includes State and institutional funds, industrial support, and private donations. He emphasized the importance, however, of the leverage P30s provide for collecting funds from these sources.

Continuing his discussion of the Cancer Centers Branch, Dr. Kimes referred to the newly revised guidelines defining the programmatic elements of a Comprehensive Cancer Center. The guidelines provide a systematic way of assessing comprehensiveness for designation by NCI as comprehensive centers. Dr. Kimes noted that about 17 centers received comprehensive designation under the original guidelines, and centers at the University of North Carolina, the University of Arizona, the University of Pittsburgh, Wake Forest University, and Dartmouth College have recently been designated as comprehensive under the new guidelines after an administrative review in the transition period. In addition, the peer review process for new cancer center support grant awards has begun, and the Fox Chase, Yale, and Roswell Park Cancer Centers have successfully undergone peer review for a total of 24 Comprehensive Cancer Centers.

Dr. Kimes stated that the strategic plan known as the Five-Year Plan for Cancer Centers would be addressed as part of the report of the Subcommittee on Cancer Centers. He expressed approval of the concept in that it represents the centers as a component that relies on the health of the entire National Cancer Program but acknowledged the difficulty of devising a plan to satisfy the diversity and individuality of all cancer centers. He expressed the opinions that NCI can work with the centers individually and in groups and that the centers will be willing partners with NCI.

Dr. Kimes reported that on May 23, 1990, a meeting was held with Dr. Samuel Broder and the Cancer Center Directors. Issues discussed included cooperation with Federal agencies important to Cancer Centers (e.g., Health Care Financing Agency, Agency for Health Care Policy and Research), availability of Group C drugs, distribution of CTEP INDS, the general clinical research centers now supported by the National Center for Research Resources, planning grants for underserved geographical areas, and construction funds. Dr. Kimes described the workshop for Center Directors as very productive, noting that it was the first of its kind in several years and was held in sequence with the meeting of the American Association of Cancer Institutes. He reported that the Directors considered and affirmed the new strategic Five-Year Plan for the Cancer Centers. Other issues discussed included disproportions in Center budgets, strategies for budget defense and maximum utilization, P30 grant guidelines and the relationship of P30s to support for high-quality clinical protocols, and the possibility of centers matching NCI funds for research in some areas of cancer prevention and control. Dr. Kimes commented that he felt the Directors' workshop and meeting with Dr. Broder did much to secure a closer, more productive working relationship between NCI and the Cancer Centers.

Dr. Kimes briefly reviewed the history of the Cancer Centers Program, pointing out that the stability in the number of centers over the past 6 years has been achieved by downward negotiation of grants when appropriation would not support full funding. He reviewed the potential for a precipitous decline in the number of centers if the language of the House Report is included in the enacted appropriations. He stated that DCBDC, after consultation with the Executive Committee, would have some possible approaches to the problems to present at the December meeting.

Addressing the recent activities of the Cancer Training Branch, Dr. Kimes reported that much work is being done to make the training programs more responsive to NCI's real research needs. Initiatives to be presented for review by DCBDC's Board of Scientific Counselors include issuing RFAs for R25 grants to support education programs in pain management and psychosocial services, collaborative education programs involving centers and schools of public health, and education programs in community outreach service. In addition, DCBDC and DCPC are collaborating on an initiative to award K07 grants for career training of cancer prevention and control researchers.

On September 12, 1990, the Branch held a workshop on Training and Clinical Research in Oncology that identified a need to increase the flexibility of current institutional and training mechanisms and initiate a new training mechanism to give Cancer Centers a broader capability to train M.D.s for careers in clinical research. Participants also concluded that clinical researchers do not have adequate access to the R01 funding mechanism. Dr. Kimes noted that DCT's Cancer Therapy Evaluation Program has been analyzing DCT's R01 and P01 portfolios and has contributed to a joint DCT-DCBDC report on the problem that will be presented to the DCT and DCBDC Boards of Scientific Counselors at their October meetings. Details of the findings will be presented to NCAB at the December meeting along with a request for concurrence with certain recommendations.

Referring to an ongoing search for funding support for some of the programmatic thrusts required under the new comprehensiveness guidelines, Dr. Kimes reported that an innovative mechanism has been identified that is supported by the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA). He noted that access to ADAMHA's mental health grants might benefit the Comprehensive Cancer Centers in times of NCI budget constraints.

In discussion, Dr. Mihich asked if qualitative differences could be distinguished between clinical/comprehensive centers and basic centers to maintain the present number of the former by funding the latter under mechanisms other than the P30 grant. Dr. Kimes noted that this issue had been addressed by the ad hoc cancer center directors' advisory group and some level of consensus had been achieved that separate funding plans should be considered in the future. He identified a further issue with respect to clinical/comprehensive centers in that these complex enterprises cannot easily be restored if they fail to receive NCI funding. He pointed out the dilemma that while 45 top-flight centers would represent a strong cancer centers program, the other 25 are extremely productive and many other institutions that could provide innovative ideas on clinical cancer research are developing an interest in becoming cancer centers.

IX. OVERVIEW OF AIDS-RELATED LYMPHOMA: IMPACT OF ANTI-AIDS THERAPY--DRS. SAMUEL BRODER, JUDITH KARP, ROBERT YARCHOAN, AND WILLIAM A. BLATTNER

Dr. Broder introduced the topic by stating that in the past 20 years non-Hodgkin's lymphoma has had an increased incidence of approximately 20 percent and an increased death rate of 22 percent. These facts are notable because this is a disease for which there is an enormous technological capability for therapy. Non-Hodgkin's lymphoma is not a rare disease: more than 36,000 Americans are affected per year.

In the early 1980s the SEER database reflected a significant increase of occurrence of non-Hodgkin's lymphoma in men aged 20 to 49, but not in women. Examining these and other data, it became clear this increase was associated with AIDS and HIV. Given this trend, Dr. Broder stated, an increase can be expected in the next few years in the number of cases of non-Hodgkin's lymphoma, many of which will be AIDS-related. He noted that this will place another burden on the U.S. medical care delivery system. For these reasons there is a need to stimulate new basic research, diagnostic, prevention, and treatment strategies for non-Hodgkin's lymphoma. Following Dr. Broder's introduction, Drs. Karp, Yarchoan, and Blattner reported on some of the work being done on AIDS-related lymphomas.

OVERVIEW--DR. KARP

Dr. Karp introduced her topic by stating that since the beginning of the AIDS epidemic an association between a variety of cancers and AIDS has been recognized. Recently, a striking increase in high-grade B-cell lymphoma has been noted and is believed to be a result of HIV infection, particularly in patients who have survived other AIDS symptoms for a considerable length of time.

The concept that viruses can cause uncontrolled cell proliferation was elucidated by Dr. Rouse in 1911, and in 1970 Drs. Temin and Baltimore discovered reverse transcriptase, a viral enzyme that allows retroviruses to express themselves in mammalian cells. The Epstein-Barr virus has been known to be associated with lymphomas since 1964, and particularly so in patients with compromised immune systems who have abnormal T-cell function.

In the 1980s, with the emerging knowledge of AIDS, the etiologic factors of B-cell malignant transformation and T-cell immunodeficiency were seen to be related and in 1982 the first recognition of AIDS-related lymphoma occurred.

Dr. Karp presented a 1986 memorandum in which Dr. Blattner raised the following questions:

- Is the severity of immunodeficiency directly correlated with the risk for cancer?
- Is the type of cancer correlated with the severity of immunodeficiency?
- Do site-specific cancer risks reflect interactions of known or suspected environmental life style or host cofactors whose effects are amplified by HIV-associated immunodeficiency?
- Does HIV modify the natural history of cancer, e.g., high-grade at presentation, etc.?
- Does the dose or duration of HIV infection, as indirectly measured by questionnaire, influence the risk for cancer?

Since the memorandum was issued, Dr. Gail and his colleagues have projected that there are likely to be 5,000 to 10,000 AIDS-related non-Hodgkin's lymphoma cases by 1992; HIV will be responsible for 25 percent of all non-Hodgkin's lymphomas by that time.

Dr. Karp reviewed the characteristic genetic changes associated will B-cell malignancies. She also noted that the lymphomas are often found in the central nervous system, the gastro-intestinal tract, and the bone marrow, a pathology that may be related to the AIDS virus, or perhaps is related to the rich reservoirs of monocytes in these areas that may serve as repositories for viral particles and lymphokine production sites. Treatment of the lymphomas involves low-dose chemotherapy, central nervous system prophylaxis, antiviral therapy, and in some instances hematopoietic simulators. Remissions are rare and recrudescence to disease is very common.

Intramural researchers associated with the AIDS Lymphoma Working Group are developing strategies for effective treatment. The working group's goals are: (1) to define cellular, humoral, and/or viral mechanisms of B-cell activation and eventual malignant transformation in AIDS; (2) to identify a means of abrogating unrestrained B-cell proliferation before irreversible clonal expansion ensues; and (3) to translate preclinical findings into clinical trials aimed at prevention and treatment. Four areas for investigation have been selected: (1) the genesis, perpetuation, and expansion of clonal B-cell activation; (2) the identification of lymphokine inhibitors; (3) the establishment of a number of lymphoma cell lines from the AIDS-related lymphomas; and (4) the identification of patients at high risk for developing lymphoma by longitudinal monitoring of serum and cerebrospinal fluid.

Extramural efforts are being solicited under two RFAs. One is from the Division of Cancer Etiology and focuses on viral causation and interplay between virus and the host genome. The other is from the Division of Cancer Treatment and aims to develop innovative clinical trials with emphasis on clinical-laboratory correlates.

CHANGING INCIDENCE OF AIDS-RELATED LYMPHOMA--DR. YARCHOAN

Dr. Yarchoan presented observations from the intramural group about the extent of AIDS-related lymphomas. In 1989, 3 percent of AIDS patients in the United States had lymphoma as their AIDS- defining ailments, representing 1,098 lymphomas nationwide. Additionally, certain HIV-infected patients may develop lymphoma after having another AIDS-defining illness. It is

estimated that between 3 and 10 percent of HIV-infected patients will ultimately develop lymphoma.

The intramural studies suggest that with the advent of antiretroviral therapy the actual number of AIDS-related lymphomas has increased and will continue to increase. The 55 patients involved in the original Phase I trial of AZT (including combinations of AZT and acyclovir, and AZT and ddC) have been followed to determine the long-term benefits and toxicities of AZT therapy. Thirty-three of the patients had AIDS, 22 had ARC with either weight-loss or thrush, and none of the patients had lymphoma at the beginning of the protocols.

At present, 8 of the 55 patients have developed lymphoma (14 percent or 8.9 percent per patient per year). Five patients had involvement of the brain, three had involvement of the other visceral organs. All of the lymphomas were typical of those found in AIDS patients. Four of the patients had small cell non-cleaved lymphoma, three had large cell immunoblastic lymphoma, and one patient had what appeared to be two separate components. Most of the patients developed lymphomas after the first two years of therapy. Dr. Yarchoan noted that in three of the patients the lymphomas were difficult to diagnose and most probably would have been missed in any other clinical setting. The eight patients were treated with a variety of regimens including cranial radiation and combination chemotherapy, but their survival was quite poor. The five with primary CNS lymphomas had a median survival of 1.8 months and the other three had a median survival of 7 months. The overall survival rate was 2.5 months.

Dr. Yarchoan emphasized that although these survival figures were poor, few of these patients would have been expected to live beyond two years in the absence of therapy. Plotting the development of lymphomas over time using the method of Kaplan and Meier, one finds that 36 months after starting on therapy, 46 percent of the patients would be expected to develop lymphomas with a 95 percent confidence interval ranging from 19 percent to 75 percent of the patients.

Dr. Yarchoan noted that an important question raised by these facts is whether lymphomas are directly caused by AZT. He stated that the facts appear to disprove the connection. AIDS patients who have never received AZT have developed lymphomas of similar types and in similar sites as patients on the drug. Patients who do not have AIDS but who are severely immunodeficient also have developed lymphomas. Animal models have not shown that AZT caused lymphomas, although there have been reports of vaginal tumors in rodents receiving life-long AZT therapy.

In conclusion Dr. Yarchoan stated that, based on the small study group of patients, the incidence of AIDS-related lymphomas will substantially increase in the next few years. He also noted important directions for research to address the problem: a better understanding of the pathogenesis of lymphomas to explore ways for preventing the condition; examination of inhibitors of B-cell stimulatory factors or other possible viral cofactors; determination of whether early therapy or HIV infection can prevent profound immunodeficiency and thereby reduce the incidence of lymphomas; development of more effective and novel therapies for HIV infection. As part of these efforts, it will be important to determine whether new therapies such as ddI may be associated with a lower incidence of lymphoma, and to develop new approaches to the treatment of AIDS-related lymphomas, particularly those that spare the bone marrow.

EPIDEMIOLOGY OF AIDS-RELATED LYMPHOMA--DR. BLATTNER

Dr. Blattner noted that over the past decade, the field of human virology, particularly retrovirology, has made tremendous progress, including the discovery of the HTLV and HIV viruses. The HTLV viruses have been found to be associated with a number of lympho-proliferative malignancies, particularly adult T-cell leukemia, which accounts for more than 50 percent of non-Hodgkin's lymphoma. HTLV may also be associated with B-cell lymphocytic leukemia, T-hairy cell leukemia, and other cancers. The HIV virus has been associated with a number of lymphomas as well as other cancers, particularly Kaposi's sarcoma. There is also emerging evidence that the papillomavirus may be associated with malignancies.

Dr. Blattner reported that during the mid-1970s, the New York State Cancer Registry identified what appeared to be an epidemic of cancer, particularly Kaposi's sarcoma, before the AIDS epidemic was recognized. These cases of Kaposi's sarcoma occurred in the "silent phase" of the AIDS epidemic, the 2 to 10 year period before emergence of clinical disease, but after infection with the virus. Kaposi's sarcoma occurs most often in high-risk populations, particularly homosexual young men. The CDC statistics show an increase in immune deficiency-associated conditions, whereas the incidence of Kaposi's sarcoma has remained constant. The CDC statistics report 4,277 cases of non-Hodgkin's lymphomas (2-3 percent of all AIDS-defining illnesses) in 139,765 reported AIDS cases as of June 1990. The majority of these AIDS-related lymphomas occurred since 1987, due partly to better reporting since 1985 and also to an increasing risk of infection.

Dr. Blattner then reported on a cohort of 245 homosexual men who were enrolled in a prospective study in 1982 and followed yearly. As of January 1990, 131 men (53.5 percent) tested seropositive for HIV, 36 percent of whom are documented seroconverters (their HIV status changed during the study). For the HIV-positive cohort, the incidence of Kaposi's sarcoma from years 1-8 of the study remained relatively constant, whereas the incidence for non-Hodgkin's lymphoma rose steadily. There has been an increased incidence for both diseases in the most recent time period. Dr. Blattner reported that researchers believe the current increases may reflect an association with progressive immunodeficiency.

Dr. Blattner then presented data from frozen sera specimens for the seroconverter cohort dating from 1982. Looking at pre-existing markers, particularly for non-Hodgkin's lymphoma and Kaposi's sarcoma, patients were found to have high titers of antibodies for Epstein-Barr virus capsid antigen compared with both the cohort with opportunistic infections and the AIDS-negative cohort. Examining individual patients who developed non-Hodgkins lymphoma, Dr. Blattner's group found the patients had developed markers for subclinical immunodeficiency as many as 5 to 6 years and as few as 2 years before their development of the lymphomas. Dr. Blattner speculated that this may contribute to the pathogenesis of the virus: selected clones of the T-lymphocytes, the memory cells, may serve as the targets for HIV infection, and the selected depletion of suppressive immunocytes may allow for the unregulated expression of a possibly oncogenic herpesvirus.

Dr. Blattner then introduced some findings of Dr. Biggar, who has developed a quantitative measure comparing the occurrence of cancers in the pre-AIDS era with cancers during the AIDS epidemic to help determine which malignancies are associated with the disease. Using this method it is possible to identify a change in the pattern of emerging tumors, particularly Kaposi's sarcoma, and the non-Hodgkin's lymphomas. Other cancers show changing rates of incidence, such as the modest elevation in anal/rectal cancer in HIV-infected men, which may reflect the

correlation found between the presence of activated human papillomavirus (HPV) infection and the level of immunosuppression. This finding suggests a future increased incidence of malignancies in HIV-infected women as their immune deficiencies continue to rise.

Dr. Blattner reported that Dr. Gail from the Biostatistics Program has developed techniques to monitor and project the future course of lymphomas in the AIDS population. Using this method Dr. Gail found the incidence of non-Hodgkin's lymphomas in young men (aged 20 to 49) approached the incidence rates of men in the aged 65 to 80 group. Projections for the 1990 incidence of HIV-related non-Hodgkin's lymphomas and Kaposi's sarcoma are 2,000 and 7,000, respectively, but the impact of anti-AIDS therapies--particularly the effects of prolonged states of immunosuppression--seem to suggest much higher rates for these cancers. Alternately, if the effect of therapy is to improve the immune status of the host and prolong survival, there may be fewer lymphoma cases. From all estimates, at the current time it is anticipated that 10 to 20 percent of non-Hodgkin's lymphomas may be associated with HIV infection.

Dr. Blattner stated that NCI's future directions for research in epidemiology include expanding surveillance and getting more precise estimates of the effect of therapy on AIDS incidence. This information will allow the development of studies to address treatment effects in cohorts treated with different drugs to determine pathogenic phases of the disease.

During the discussion following the presentations, a question was raised by Dr. Frost about the correlation between the incidence of lymphomas and the presence of Epstein-Barr or other herpesviruses. He pointed out that some of the patients were treated with AZT and others received acyclovir in addition to the AZT, and wondered if the acyclovir had an effect on the incidence of lymphomas. Dr. Yarchoan answered that no differences were seen, partly because of small sample size, and partly because all patients were HIV-positive at the time the study began, with varying levels of immunosuppression.

Dr. Temin asked for a comparison of survival and response to treatment rates of the HIV-related non-Hodgkin's lymphoma cohorts. He also asked whether the Kaposi's sarcoma and lymphomas were mutually exclusive. Dr. Yarchoan answered that the HIV-related non-Hodgkin's lymphomas were much worse than lymphomas overall. He further stated that the Kaposi's sarcoma and non-Hodgkin's lymphomas have been noted to occur together. He elaborated that the steroid treatment for the lymphomas can cause an exacerbation of the Kaposi's sarcoma, which presents a problem in treating patients.

Dr. Temin asked whether HTLV-I or II was involved in the etiology of HIV-infected or non-HIV-infected lymphomas. Dr. Blattner replied that there is some evidence that HTLV infection accelerates immune deficiency, and cited anecdotal reports of T-cell leukemia in HIV-infected individuals who are also HTLV-infected. He stated that Dr. McGrath at the University of California, San Francisco, has found evidence for an indirect mechanism that perhaps answers the question of whether an HTLV-like virus may be involved in some AIDS lymphomas. This may be a focus for new research in areas where HTLV is more common than in the United States.

X. LEGISLATIVE UPDATE--MS. DOROTHY TISEVICH

Ms. Tisevich reported that NCI arranged a pre-release briefing for Congressional staff on the NCI report entitled "Cancer in Populations Living Near Nuclear Facilities," and has distributed nearly 200 copies to congressional offices.

On the subject of the reauthorization of NCI's special authorities, Ms. Tisevich reported that on June 18, 1990, the House Energy and Commerce Subcommittee on Health and the Environment held a hearing on the Reauthorization of NIH at which Dr. William Raub, Dr. Richard Adamson, and Dr. Claude Lenfant testified. The major focus of the hearing was on findings of the General Accounting Office (GAO) study of NCI's implementation of its policy to include women in study populations in NIH-funded research. Mark Nadel of GAO testified that the policy had not been adequately applied across NIH and that demographic data on NIH study populations were not readily available. Representatives Snowe, Schroeder, Conte, and Walgren also testified, arguing for inclusion in the NIH Reauthorization Act of several bills which they are sponsoring. Ms. Tisevich referred Board members to their legislative update packages for information on provisions of those bills. NIH reauthorization bills were introduced in the Senate on July 16, 1990, and in the House on September 18, 1990.

Ms. Tisevich also noted that the Women's Health Equity Act, introduced in both Houses in late summer, includes 20 separate bills to develop disease prevention activities responsive to the needs of women, to promote greater equity in the delivery to women of health care services, and to extend research on women's health issues. In addition, the Act would create an Office of Women's Health under the Assistant Secretary for Health and the Surgeon General, a National Center for Women's Health Research at NIH, and an NIH intramural program in obstetrics and gynecology, and would codify existing policies of NIH and ADAMHA to require the inclusion of women and minorities in research study populations.

Finally, Ms. Tisevich pointed out that, in response to a request from Congress, the Office of Technology Assessment (OTA) released a report on September 19, 1990, entitled "Unconventional Cancer Treatments." The report includes chapters on various types of unconventional treatments, including one on immunoaugmentive therapy (IAT) that was a response to a request that OTA evaluate IAT and design a clinical trial for its evaluation. Also explored are the ways in which people find out about these treatments, claims made by proponents, sources of information, and legal issues. Ms. Tisevich pointed out that while the report does not offer recommendations, several options are provided for consideration by appropriate agencies. They include options for (1) gaining further information on the use of unconventional cancer treatments in the United States, (2) gathering and making information available on unconventional cancer treatments and practitioners, (3) improving information on the efficacy and safety of treatments used by U.S. citizens, and making this information available to cancer patients, and (4) making available information on legal sanctions against practitioners and health problems related to unconventional treatments. Ms. Tisevich noted that NCI is currently reviewing the options in the OTA report to determine the feasibility and appropriateness of their application and is preparing a response.

The discussion following Ms. Tisevich's presentation centered on the possibility of assistance from NCAB and the DCT Board of Scientific Counselors in preparing NCI's response to the OTA report. It was decided that the Subcommittee on Information and Cancer Control, with the help of the DCT Board, will assist in preparing NCI's response. The Subcommittee's draft will be presented for consideration at the December NCAB meeting.

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

Dr. Raub began by saying he had requested time to address the Board on two important issues: NIH-sponsored research related to women's health and cost containment for NIH research grants. Regarding the first issue, he reported that NIH recently received unfavorable publicity

with respect to its research related to women's health. Members of Congress and others charged that NIH pays inadequate attention to women's diseases, which are defined as those that either are specific to women, such as ovarian cancer, or have a disproportionately large impact upon women, such as breast cancer or lupus. In addition, there was criticism that NIH's recruitment of women to participate in clinical trials associated with diseases or disorders affecting both genders is inadequate. Furthermore, although an NIH policy exists stating that high priority is given to women's diseases and special efforts are made to ensure equal representation in clinical trials, the General Accounting Office (GAO) determined that NIH internal procedures for implementing that policy are inadequate, which finding triggered a series of congressional hearings on these issues.

Dr. Raub emphasized to the Board that if there is any truth to these charges, that would be entirely unacceptable to NIH. He explained that the issue of apparent inadequate attention to women's diseases is part of the general issue of how research programs are balanced; that is, how much a given Institute funds research on one disease as compared with other diseases. The debate on this issue was fueled when several members of the Congress cited a figure that was calculated by an internal NIH women's advisory group in 1987. Dr. Raub said this advisory group, taking a deliberately narrow definition of women's diseases, calculated that in that year 13 percent of NIH's expenditures funded research related to women's diseases. He pointed out that had the group calculated the analogous figure with respect to men's diseases, it would have been only approximately 5 percent. He said another 50 percent is funded for research relevant to diseases that affect both genders, which leaves approximately the last third, which is funding for basic scientific research.

Dr. Raub noted to the Board that during these debates, the media highlighted the action by the NCI and the NCAB to reverse the decision to proceed with the Women's Health Trial (WHT). According to Dr. Raub, as the action was portrayed in the media, the sole basis for the Board's decision not to go ahead with the 10-year, approximately $100 million study was that it was too expensive, although NIH has funded studies elsewhere of comparable size and duration that had male-only cohorts. He said the scientific issues underlying the decision not to proceed with the WHT were lost in the coverage. They included the nature of the etiologic role of fat in the diet with respect to breast cancer, concerns about compliance with a low-fat diet, concerns about how to monitor the adequacy of compliance, and the overall concern about the trend that may occur over the next decade of many people adopting low-fat diets for health promotion in general.

With regard to the representation of women in clinical trials, Dr. Raub said the National Heart, Lung, and Blood Institute (NHLBI) was the primary focus of the criticism because it has conducted studies on cholesterol reduction and other interventions with respect to the prevention of heart disease that were conducted with male-only cohorts. He commented that the cholesterol studies did not come under particularly heavy fire because in the judgment of NHLBI, the American Heart Association, and others, the results can be extrapolated to both genders. Therefore, most of the advice given about cholesterol levels is said to apply to women as well as to men. In contrast to the cholesterol studies, another NHLBI heart disease prevention study was the target of heavy criticism. It involved taking an aspirin, beta carotene, or a placebo every day, and was carried out on approximately 30,000 male physicians. Dr. Raub said the finding, while not definitive, was that the aspirin had a preventive effect; however, few researchers are willing to extrapolate this effect to the other gender. Therefore, there has been criticism that a major investment was made by NIH, producing a result of reasonably definitive character, but one that does not apply to more than one-half of the population.

When NIH was examined overall, in general the representation of women in clinical trials was found to be very good, with NCI ranking near the top, Dr. Raub said. He noted that the GAO report dealt strictly with procedural issues, and did not examine the data bases of clinical trials results. Because it relied on interviews with a number of staff members, it tended to be anecdotal rather than quantitative. GAO reported instances where NIH staff members in positions responsible for carrying out the women's health policy were not aware or only vaguely aware of the policy, or were aware of the policy but felt it was too difficult to implement.

Dr. Raub said that after two hearings, a much better understanding was reached between NIH and Congress. He added that while the debate was full of hyperbole, NIH acknowledged that it can and must improve its performance in certain areas. He reported that NIH has refined and restated it women's health policy and this fall began a series of sessions on the policy for its program and review staff. Furthermore, a new Office of Research on Women's Health within the Office of the NIH Director has been created. Dr. Ruth Kirschstein, the Director of the National Institute of General Medical Sciences, has been appointed Associate Director for Research on Women's Health. Dr. Raub said Dr. Kirschstein has been active in the area of women's health, and credited her with much of NIH's progress and the turnaround in its relationship with the Congress on this issue.

Dr. Raub expressed confidence that NIH's strong commitment to women's health will be strengthened as a result of the debates on the issue. He said NIH will gain not only more insight about itself, but also stronger ties to a broader segment of the community and to Congress. Institutes such as NCI, which make major investments in research and have leading programs on diseases such as breast cancer, stand to benefit from the broader recognition of and emphasis on these projects. He stated that NIH's basic mission is to improve human health, and ideally the research it funds should produce results that can be broadly extrapolated and not be confined to one gender, age group, or race.

The second issue Dr. Raub addressed was the issue of cost containment for research project grants. He reported that this year's House Appropriations Committee Report sends a strong but mixed message regarding research funding appropriations for NIH. He said that on the one hand, the committee would like to allocate approximately $1 billion more to NIH than the President requested, which is an unequivocal endorsement of biomedical research in general and of the Institutes' activities in particular. On the other hand, the committee's language accompanying the budget recommendation is very specific as to how to resolve what the committee believes is an unsatisfactory system for containing the growing costs of research grants. Dr. Raub said the Senate is likely to agree in principle with the House Report, and probably will come to terms with its recommendations.

Dr. Raub observed that the House Report addresses three major issues. One is that the costs of research grants are not adequately controlled by NIH's system, as evidenced by the fact that the average cost of an NIH research project grant has increased every year in an amount greater than the prevailing inflation rate. Secondly, when NIH increased the duration of research project grants, resulting in a change from an average of 3 to 4.2 years, the rising costs problem was made worse because grants were being kept in the system of funding commitments longer. He noted that for 4 years in the middle 1980s, NIH was able to make approximately 6,000 new or competing renewal research grants each year. As these commitments rolled through the system, they were magnified somewhat by the increase in the average duration of grants and by the increase in their average cost. All of these factors came together against an FY 1990 budget level that did not

allow for funding both the noncompeting grants and new grants. The problem thus manifested itself in a major drop in the number of new and competing renewal research grants.

The third issue addressed by the House is leadership, Dr. Raub reported. The committee believes that not enough is being done, either by NIH or by the larger scientific community, to deal with the unproductive dissent and strident advocacy that has occurred with respect to biomedical issues. He said the committee wants NIH to focus that energy and provide both short-term and long-term leadership to the biomedical community. Using its own recommended billion-dollar increment, the committee suggested that NIH strive for 6,000 new and competing renewal research grants, a project grant duration of approximately 4.0 years, and the elimination of the practice of downward negotiations. To achieve these goals, it suggests a set of actions to be taken with respect to the peer review system and by the awarding Institutes. The committee specifically calls for tighter scrutiny in the peer review system of research budgets. It also suggests the concept of taking the total cost of a grant into consideration in the decision to make an award, i.e., price competition. Dr. Raub said that within the NIH grants administration system, the focus is primarily on the scientific and technical quality of the proposals, as perceived by the two levels of the peer review system. By contrast, in the contracting and procurement business in general, price competition is the crux of funding decisions and the goal is to get a technically first-rate product at the lowest possible cost. The committee is suggesting that NIH consider all of the potential cost containment tools, including price competition.

Dr. Raub said he believes the actions suggested by the committee would not cause a major management problem for the Institutes; however, the philosophical and policy aspects of these issues will need discussion and debate.

Dr. Raub then described NIH's current approach to addressing the cost containment issue. He said a group within the Office of Extramural Research in the Director's Office and in the Division of Research Grants examined cost containment options and presented them for review by the Institute, Center, and Division Directors. A report will be published when these options are sufficiently refined. A statement also will be published in the *NIH Guide for Grants and Contracts*, and a series of public meetings will be held around the country giving interested individuals and representatives of organizations the opportunity to share their ideas and criticisms. Dr. Raub said the Advisory Committee to the NIH Director will feature this issue at its meeting this fall. Ideas and options will be distilled at that meeting, and then will be shared with the National Advisory Councils and Boards in advance of their next meetings. He informed Board members that their criticism and advice will be solicited on the needs of NIH and biomedical science, and specifically on the needs of NCI.

Dr. Raub said Congress wants NIH to take the lead within the biomedical community and to devise a coherent plan to deal with the issue of cost containment. He concluded by expressing his hope that the various activities undertaken by NIH will result in such a plan, which NIH will present at the congressional appropriation hearings in the spring.

XII. FLUORIDATION OF DRINKING WATER AND SUBSEQUENT CANCER INCIDENCE AND MORTALITY--DRS. RICHARD H. ADAMSON AND ROBERT N. HOOVER

Dr. Adamson, Director, DCE, introduced the report on fluoridation in drinking water by citing the draft results of a study conducted by the National Toxicology Program (NTP) in response to public concerns that no government bioassay of sodium fluoride had been performed. The Department of Health and Human Services reported in April 1990 the results of a study of

B6C3F1 mice and F344 rats exposed to pre-doses of 25 ppm, 100 ppm, and 175 ppm of sodium fluoride (which correspond to 11 ppm fluoride, 45 ppm fluoride, and 79 ppm fluoride) as well as a control group of animals. There was no evidence of carcinogenicity in female rats at any dose of sodium fluoride, none in any male or female mice, and a clinical evidence of osteogenic sarcoma in the male rats, which were 1 out of 50 at the 100 ppm dose, and 3 out of 80 at the 175 ppm dose. Dr. Adamson said this study prompted an update of DCE's 1976 review and study of fluoridation of drinking water and its relation to cancer incidence and mortality, which Dr. Hoover would present. He noted that the DCE report will be part of a larger DHHS report on both risks and benefits of fluoridation.

Dr. Hoover, Chief, Environmental Epidemiology Branch, DCE, noted that fluoridation of drinking water to prevent dental caries has been controversial for more than 40 years and claims of increased risk for cancer have been used to strengthen the arguments against fluoridation.

Dr. Hoover summarized the results of the approximately 50 studies that have been conducted over the past 40 years, including the one done by NCI in 1976, to evaluate the risk of malignancy associated with fluoridation using cancer counting mortality data from 1950 through 1969. The 1976 study concluded that there were no patterns of increased risk of cancer, death, or other adverse results from the fluoridation. He noted that all of the studies done in the past 40 years have been scrutinized by panels of experts including the International Agency for Research on Cancer, the National Academy of Sciences, and the Royal Statistical Society. All came to the same conclusion: there is no evidence of an association between fluoridation of drinking water and an increased risk of cancer.

Dr. Hoover reviewed the results of the NTP study, which found only 1 osteosarcoma out of 50 male rats exposed to 100 ppm of sodium fluoride and 3 osteosarcomas out of 80 male rats exposed to 175 ppm sodium fluoride, and there was another osteosarcoma in the soft tissue, not in the bone. He noted that these 4 incidences of cancer are not statistically different from the 0/80, but the **trend** is statistically significant and led to the judgement that there was equivocal evidence of carcinogenicity in one sex. He noted that the DCE update study was made as one response to the new concerns raised by the NTP study.

Dr. Hoover reported that in updating the mortality study done in 1976, DCE staff examined all counties in the United States that were at least 50 percent urban to determine which were "abruptly fluoridated," changing their drinking water over a very short period of time; 131 counties with a total population of 40,000,000 were found that met this definition. In addition, counties where less than 10 percent of the population was drinking fluoridated water, either naturally or artificially, were searched for, and 195 such counties with a total population of about 30,000,000 were found. The mortality data from 1950 through 1985 for all of the counties were assembled and compared using intervals before fluoridation (5 years) and after fluoridation (35 years) and using the standardized mortality ratio as a measure of risk. Dr. Hoover explained that DCE staff calculated the cancer deaths expected in each fluoridated county, if the rates from the nonfluoridated counties would have prevailed. The statistics were adjusted for age, race, time, and region. Then the data on actual observed cancer deaths were accumulated and the ratio of expected vs. observed cancers was calculated. No evidence was found of the effect of fluoridation on cancers in the bones or joints, or in 28 other sites for either sex.

Dr. Hoover said DCE's second response to the concerns raised by the NTP study was to evaluate the cancer incidence data using the SEER database that has been in operation since 1973. From the general rates in the SEER program, an update of the information about osteosarcoma or

joint cancer was performed by splitting the data into two intervals, 1973-80 and 1981-87. Adjusting for age, the percent change increased slightly but with no statistical significance in bone and joint cancer for both sexes. Looking at age-specific rates of osteosarcoma for both sexes combined, there was found to be much random variation without consistent evidence. Dr. Hoover noted that there was an increase in the incidence of bone cancer in young adolescents in the 1981-87 interval compared with the 1973-80 interval and it was more prominent in males.

To investigate whether this increase was related to fluoridation, DCE used the same method described above and compared counties where water supplies were abruptly fluoridated with those never fluoridated for the entire time period as identified in the SEER data. No county's water supply actually underwent fluoridation during SEER; therefore there were no comparative prefluoridation data, but examination of dose response and duration response was accomplished by looking at duration of fluoridation from less than 5 years to 15 or 20 years exposure. Dr. Hoover pointed out that the resulting table of mortality ratios, incidence ratios, and observed number of deaths showed slightly higher rates of bone and joint cancer in both sexes and osteosarcoma in both sexes and in males in particular, for fluoridated counties than nonfluoridated counties. These rates were unrelated to timing or duration of fluoride exposure and actually declined with increased duration of fluoride. When 25 cancer sites were examined in addition to joint and bone, there was no evidence of dose or duration response.

Dr. Hoover cautioned against overinterpretation of the negative findings, pointing out that this is a correlational study of fluoride status and mortality and no data on individuals have been included. He added that although it is a correlational study, it is a powerful one because entire counties switched water supplies. A second caveat was that people are exposed to fluoride from sources other than water--e.g., dentifrices, foods--but 60 to 70 percent of the systemic fluoride in humans is from drinking water in those areas with fluoride programs. Finally, Dr. Hoover pointed out that as in any investigation, very small increases in risk would not be detectible if fluoridation at 1 ppm in drinking water is responsible for only a few osteosarcomas in millions of people. With these caveats in mind, Dr. Hoover said, DCE investigators reached the following conclusion: In a study of more than 2,000,000 cancer deaths and 125,000 incident cancer cases, no trends were found in cancer risk associated with the consumption of fluoridated water. Dr. Hoover noted that 40 years of epidemiologic data have reached the same conclusions. After review, the DCE report will be transmitted to the DHHS committee responsible for the larger study.

In response to questions, the following additional information was provided by Drs. Hoover, Adamson, Broder, and Greenwald:

- DCE has a program of studies that monitors geographic variations in cancer incidence and mortality. Areas where excesses or emerging excesses are identified are investigated by doing field studies. The evaluation for other exposures of public health interest that are not seen in the data or on the maps is episodic and dependent somewhat on the concerns raised by the community.

- With respect to nuclear power, NCI will do a 5-year followup study, but indepth neighborhood studies or studies in the vicinity of nuclear facilities will be in the purview of State public health agencies and CDC.

- The NTP study was mandated by Congress in response to concerns raised by groups of citizens opposed to fluoridation. NCI undertook the followup study because it was the

Government agency that could most rapidly respond to public concerns raised by the NTP study. Investigators were mobilized from DCE and DCPC for the emergency program to determine whether there was a public health consideration and to disseminate the findings.

- Insofar as has been determined, the SEER database works effectively in a number of areas related to the mission of NCI.

The relevance of studies of maximum tolerated doses (MTDs) of chemical substances to lower doses was questioned, and Dr. Miriam Davis of NTP responded by referring Board members to two NTP reports that address the issue: (1) a report to the NTP Board of Scientific Counselors of a study that correlates pathological evidence of toxicity with pathological evidence of carcinogenicity for MTDs and lower doses of more than 400 chemicals; (2) a published paper of an NTP study of tumor formations caused by MTDs and lower doses of a whole data set of chemicals. Dr. Adamson noted that this is an issue to be addressed by the Subcommittee on Environmental Carcinogenesis, and Dr. Davis agreed to provide copies of both reports.

In response to a question about the possibility of extending NCI's surveillance program to Eastern European countries, Dr. Adamson reported that joint studies of worker populations and environments are being considered and have been proposed in the By-Pass Budget; feasibility studies are ready to be implemented when funding is available.

XIII. SUMMER SCIENCE ENRICHMENT PROGRAM: DESCRIPTION AND PLANS FOR EVALUATION--DRS. PETER GREENWALD AND CLAUDIA BAQUET

Dr. Greenwald (Director, DCPC) introduced the Summer Science Enrichment Program by stating that it was initiated by Dr. Broder and led, planned, and implemented by Dr. Claudia Baquet. Additionally, Dr. Greenwald introduced Dr. William Darity, Professor Emeritus of Public Health, University of Massachusetts, Amherst, former member of the DCPC Board of Scientific Counselors and Chairperson of the Advisory Committee for the Summer Science Enrichment Program; and Dr. Linda Burhansstipanov, head of the DCPC Native American Cancer Control Program, who worked with Dr. Baquet on the program.

Dr. Baquet (Associate Director, Cancer Control Science Program, DCPC) began the overview of the NCI Summer Science Enrichment Program (SEP) by stating that its goal is to encourage underrepresented minorities and underserved youth to pursue professional careers in science, mathematics, and/or research. She noted that the slogan for SEP became "Together we aspire, together we achieve." The following is a description of the 1990 summer session of SEP and plans for its evaluation as presented by Dr. Baquet.

The SEP Advisory Committee worked long hours, on weekends and nights, to develop curricula and select students. Dr. Darity chaired the committee of 11 members from 6 states, which included African-American, Hispanic, American Indian, and Caucasian members. Professionally, the committee included a parasitologist, two mathematicians, an electron microscopist, a physicist, language arts teachers, physicians, and a former university dean.

SEP was conducted as a pilot program, this past summer's session being the first of two. The 6-week session was conducted from July 1 through August 11 at Hood College in Frederick, Maryland, one mile from NCI's Frederick Cancer Research and Development Center. All students, faculty, and staff lived in on-campus dormitories.

Students, selected by the Advisory Committee and NCI program staff, came from 25 states, including Alaska, Hawaii, and the District of Columbia. There were 107 students attending, 49 males and 58 females of the following racial/ethnic backgrounds: 48 African-American, 33 Hispanic, 12 American Indian, 6 low-income Caucasians (primarily from West Virginia), 4 Asian refugees, 2 Native Hawaiians, and 2 Native Alaskans. All students were scheduled to enter 10th grade in September and had expressed an interest in science, mathematics, and/or computer science.

Program staff consisted of 2 biology teachers, 2 mathematics teachers, 2 computer science teachers, 1 chemistry teacher, 1 physics teacher, and 1 language arts teacher. Additionally, there were 2 recreation leaders, 2 instructional aides, 5 residence hall counselors for the female dormitory and 5 for the male dormitory. The staff members were of various racial/ethnic backgrounds.

The SEP schedule included classes 4 days a week from 8:00 a.m. to 3:00 p.m. and a field trip on the fifth weekday. The trips were both educationally and culturally based, e.g., attending a pow wow in Maryland. Evening programs included seminars on the following topics: status of the world's rain forests, slow viruses, status of AIDS research, snakes and poisonous plants, and human genetics. Recreational activities were held as well.

To stimulate academic competition as well as emphasize teamwork, students were grouped into teams to study topics such as DNA structure, replication of protein synthesis, impact forces, synthesis of organic fibers, the mathematical process of developing fractiles, and sensory organs. Students were also paired with one of 8 USDA or 92 NCI scientists as a part of SEP's adopt-a-scientist program, which was created to facilitate mentors. The students were afforded direct observation and/or participation in their mentors' projects.

Evaluation of the program is in progress. Typically, SEP employed a pre-test/post-test design for cognitive and affective functioning; students' evaluations of the program, instructors, and staff; teachers' evaluations of students; instructional aides' and residence hall counselors' evaluations of the program and students. Cognitive assessment was based on 14 multiple choice items of general science or biology knowledge. Affective assessment consisted of 7 affective, opinion, or self-efficacy items such as "If your academic schedule allows you to select a certain elective, what would you take?"

Pre-tests were administered on July 6, post-tests on August 7, and a followup assessment will be administered in February 1991. During the 4 weeks between the pre- and post-tests, students' cognitive knowledge increased approximately 37 percent. On affective items, specifically the one cited above, almost two-thirds of the students selected a science, mathematics, and/or computer science course as their choice on the post-test.

During the current academic year, SEP has planned the following types of reinforcement to consolidate students' gains made over the summer: individual letters of appreciation, which point out that students were selected from a nationwide pool of 600 candidates and designate them as a national resource; a personalized certificate; a clipboard; notebook; a picture with the Surgeon General, Dr. Novello; a science or mathematics book; and specific cultural items. Over the course of the year, they will correspond with their adopted scientists and receive a quarterly SEP newsletter.

During the coming year, SEP staff plan to track the number of science-related elective courses selected by the students and the number of students who select college preparation academic tracks versus vocational tracks, and then examine the attrition rate during the program.

In response to questions, the following additional information was provided by Drs. Broder and Baquet:

- A budget of $500,000 has been estimated for this 2-year pilot program, which includes room and board, airfare, insurance, and logistical support.
- NCI's commitment to SEP represents an effort to reach underserved populations and at the same time promote training for careers in cancer research.
- Assessment of the value of SEP on a short-term basis will be based on the selection by the 10th grade participants of science, mathematics, or computer-related courses in their last years of high school and their choices of colleges, grade point averages, and performance on standardized mathematics and science tests.
- NCI has ensured followup to the intensive summer session by arranging for public health specialists and cancer control scientists to serve as mentors to the students in their home states.
- When the 2-year pilot program ends, all tests and assessments will be analyzed by Dr. Baquet and her staff, who will recommend a course of action to Dr. Broder that could include the issuance of an RFA to replicate the program in other localities. In the absence of a mechanism to provide extramural funding, Dr. Baquet and her staff have offered to provide technical assistance to institutions interested in starting a program like SEP.

XIV. SUBCOMMITTEE REPORTS

SUBCOMMITTEE ON AIDS--DR. HOWARD TEMIN, CHAIRPERSON

Referring members to the written report of the Subcommittee meeting, Dr. Temin presented a summary as follows:

Dr. Michael Grever and Dr. John Bader discussed the large-scale AIDS drug screen to select active antiviral agents. To date 100,000 tests have been performed on 37,000 different compounds, approximately half of which are natural and half synthetic. One to two percent of these compounds have shown promise preventing HIV replication. Seven compounds are going to Phase I trials.

Dr. Robert Yarchoan, Dr. Carla Pettinelli, and Dr. Philip Pizzo gave separate reports on the pharmacokinetic properties of dideoxyinosine (ddI); Phase I/II and Phase II/III clinical trials of ddI by NIAID in collaboration with NCI, Bristol-Myers, and FDA; and ddI clinical trials in children, respectively. The Subcommittee concluded from these reports that useful drugs were being produced for use in antiretroviral therapy.

The report of the Subcommittee on AIDS was approved as presented.

SUBCOMMITTEE ON CANCER CENTERS--DR. JOHN DURANT, CHAIRPERSON

Noting that the Subcommittee had not met since May, Dr. Durant provided an informational update on the status of the strategic (or 5-year) plan for cancer centers. He reminded the Board that the Senate Appropriations Committee had directed NIH to contract with the Institute of Medicine (IOM) to report on the state of the Cancer Centers Program. The IOM report recommended the development of a strategic plan, which was drafted by NCI staff and extensively revised under the auspices of the Subcommittee on Cancer Centers, with the assistance of a number of cancer center directors. Dr. Durant stated that the re-draft has received widespread distribution and review and has been submitted with the By-Pass Budget to the President, Congress, and Office of Management and Budget.

He noted that the focus of the plan is to regain momentum in discovery and education and to develop mechanisms of collaboration to address a number of social issues. Additionally, types of information were suggested that center directors could provide for inclusion in NCI's report to the Subcommittees and Congress about the Cancer Centers Program.

Turning next to the issue of dissemination of clinical trials information, Dr. Durant reported on the NCAB workshop held in January. He noted that although there were residual objections to the NCI concept of issuing clinical updates, most of the participants agreed that the principles followed in the announcement on Levamisole/5-FU therapy for colon cancer addressed most of their concerns. The participants received assurances that the announcements would be infrequent and would be the result of a collegial effort between NCI and the investigators.

Dr. Durant stated that both the strategic plan and planning guidelines for clinical updates were distributed and the comments received in response did not change the substance of the documents.

The report of the Subcommittee on Cancer Centers was approved as presented.

SUBCOMMITTEE ON INFORMATION AND CANCER CONTROL FOR THE YEAR 2000--DR. DAVID BRAGG reporting for MRS. HELENE BROWN, CHAIRPERSON

Referring Board members to the written report, Dr. Bragg stated that the Subcommittee reviewed and approved concepts for two contracts in the Office of the Director, NCI. The first concept for a new contract in NCI's International Cancer Information Center was presented by the Project Officer, Kent Hever. The contract would provide monthly updating and system maintenance of MUMPS and the "C" version of PDQ for 3 years, with two 1-year options for renewal. Costs would be $98,614 for year 1, rising to $119,866 in year 3. The second concept was for a support services contract for the management information systems supported by NCI's Office of Administrative Management. The contract was proposed for 5 years, with year 1 costs estimated at $380,292, rising to $607,866 in year 5.

The Subcommittee also discussed the format for its consideration of the concept for recompetition of Cancer Information Services, probably at the February meeting.

The report of the Subcommittee on Information and Cancer Control for the Year 2000 was approved as presented.

SUBCOMMITTEE ON PLANNING AND BUDGET--DR. LOUISE STRONG, CHAIRPERSON

Dr. Strong reported that the Subcommittee discussed the House Appropriations Committee budget recommendations, beginning with a review of the possible effects of a Gramm-Rudman-Hollings sequestration on the NCI budget. Following that, the House markup was compared with the FY 1991 President's Budget. The House recommended a 9.1 percent increase for NIH with a 5.5 percent or more than $90 million increase for NCI, not including the NRSA training awards. The total recommended for NCI then was $1.7 billion. Dr. Strong pointed out that the House appeared to be favorably impressed with the advances in biomedical sciences and research. The House markup for NCI recommended the following increases over the FY 1991 President's Budget: $50 million for research project grants; $8 million for centers; up to $7 million for construction if the construction program is reauthorized; and $7 million specifically for prevention and control.

The Subcommittee then discussed the House directives included in its markup, primarily the need for more aggressive cost control and for the development of a longer term financial management program. Of specific interest to the House were cancer centers, clinical trials, community-based programs, construction, international activities (perhaps including epidemiologic studies in Eastern Europe), mortality rates, programs for cancer of the prostate, proton beam therapy, cancer vaccine research, cancer prevention and control, and breast and cervical cancer screening.

Dr. Strong noted that the House also requested reports within 6 months on psychological services provided by cancer centers, recommendations for funding for cancer vaccine research, and a specific spending plan for cancer prevention and control.

The report of the Subcommittee on Planning and Budget was approved as presented.

XV. NEW BUSINESS AND ADJOURNMENT--DR. DAVID KORN

Dr. Korn asked for and received a motion to approve the minutes of the May meeting; Mrs. Pollin seconded the motion. There was no discussion, and the minutes were unanimously approved.

Dr. Korn reminded Board members of two important issues to be addressed in the time before the next meeting: (1) Regarding the report on unconventional cancer treatments, the NCI response will be coordinated through DCT and its Board of Scientific Counselors, through the Subcommittee on Information and Cancer Control for the Year 2000, and back to NCAB for review and concurrence at the December meeting. (2) During the closed session, the Board requested that a policy be developed regarding OIGs and MERIT awards, focusing on whether a proportion of funds in the RPG pool should be fixed at some level or within some range, to recognize outyear obligations in response to the House Appropriations Subcommittee urgings. It is anticipated that NCI will submit a recommendation in response to that request through the Subcommittee on Planning and Budget and back to the full Board at the December meeting.

Dr. Wells asked if the December 1992 meeting could be rescheduled for November. Mrs. Bynum agreed to check the availability of conference space and circulate a calendar with possible dates to Board members.

Ms. Bynum reminded the Board that she and Mr. Amoruso had raised a question of review for Office of the Director (OD) contracts at the last meeting, and decision-making was postponed to this session. Mr. Amoruso reiterated the issue: OD contracts are more appropriately reviewed by the Subcommittee on Information and Cancer Control for the Year 2000 than by special review committees set up by the Board. Noting that this Subcommittee has the substantive knowledge and ability to put OD contracts and programs into context, he suggested that this might be a good opportunity to eliminate a subcommittee.

Dr. Korn opened the issue for discussion, and Ms. Bynum confirmed that decisions have been made under similar situations to send initiatives that do not concern cancer information to the most relevant Board or programmatic Division for substantive review. It was the consensus of the Board to terminate the Subcommittee on Contracts for the Office of the Director.

Dr. Temin announced the death of a colleague and asked that a resolution be accepted by the Board as follows: "The National Cancer Advisory Board regrets the unexpected death of Rex Risser, notes his numerous contributions to cancer research, and expresses condolences to his parents, the Rissers, of Cedar Rapids." Dr. Bragg moved that the resolution be accepted, and approval was unanimous.

Dr. Temin raised the issue of too many qualified investigators, too many good institutions, too many solvable problems for the amount of money available in times of limited funding. He asked that the Board consider how to promote progress of cancer research and maintain the cancer research institution throughout the country. He pointed out that the National Institute of General Medical Science has recommended in a report issued by the Institute of Medicine that a cap be placed on the amount of money awarded to any one researcher in order to spread available resources around in times of constrained funding. It was suggested that the capping could be a result of consideration of other factors besides the general merit of the proposed research, such as the total research funds available to an individual researcher. If these funds exceeded $500,000 in direct costs, special analysis and justification would be required to receive funding. Dr. Temin explained that such a policy might help to provide a balance between new and established investigators competing for the same narrowed fund pool and should be considered by the Board. Dr. Broder suggested that Division Directors take the issue to their respective Boards of Scientific Counselors and ask the Chairperson of the Board (or an appointed delegate) to be prepared to discuss the issue at the December NCAB meeting. Copies of the IOM report should be distributed in advance of the December meeting as background information.

Dr. Korn raised another issue. He received a letter informing him that *Family Circle Magazine*, a widely circulated family-oriented publication, contains extensive cigarette advertising. Since the magazine also has a health and medical advisory board with several well-known physicians including Michael DeBakey and T. Berry Brazelton as members, the person sending the letter expressed the opinion that the magazine exploits its readership by accepting this sort of advertising. Dr. Korn proposed that he send a very strongly worded letter to the publisher of the magazine on behalf of the Board. His proposal was approved, and Dr. Bragg suggested sending copies of the letter to the physicians on the magazine's medical advisory board.

Dr. Bragg made a motion for adjournment, which was seconded and approved. The 75th meeting of the National Cancer Advisory Board was adjourned at 12:50 p.m.

11/27/90
Date

David Korn
Dr. David Korn, Chairman