DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

NATIONAL INSTITUTES OF HEALTH

NATIONAL CANCER INSTITUTE

NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
February 6-7, 1989

Building 31, Conference Room 6
National Institutes of Health
Bethesda, Maryland

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

Summary of Meeting*
February 6-7, 1989

The National Cancer Advisory Board (NCAB) reconvened for its 69th regular meeting at 8:30 a.m., February 6, 1989, 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
Dr. Bernard Fisher
Dr. Phillip Frost
Mr. Louis V. Gerstner, Jr.
Dr. David Korn
Dr. Walter Lawrence, Jr.
Dr. Enrico Mihich
Mrs. Irene S. Pollin
Dr. Louise C. Strong
Dr. Louis W. Sullivan (absent)
Dr. Howard M. Temin
Dr. Samuel A. Wells

President's Cancer Panel

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

***Ex Officio* Members**

Dr. David Rall, NIEHS
Mr. Richard Lemen, NIOSH
Captain Bimal Ghosh, DOD
Dr. John Johnson, FDA
Dr. James Robertson, DOE
Dr. Murray Cohen, CPSC
Dr. Ralph Yodaiken, DOL
Dr. William F. Raub, NIH

Members, Executive Committee, National Cancer Institute, NIH

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

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*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

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

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

Dr. George Langford, Program Director for Cell Biology, National Science Foundation, Washington, D.C., representing the National Science Foundation.

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

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

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

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

Dr. Vivian Pinn-Wiggins, President-elect of the National Medical Association and Chairperson of the Pathology Department, Howard University, Washington, D.C., representing the National Medical Association.

Ms. Yvonne Soghomonian, Associate Director, the Candlelighter's Childhood Cancer Foundation, Washington, D.C., representing the Candlelighter's Childhood Cancer Foundation.

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

I. CALL TO ORDER, OPENING REMARKS, AND CONSIDERATION OF DECEMBER 5-6, 1988, NCAB MEETING MINUTES--DR. DAVID KORN

Dr. Korn, Chairman, called the 69th 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 then 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 S. Bynum, Director, Division of Extramural Activities (DEA), within 10 days of the meeting.

Approval of the December meeting minutes was postponed until the following day's session. Dr. Korn noted that the issue of Board meeting format was to be discussed as an item of new business.

II. FUTURE MEETING DATES

Dr. Korn called the Board members' attention to the following confirmed meeting dates: May 15-17, 1989; September 18-20, 1989; December 4-6, 1989; January 29-31, 1990; and May 14-16, 1990. Dates to be confirmed are October 1-3, 1990, and December 3-5, 1990. Dr. Korn pointed out that the meetings were scheduled for a 3-day period, pending further discussion of the issue. In response to a request for reconsideration of dates for September (due to a conflict with the Conference on Antimicrobial Agents and Chemotherapy), Mrs. Bynum indicated that she would investigate the possibility of changing the dates.

III. REPORT OF THE PRESIDENT'S CANCER PANEL--DR. WILLIAM P. LONGMIRE FOR DR. ARMAND HAMMER

In Dr. Hammer's absence, Dr. Longmire read the Panel report. Dr. Hammer noted that, since the last Board meeting, events had occurred which would be of great importance to the cancer community, namely, inauguration of a new President, appointment of a new Director of NCI, and designation of a new Secretary of Health and Human Services (DHHS). He expressed confidence that the new team would build on the accomplishments of the past and expand present opportunities for further progress in the fight against cancer.

On behalf of himself, Dr. Longmire, and Dr. John A. Montgomery, Dr. Hammer assured Dr. Samuel Broder, new NCI Director, of the cooperation and support of the President's Cancer Panel in the months and years ahead. He commended the selection of Dr. Louis Sullivan for the post of Secretary, DHHS, and noted that Dr. Sullivan's service on the NCAB gives him a special understanding of the National Cancer Program and the problems facing NCI. In expressing confidence that President George Bush would give increased support to NCI activities, Dr. Hammer reminded the Board that in June 1988, then-Vice President Bush requested that the Panel undertake review of the drug approval process for cancer and AIDS drugs and noted in the letter to Dr. Hammer that this study had the potential to significantly benefit cancer patients and cancer treatment research. Dr. Hammer said he believed this statement was an expression of the President's commitment to the cause of accelerating research and treatment for cancer victims and noted that a committee had been established under the chairmanship of Dr. Louis Lasagna and included Dr. Gertrude Elion, NCAB member, among its distinguished membership.

The first meeting of the National Committee to Review Procedures for Approval of New Drugs for Cancer and AIDS was held on January 4. Dr. Hammer presented the Committee with its charge and noted that while safety and efficacy must remain of paramount importance in

permitting the use of new drugs, it is also critical that the Food and Drug Administration's (FDA) regulatory procedures not unduly deter the rapid transfer of new agents to patients with cancer and AIDS. He expressed confidence that the Committee would produce recommendations for improvements in the drug approval process that would combine safety and speed. Dr. Hammer stated that the Panel had advised the Committee members to consider themselves completely independent of any specific orientation and to weigh all of the issues as they see them, to call witnesses they feel should be heard, and to arrive at decisions they see as just and proper, all to an end that will assure the protection and advantage of the cancer and AIDS victims. He said the NCAB would be informed periodically of the Committee's activities and welcomed, on behalf of the Committee, input from Board members.

Turning next to a discussion of the Panel's 1989 activities, Dr. Hammer stated that the Panel plans to continue visiting cancer establishments throughout the country, beginning on March 6 with a meeting at Howard University in Washington, DC. In addition, the Panel is in the final stages of preparing its annual report to the President and Congress on the National Cancer Program as operated by NCI. Dr. Hammer described the report as generally optimistic and noted the Panel's support of the ongoing programs of NCI. He said the Panel attributed the continued progress in research and the advances in treatment to a well-balanced program and the effective use of available funding and credited Dr. Vincent DeVita, former Director of NCI, for much of the progress. He added that the Panel is confident Dr. Broder will continue to expand on this record of achievement.

While acknowledging the achievements of the National Cancer Program, Dr. Hammer pointed out that thousands of people die each year from cancer and that cancer will soon become the primary cause of death in the United States, due partly to the aging of the American population. He cautioned against complacency in the face of this probability and stated that the Panel is concerned that recent budget increases for cancer research and training have not been sufficient even to sustain existing activities (e.g., only 25 percent of approved grants will be funded by NCI this year).

Dr. Hammer said he hopes to present personally the completed Panel report to the President and his advisors and to Congress, calling attention to the bypass budget, which, he said, makes a compelling case for increased support to the National Cancer Program. He stressed the need to bring the bypass budget, which is prepared by NCI under a special authority granted by the Cancer Act, to the attention of as many people as possible.

While recognizing the need for restraint in government spending, Dr. Hammer warned of the dangers of losing the momentum that has been built up with great effort and not being able to capitalize on present cancer research opportunities. He stressed the need for extra effort to prevent these dangers from materializing, and he expressed his commitment to vigorously pursue the Stop Cancer campaign. He reported that the campaign is progressing well and expressed the hope that Congress will match the $12.5 million already raised, thereby providing $25 million for cancer research projects which are found worthy of support.

In discussion, the point was made that prevention of cancer and AIDS, as well as treatment of the victims of these diseases, are important concerns of NCI.

IV. NCI DIRECTOR'S REPORT--DR. SAMUEL BRODER

Dr. Broder expressed pleasure at making his first presentation to the NCAB as Director of NCI. He extended congratulations to Board members, Dr. Louis Sullivan on his nomination to

become Secretary of Health and Human Services, to Mrs. Nancy Brinker on her induction in the Texas Women's Hall of Fame, and to Dr. Gertrude Elion on her award of the Nobel Prize in Medicine.

Dr. Broder summarized the increased momentum of cancer research, citing significant developments in the science and application of cancer prevention and early detection, improved understanding of the genetic and molecular basis of cancer, characterization of physiological growth factors and their receptors, elucidation of new families of viruses such as retroviruses, improved understanding of cancer drug resistance and development of strategies to reduce this resistance, increased expertise in the use of monoclonal antibodies and genetically engineered products to treat cancer, development of new adjuvant therapies, and the use of advanced computer technology to design new strategies to treat cancer and AIDS. By virtue of these and other accomplishments of the National Cancer Program, many thousands of lives have been saved. However, Dr. Broder also pointed out that understanding of cancer remains incomplete, and cancer treatments do not heal every patient. In addition, some people--notably women, adolescents, and certain minorities--continue to smoke, although it is known with certainty that smoking contributes to one-third of all cancer deaths.

Dr. Broder underscored the importance of considering lung cancer a women's health issue, noting that in the 1989 estimates, lung cancer will cause more deaths among women than breast cancer. He suggested the need to make cancer in women a priority health issue and to develop research programs in basic science, prevention, early diagnosis, and treatment to deal with these cancers.

Dr. Broder also expressed concern about the disproportionate burden of cancer incidence and mortality suffered by blacks. He stated that a broadly based approach, addressing various factors such as smoking, nutrition, and patterns of medical care, is needed and would require the participation of all components of NCI.

Rather than accepting these problems as justification for pessimism, Dr. Broder said that they should serve as indications of what can and needs to be done. He identified basic research as NCI's highest priority. He noted that current knowledge about oncogenes is a direct outcome of such basic research. More than 40 oncogenes are known, and the specific protein products of important oncogenes have been isolated and their mechanisms identified. These oncogene products are frequently abnormal versions of growth factor receptors, and research is now exploring ways of blocking the expression of "undesirable" genes, using antisense constructs. Dr. Broder said that this information is highly likely to have important clinical applications.

During the past 2 years, information from basic laboratory research has emerged about suppressor genes or anti-oncogenes. Dr. Broder described a two-hit process of tumor development in which genes that would suppress a tumor are lost or inactivated through inherited mutations and environmental factors. He said eventually it may be possible to replace a suppressor gene or a relevant product to prevent a tumor from developing.

Dr. Broder identified research on cancer causation and prevention as another high priority. Research has provided information about the association of various substances with cancer in humans, and Dr. Broder cited a recent study suggesting that vegetables in the allium family may protect against cancer of the stomach. He reiterated NCI's commitment to learning about which dietary components prevent or contribute to the development of cancer to provide the basis for information to guide the public and the food industry. Genetic changes and the interactive effects of substances, such as cigarette smoke and radon, are other important areas of study.

Turning next to chemoprevention, Dr. Broder said studies are in progress to determine whether the addition of synthetic or natural nutrient supplements to the diet can lower cancer incidence. Agents being studied include folic acid, vitamin B_{12}, retinoic acid, beta-carotene, vitamin C, and vitamin E. Dr. Broder stated that NCI plans to expand the basic research capacity of its intramural program in cancer prevention and nutrition as a way of stimulating more investigator-initiated basic research in this area.

Dr. Broder briefly digressed to emphasize the magnitude of the lung cancer problem. He pointed out in the beginning of this century, lung cancer was a rare disease, and today it is a disease that does not have to be a part of our lives. The information about the health consequences of smoking is irrefutable.

Dr. Broder identified early diagnosis as another priority, calling for the widespread application of established technologies such as mammography and the development of new technologies. Such new techniques include a painless urine test for bladder cancer that detects an autocrine motility factor and the use of monoclonal antibodies directed at antigens on lung cancer cells. These techniques offer the possibility that cancer can be diagnosed at early, more treatable stages.

Dr. Broder emphasized that NCI also would continue to apply the fruits of basic research to new therapeutic strategies. In addition to the development of three to five agents per year as Phase I experimental drugs, Dr. Broder mentioned that intramural investigators also are reexamining old drugs used for the treatment of noncancer diseases. One such drug, suramin, is now being rapidly developed as a new treatment for prostate cancer. Suramin has reproducibly brought about tumor regressions in men whose tumors no longer responded to first-line hormonal therapies.

Dr. Broder stated that biological response modifiers (BRMs) will continue to be a major focus of treatment research. New combinations of BRMs are being tried, and successes have been achieved in treatment of previously intractable malignancies, including advanced melanoma and kidney cancer. Significant responses have been observed using alpha-interferon and chemotherapy to treat multiple myeloma. Dr. Broder identified other priorities in treatment research as adoptive cellular therapy, including the concept of gene transfer, combined chemotherapy and radiation, and adjuvant therapy.

Dr. Broder pointed out that major advances in breast and colon cancer have come out of the NCI-funded clinical trials by the clinical cooperative groups. He described the cooperative group program as a valuable national resource, both as a vehicle for transferring basic research knowledge and for facilitating information flow from the community.

NCI will continue to track progress against cancer through the Surveillance, Epidemiology, and End Results (SEER) program. Dr. Broder said plans are to add registries to the program to improve coverage of black and Hispanic populations. He also emphasized that NCI would continue its comprehensive program of translating information into action through the cancer centers, cooperative groups, community oncology programs, outreach activities, public information activities of the Office of Cancer Communication, the International Cancer Information Center, which includes PDQ and the toll-free nationwide cancer information service, as well as a major cancer prevention awareness program.

Turning to AIDS, Dr. Broder affirmed NCI's strong commitment to fight against AIDS and its related disorders, in collaboration with the National Institute of Allergy and Infectious

Diseases (NIAID) and other institutes. He noted NCI's vigorous efforts in AIDS vaccine development and the development of treatments for AIDS. AZT is already in clinical use, and dideoxynucleosides are now in large-scale testing. Dr. Broder cited preliminary results indicating that dideoxyinosine (ddI) may stop AIDS virus replication in patients. In collaboration with the private sector, NCI is testing genetically engineered agents, such as granulocyte macrophage colony-stimulating factor (GM-CSF), which stimulates the bone marrow, and CD4, a protein that can bind to the AIDS virus. Dr. Broder remarked that as new treatments for AIDS extend life, there will be a need to treat the cancers that frequently complicate AIDS.

In concluding his presentation, Dr. Broder addressed several administrative issues. He pointed out that while NCI will maintain its commitment to support investigator-initiated research, its mission requires that other activities also be given high priorities. Dr. Broder reemphasized the importance of the cancer centers program and the clinical cooperative group program for implementing national priorities and achieving success in cancer prevention and control and early diagnosis and treatment. He also stressed the fact that NCI has acted as a catalyst to stimulate not only cancer research, but also the overall excellence of American biotechnology. For example, NCI's supercomputer is a national resource for basic biomedical research on the structure-activity relationships of drugs and macromolecules and the sequencing of human and viral genes. Dr. Broder concluded by stating that although some measure of satisfaction can be taken from the progress achieved against cancer, the sobering reality is that many challenges remain--some forms of cancer are still not treatable, and others, while treatable, are not yet curable.

The following points were raised in discussion:

- An important component of continued progress in biomedical research is support for biomedical research training.

- NCI is committed to proceed with the establishment of an intramural nutrition research program.

- NCI serves as a source of information to Congress, but cannot ask Congress for legislative action; however, the NCAB, both as a Board and as individuals, can approach Congress.

- The Subcommittee on Information and Cancer Control for the Year 2000 may consider strategies for actively conveying information to Congress, private businesses, and other groups.

- Discussion of cigarette smoking should be presented in a format that conveys the message that there are no doubts about the health consequences of smoking.

- NCI's efforts can be enhanced by joining with other groups like the American Medical Association and voluntary health agencies.

BUDGET UPDATE

As introduction Dr. Broder stated that the budget to be discussed was President Reagan's budget, and it was not known what modifications might be forthcoming from President Bush. In FY90, NCI is to receive 32 additional FTEs for AIDS activities and 28 fewer FTEs for cancer activities, with a net increase of 4 FTEs. Dr. Broder pointed out that since FY84, NCI has lost

more than 400 FTEs for cancer activities, a reduction of nearly 20 percent, somewhat mitigated by an increase of 148 FTEs for AIDS during the same period. These reductions in personnel ceilings directly and indirectly affect NCI's activities and programs.

In reviewing the FY89 budget, Dr. Broder noted the increase of $103 million or 7 percent over FY88. About 80 more research project grants will be funded than last year, although the number of competing awards will be about 250 fewer. It will be necessary to negotiate a 10 percent reduction for competing grants and about a 4 percent reduction for noncompeting grants. Dr. Broder said a funding plan for cancer centers is being developed, and realistically, it can be expected that several existing grants will be phased out and other grants negotiated downward.

NIH has proposed increasing stipends for the National Research Service awards for FY89. This would result in a decrease of about 150 NCI training slots below the FY88 level. NIH is considering several options to minimize the reduction of trainees, including a request for authority to redirect funds from the research project line into training grants, which would amount to $1.6 million from NCI research grant funds and 73 fewer trainee positions.

Turning to the FY90 budget, Dr. Broder said NCI is slated to receive an increase of $74.5 million, for an overall budget, including AIDS, of $1.646 billion. He pointed out that it is again being proposed that AIDS funding for the Public Health Service be consolidated in the Office of the Assistant Secretary for Health. The cancer portion of NCI's budget will increase by $46 million and of this amount, 80 percent will be committed to investigator-initiated research. Compared with NIH as a whole, NCI has received slightly lower budget increases. NCI constitutes about 22 percent of the entire NIH budget, down from 34 percent in 1976. NIH has budgeted $100 million for the human genome project.

Dr. Broder said that in spite of the increases for research project grants in FY90, downward negotiations will be required to fund approximately the same number of grants as this year. Cancer centers will receive about a $1 million decrease in 1990, but with the incorporation of some AIDS money, the centers' budget will be level. The clinical cooperative groups will receive a very slight increase. Dr. Broder noted that the total budget for the research grant category is more than $927 million or about 60 percent of NCI's total budget. Other items in the FY90 budget include a 3.4 percent increase for National Research Service awards, a slight reduction in contracts, a 5.8 percent increase for intramural research, which includes mandatory increases for personnel salaries and benefits and the NIH Management Fund, a $3.5 million decrease for research management and support (mandated by the Office of Management and Budget), a level budget for cancer prevention and control, and no funds for construction.

Dr. Broder next discussed the AIDS component of NCI's budget, which will increase by 23 percent in 1990. About $5 million of the cancer centers' budget will be related to AIDS research. The intramural program will increase by $12 million for AIDS activities. Considering both cancer and AIDS, research project grants will receive one of the largest increases (6 percent) of any of the mechanisms. The 1990 budget permits the support of more than 100 additional competing awards, up to a total of 822, with an expected 30 percent funding rate. The funding for R01 grants is expected to approximate this year. Dr. Broder stated that reductions to individual grants will be necessary--about 10 percent for competing grants and 4 percent for noncompeting grants. He announced that the House budget hearings are tentatively scheduled for March 22 and Senate hearings for mid-April.

In discussion, it was noted that much of the budget information presented is preliminary and may be subject to change. Flexibility within the budget is limited, but changes in one component may have unintended effects on other components.

V. LEGISLATIVE UPDATE--DR. MARY KNIPMEYER

Dr. Knipmeyer stated that since her last report in September 1988, Congress had acted to renew the National Cancer Act for 2 years as part of the Health Research Extension Act of 1988. Because the reauthorization was for only 2 years, the next bill to renew the National Cancer Act will be introduced in the 101st Congress. Other legislation of interest enacted by the 100th Congress related to radon (P.L. 100-55, Amendment to the Toxic Substances Control Act) and tobacco (P.L. 100-647, Technical and Miscellaneous Revenue Act of 1988). Dr. Knipmeyer noted that Senator Tom Harkin (D-Iowa), the new Chairman of the Senate Appropriations Subcommittee on Labor, HHS, Education, and Related Agencies, had visited NIH and met with Dr. Broder.

Concerning current legislative issues of interest, Dr. Knipmeyer pointed out that many of these issues also are being addressed at the State level. Ten AIDS bills have been introduced in Congress, as well as several relating to animal welfare. Dr. Knipmeyer said regulations under the Animal Welfare Act are still being reviewed by the Office of Management and Budget. She noted renewed interest in continuing and extending the smoking prohibition on commercial airline carriers. A new bill would disallow tax deductions for promoting or advertising tobacco products, and a resolution would encourage more public service announcements and information dissemination to the public about the health consequences of smoking and smokeless tobacco. Other bills are intended to increase the excise tax on cigarettes and smokeless tobacco. Bills related to nutrition monitoring include sections on procedures for providing dietary guidance to all Americans as well as various subpopulations. The Medicare Catastrophic Coverage Act includes provisions for screening mammography coverage. Dr. Knipmeyer noted a resolution designating the week of April 16 as National Minority Cancer Awareness Week.

Commenting on congressional committee membership changes, Dr. Knipmeyer mentioned the retirement of Senator Lawton Chiles and appointment of Senator Harkin to chair the Senate Appropriations Subcommittee. Senator Arlen Specter (R-PA) is expected to take the ranking minority position on the Subcommittee, with Senator Mark Hatfield (R-OR) remaining the ranking minority on the full committee. Membership on the House Appropriations Committee is largely unchanged.

VI. PROGRAM PROJECT GRANT PROGRESS REPORT--DR. ROBERT HAMMOND

Dr. Hammond began by pointing out that this review round is the first in which all of the NCI program project grant applications have been reviewed by ad hoc review committees, rather than standing or chartered committees. Summarizing background information, Dr. Hammond recalled that the Program Project Working Group had presented recommendations to the NCAB in February 1987. The recommendations called for more interaction between program staff and applicants, initial reviews by special committees, and discontinuation of automatic site visiting, along with some operational changes. The Board agreed to the recommendations on a trial basis, and an implementation plan was developed and presented to the Board in May 1987. The plan provided for the publication of new guidelines, which were officially released in the summer of 1988. The guidelines included new instructions for the P01 applications that are compatible with the DRG format. The guidelines also outlined procedures to encourage constructive dialogue between NCI program staff and applicants.

Dr. Hammond said the program project reviewers pool now includes more than 200 senior scientists, spanning broad areas of expertise. Names were provided by program staff, the Grants Review Branch, and executive secretaries and drawn from the rosters of former NCABs, divisional Boards of Scientific Counselors, and program project grantees. Operational changes, intended to ensure the quality of the review, include standardization of mailings to reviewers, thorough orientation of review panels, and use of the NIH-wide scoring procedure.
Dr. Hammond suggested that the goals of the original recommendations have been achieved, and procedures are in place for continued strengthening of interactions and improving quality control. He said that NIH is developing an evaluation plan to compare the new ad hoc committee review procedure with the standing committee review previously used.

The following points were raised in discussion:

- NIH-wide scoring refers to use of merit descriptors (e.g., outstanding, excellent) that are linked to a range within the priority score system.

- Based on the first few applications that have been reviewed according to the new procedures, scores seem to be more evenly distributed over the scoring spectrum, rather than tending toward the positive end.

- The new procedure should enable program staff and the Executive Committee to look at the range of applications and make substantive decisions based on quality.

- The question of whether there will need to be a special funding plan for P01s reviewed under the new system has not been addressed, although the Executive Committee will probably set a payline based on the outcome of this and subsequent review rounds.

- Efforts will be undertaken to ensure that narrative in the summary statement matches the score.

VII. A MOLECULAR APPROACH TO TUMOR CLASSIFICATION--DR. MARK ISRAEL

Referring to the few universally and invariably successful cancer treatments, Dr. Israel stated that his laboratory has been studying the underlying characteristics of human tumors to develop specific therapies or use currently available therapies in a more specific manner. This line of investigation evolved in response to the recognition that among children with neuroblastoma, a common solid tumor that does not respond well to currently available therapies, there is a genetically definable subgroup who can be treated very efficaciously. Although this subgroup is histopathologically indistinguishable from other neuroblastomas, it was subsequently recognized to be genetically distinct and to have a distinct clinical syndrome. This tumor is now more widely known by the name neuroepithelioma. Although all these tumors involved neuronal cells, neuroblastomas were found to secrete adrenergic transmitter chemicals and neuroepitheliomas synthesize cholinergic transmitters. This finding suggested that it might be possible to recognize other different biologic entities among these tumors based on their correspondence with different stages of the normal development of neuronal tissue.

Dr. Israel pointed out that although all of a person's cells have the same genetic material, different genes are turned on in different cells at different times to produce the complex human organism. Recognizing that tumors are not homogenous, the development of malignancy was studied from the perspective that it might be related to normal developmental events. Dr. Israel said the tools of molecular biology were used to identify genes that define the fully matured,

adult adrenal chromatin cell. Neuroblastoma is thought to occur in embryonal cells that give rise to chromaffin tissue. A battery of genes that were turned on in chromaffin tissues was isolated, enabling study of why these genes were not turned on in tumor cells. Some genes were found to be expressed very early in normal development, while others were expressed only at later times.

Dr. Israel explained that the next step was to examine neuroblastoma tumor cell lines for the expression of those marker genes. The pattern of expressed genes that emerged in the tumor cells precisely mimics the temporal sequence in which these genes are turned on during normal human development. This finding led to the development of a series of questions about the biological differences in tumors and their responses to therapy. Dr. Israel stated that the goal of ongoing research is to determine whether different therapies can be developed that will address the underlying pathologic event that leads to each of these different tumor types. Data indicate that the underlying pathologic alterations are likely to be different among cells. For example, it was observed that some tumor cell lines will grow in mitogen-free medium, indicating that the tumors make their own growth factors. Therefore, Dr. Israel suggested, specific therapy should address the specific growth factor alteration rather than simply the histopathologically defined type of tumor.

Dr. Israel said that another investigation is directed at identifying the body's normal signals for telling cells to go ahead and mature to the next stage of development. Retinoic acid is the only known morphogen or substance capable of physiologically directing differentiation. When neuroblastoma tumor cells are incubated with retinoic acid, they become neuronal in appearance and acquire a variety of new gene products and the ability to transmit electrical impulses. Dr. Israel recalled that several years ago, his laboratory had demonstrated that treatment of neuroblastoma with retinoic acid leads to the alteration of the expression of the N-*myc* oncogene within a few hours.

Further studies, using transfected N-*myc* oncogenes, verified that the expression of this single, potentially pathologic gene can completely alter development. The question remains whether the molecules that direct normal development can be approached as therapeutic modalities. Dr. Israel commented that this approach also might be useful in common tumors of adulthood that occur in renewing tissues, such as colon, breast, and lung epithelium, where cells go through a series of steps during differentiation before becoming mature epithelial tissue.

Points raised in discussion included the following:

- Neuroblastoma cells that secrete insulin growth factor 2 stop secreting it when administered retinoic acid.

- N-*myc* may function to block differentiation at a number of different steps in the process.

- Retinoic acid has not been shown to be present *in vivo*. The biologically active congeners of the acid are known to be present during normal development.

- Neuroblastoma IV-S spontaneously remits in almost every case and is not treated.

VIII. TUMOR-INFILTRATING LYMPHOCYTES: ROLE IN CANCER THERAPY AND AS A VEHICLE FOR GENE TRANSFER--DR. STEVEN ROSENBERG

Dr. Rosenberg opened his presentation by stating that one goal of his studies is to develop a method for mediating the rejection of established growing human tumors by the adoptive transfer of lymphoid cells with antitumor reactivity into cancer patients. He explained that his early work, first described in 1980, dealt with lymphokine-activated killer (LAK) cells. By incubating peripheral blood lymphocytes of cancer patients with interleukin-2 (IL-2) under appropriate conditions, LAK cells were generated that were capable of destroying cancer cells but not normal cells in tissue culture. The adoptive transfer of these cells mediated tumor regression. Over 300 patients now have been treated with either high-dose IL-2 alone or IL-2 plus LAK cells, and complete tumor regression has been achieved in 10 to 12 percent of patients with metastatic renal cell cancer and with malignant melanoma. Dr. Rosenberg said that in over half of the 18 patients who achieved complete regression, the tumors have not recurred for up to 4.5 years. Approximately another 20 percent of patients with renal cell cancer and malignant melanoma had at least 50 percent reduction in tumor burden.

Dr. Rosenberg stated that in seeking a more potent cell for use in adoptive immunotherapy, he and his colleagues tested cells from peripheral blood, from the thoracic duct, from draining lymph nodes, and from those cells infiltrating the tumor itself, tumor-infiltrating lymphocytes (TILs). TILs can be grown in IL-2 by culturing a single-cell suspension from a freshly resected tumor that contains a few lymphocytes and a large number of tumor cells. TIL cells that bear IL-2 receptors are activated by the tumors and grow under the influence of IL-2. As they proliferate, they kill the tumor cells, so that in about 10 days the tumor cells are eliminated, leaving pure populations of lymphocytes. Large populations of lymphoid cells can be generated, up to 2 or 3 x 10^{11}, for use in clinical trials.

In *in vivo* models, Dr. Rosenberg said that TILs were found to be from 50 to 100 times more potent in their antitumor activity than LAK cells. TILs have been generated from more than 100 different tumors. In about half of patients with malignant melanoma, it is possible to isolate TILs that have absolutely specific lytic activity against the tumor from which they were derived. LAK cells, on the other hand, will lyse transformed cells nonspecifically. The ability of TILs to lyse tumor cells is restricted by the major histocompatibility (MHC) locus because they are cytolytic T lymphocytes, whereas LAK cells are not MHC restricted.

Dr. Rosenberg stated that by generating TILs from the lymph nodes and from the tumor itself and constantly restimulating these cells with tumor cells *in vitro*, he and his colleagues have been able to identify specific lytic cells from patients with breast cancer and lung cancer, and these studies are being expanded to include other tumors. He described these *in vitro* results as the best available evidence that at least some patients with growing cancers mount an immunological response against their own cancers.

Dr. Rosenberg summarized the clinical trial protocol for the TIL therapy. The tumor is resected under local anesthesia, and the cells removed from the tumor are grown for 3 to 6 weeks. The patient is then immunosuppressed with a single dose of cyclophosphamide. The patient is treated with TILs and IL-2, and after approximately 1 week a second cycle of IL-2 is given to support the *in vivo* growth of the TILs. In responding patients, treatment with TILs is now repeated every 2 months.

Dr. Rosenberg showed the results of treatment of the first 20 patients with TILs. He explained that the early patients did not receive the second cycle of IL-2. He said that all of

these patients had advanced metastatic cancer and had received other standard treatments that had not succeeded. Nine of the 15 patients who had no previous immunotherapy had objective regressions. Of the five patients who had previously failed treatment with IL-2 and LAK, two achieved good partial responses with TILs and IL-2. These early studies provide further evidence that TILs have more potent antitumor activity than LAK cells or IL-2 alone.

Dr. Rosenberg described three patients who experienced substantial regression of lesions with TIL treatment. He explained that TIL traffic through the body can be tracked by using indium-111 label and that these cells clearly aggregate at the primary as well as secondary tumor sites. Better imaging has been achieved with labeled TILs than with monoclonal antibodies so far studied.

Dr. Rosenberg said that he and his colleagues are investigating ways to try to improve the antitumor effect of TILs. One method, which is effective in animal models, is to upregulate the MHC antigens on tumors by administering combined lymphokines in conjunction with TILs. Because TILs recognize tumor cells by MHC antigens on the cell surface, treatment with TILs and a combination of interferon and tumor necrosis factor, two lymphokines that upregulate these MHC antigens, increases the ability of the TILs to kill tumor cells dramatically. Treatment with TILs and alpha- or gamma-interferon also increases the expression of MHC antigens on the surface of tumor cells. Dr. Rosenberg noted that a paper in the January 1989 issue of the *Journal of the National Cancer Institute* described a mouse study in which he and his colleagues found that treatment with TILs, IL-2, and alpha-interferon increases the potency of TILs by 3- to 5-fold over treatment with TILs and IL-2 alone. A protocol for this treatment has been approved by the NCI Clinical Research Committee and by the FDA, and Dr. Rosenberg announced that he hoped to begin treating patients within the month.

Dr. Rosenberg stated that the gene-transfer technology may represent another way to improve the antitumor effect of TILs. Gene transfer involves the insertion of a functioning gene into cells to give these cells desired properties. Dr. Rosenberg remarked that TILs may be the first vehicle for doing gene-transfer experiments in humans. He said that the protocol to introduce new genetic material into TILs and transfer these cells to patients has undergone an extensive review, and it has now been approved by the Clinical Research Committees of the NCI and the National Heart, Lung, and Blood Institute, as well as the Recombinant DNA Advisory Committee (RAC) and the Gene Therapy Subcommittee of the RAC. The protocol has also been approved by the FDA and signed by the director of the NIH, which gives Dr. Rosenberg and his colleagues the final approval to perform these experiments in humans.

The RAC insisted that five criteria be met before they would grant permission to proceed with the gene-transfer protocol. Dr. Rosenberg and his colleagues had to show that 1) the marker gene can be inserted in the TILs, 2) the TILs are not significantly altered by the insertion, 3) these marked TILs can be detected in animal models, 4) there is a low risk to the patient, and 5) there is no risk to the public.

Dr. Rosenberg explained that the initial gene-transfer studies have two purposes. The first is to insert into the TILs a gene that codes for resistance to the antibiotic neomycin, which will allow TIL survival and distribution to be tracked in patients on a long-term basis. TIL traffic can only be tracked for approximately 10 days using indium-111 because of the short half-life of this material and because of the spontaneous loss of indium from cells. The neomycin resistance will be a permanent part of the genetic makeup of the TILs and therefore provide a permanent label for the TILs as well as a means for isolating TILs in the future. The second purpose of transfer studies is to insert into the TILs genes that code for cytokines that will improve the TIL

therapeutic effectiveness. Genes for cytokines such as tumor necrosis factor, alpha-interferon, and IL-2 can be inserted into TILs, so that the cells produce large amounts of these cytokines and improve the antitumor activity of TILs.

The first gene-transfer protocol for patients involves taking an aliquot of 10 percent of a TIL culture about 1 week after the TIL culture begins to grow. These TILs are then infected with the vector containing the gene coding for neomycin resistance, selected in G418, and expanded. Ninety percent of the TILs infused into the patient are left uninfected to make sure that there is no interference with the therapeutic activity of the TILs. However, the 10 percent gene-transformed TILs will allow for TIL tracking.

Dr. Rosenberg concluded by saying that several other techniques for improving TIL effectiveness are currently under active investigation and, with further work, the ability to adoptively transfer lymphocytes with antitumor activity into patients can be converted into more practical effective treatments for patients with cancer.

The following points were raised in discussion:

- TILs require much less IL-2 (.5 unit/ml vs. 1,000 units/ml) than LAK cells to support their survival both *in vitro* and *in vivo*. Although maximum doses of IL-2 have been used in the preliminary TIL trials, it should be possible to reduce the amount of IL-2, thereby reducing the toxicity of the therapy.

- No correlation has been found between the cell phenotype and its ability to mediate *in vivo* tumor regression.

- No cross-reactivity has been observed in TIL cells with specific activity.

- It is not known whether the specificity of TILs is based on MHC or tumor antigens.

- Indium-labeled TILs home to tumor sites, but this ability does not necessarily correlate with response to therapy (details in paper in *Journal of Clinical Oncology*, January 1989).

- Laboratory correlates of response to TILs have not yet been identified.

IX. PEDIATRIC AIDS--DR. PHILIP PIZZO

Dr. Pizzo, Chief of the Pediatric Branch, Clinical Oncology Program, Division of Cancer Treatment (DCT), began by drawing parallels between AIDS and cancer in children. He noted that both are relatively rare diseases in the pediatric population and that the 1,200 cases of AIDS in children reported to the Centers for Disease Control (CDC) comprise approximately 2 percent of the entire population of HIV-infected individuals, the exact percentage of pediatric cancer cases among the total number of cancer cases. In addition, he expressed the belief that, as in cancer, research on pediatric AIDS may help to guide insights into therapy and potentially into prevention of the disease. He illustrated that the major causes of mortality vary among various age groups, and pointed out that cancer is the third most common cause of mortality among children between 1 and 4 years of age. He emphasized that although the mortality rates for the major pediatric diseases have remained static for the past decades, there is an increasing rate for AIDS in pediatric, adolescent, and young adult populations.

Dr. Pizzo stated that most cases of pediatric AIDS are accounted for by the perinatal route of acquisition, which currently comprises approximately 80 percent of all pediatric cases. Based upon the number of known intravenous drug-using women of childbearing age, estimates have been made which project that 10,000 to 20,000 cases of AIDS will be diagnosed in the pediatric population over the next several years. Dr. Pizzo predicted that although transfusion and coagulation factor replacement have contributed to a small percentage of HIV infection in children, this percentage will decrease to unappreciable numbers over time.

Dr. Pizzo further noted that because of the association of perinatal acquisition of AIDS with intravenous drug use, the prevalence of HIV infection in infants is high in the major U.S. cities such as New York City (i.e., 3 percent) and Newark, New Jersey (i.e., 4 percent). He projected that the distribution of pediatric AIDS in the future will be predominantly a disease of infants and young children, in whom perinatal transmission will account for the majority and postpartum drug transmission as in breast-feeding for a much lesser percentage, and then a disease of teenagers and young adults, in whom more "traditional" routes of acquisition such as sexual transmission and intravenous drug use will apply.

Dr. Pizzo stated that the Pediatric Branch studies have focused on infants and young children, and the key question of when HIV transmission occurs. He explained that perinatal transmission may be acquired *in utero*, as with rubella, cytomegalovirus, and other viruses, or transmission may occur intrapartum, as with hepatitis B, through the exposure to blood during delivery or due to maternal-fetal transfusion (e.g., for Rh sensitization), with a small percentage occurring postpartum. In support of intrauterine transmission are the facts that virus has been found in 13- to 20-week fetuses, placental abnormalities in association with HIV-infected children have been demonstrated, virus has been isolated from cord blood, and a series of craniofacial dysmorphic features that suggest congenital infection have been reported.

Dr. Pizzo then enumerated the differences between the clinical manifestations of HIV infection in children and that in adults. Kaposi's sarcoma and other AIDS-related malignancies are less common in children, and AIDS-related opportunistic infections rarely occur in children. Also, the degree of lymphopenia associated with symptoms appears to be different, with symptoms not occurring in adults until the T4 helper cell ratio is below 250 and significant disease occurring in children at much higher CD4 values. The fact that recurrent or serious bacterial infections are more common in pediatric than in adult AIDS patients is related to the fact that a B-cell defect precedes the T-cell deficiency in children and is associated with a dysgammaglobulinemia. In addition, lymphocytic interstitial pneumonia occurs in 30 to 50 percent of children and appears to be restricted to that population.

Dr. Pizzo stated that neurodevelopmental abnormalities will probably occur in the vast majority of HIV-infected children over time. The clinical manifestations include loss of developmental or motor milestones in young children and loss of intellectual functions associated with poor school performance in older children. In both age groups, there are associated neurological deficits and laboratory abnormalities including EEG and CSF abnormalities, and most notably, changes seen by CT scan, particularly cortical atrophy and ventricular enlargement, the presence of calcification and contrast enhancement in the basal ganglia and frontal lobes, and abnormalities of white matter.

Dr. Pizzo reported that, based on the above-mentioned factors, the CDC has proposed a classification system for the population younger than 13 years of age. This classification system has three categories: P0 for indeterminate infection, P1 for asymptomatic infection, and P2 for symptomatic infection. Most initial therapeutic studies have focused on the P2 group. Dr. Pizzo

emphasized that therapeutic trials in HIV-infected children must be placed within the context of the principles learned from the management of children with cancer. That is, a multi-modal, multidisciplinary approach should be used, recognizing that AIDS afflicts the entire spectrum of pediatric patients. This approach relies upon the collaboration of a multidisciplinary team of physicians and ancillary staff necessary to provide the medical as well as the psychosocial and financial support of these patients. Based on these principles, the Pediatric Branch began a series of studies with antiretroviral therapy approximately 2 years ago.

Dr. Pizzo described the first of these studies, which focused on AZT. Two strategies were investigated: AZT administered by continuous intravenous infusion and AZT administered as a daily divided dosage. The first study was conducted only at the NCI in collaboration with investigators within the Pediatric Branch and elsewhere within the NCI, while the second study was conducted in collaboration with investigators at Duke University, the University of Miami, Burroughs Wellcome, and the Pediatric Branch. Both trials focused on a high-risk population, that is, children who were seropositive and fell into class P2. At the time of entry into these trials, the children had to be free of active opportunistic infections and could not be receiving any other medications, including gammaglobulins or steroids.

First describing the continuous infusion study, Dr. Pizzo explained that the strategy was based on assumptions from the *in vitro* data which demonstrated that a constant, steady-state level of AZT was required to inhibit HIV replication. The trial was designed to determine whether serum and CSF concentrations of AZT that were constantly above an inhibitory level would impact the infection and was based on the knowledge that AZT has a short half-life and that compliance would present problems in the pediatric population. Almost the entire study was conducted on an outpatient basis, with the children regularly receiving clinical evaluations, immunological assessments, pharmacological evaluations, and a detailed serial neurodevelopment assay that included head CT scans, CSF examinations, and detailed age-appropriate psychometric assessments.

Dr. Pizzo stated that the 21 patients who were entered on the continuous infusion study had an average age of just under 5 years. Thirteen of the 21 patients had evidence of neurological deficits or encephalopathy before beginning AZT therapy. These patients had a laboratory profile that mimicked the disease, with about half of them having CD4 counts less than 200 and a T4/T8 ratio of 0.18. Dr. Pizzo underscored that hematologic abnormalities are perhaps more common in the pediatric than in the adult population, and that anemia and a low neutrophil count were present in many of the children before AZT therapy.

Dr. Pizzo emphasized the importance of the pharmacokinetics of AZT administered in this study as an intravenous bolus, showing that a peak level above 1 μM can be achieved. He illustrated that the half-life of AZT in the pediatric population is 1.1 hours, with a bi-exponential decay of 10 and 96 minutes, meaning that if AZT were given every 6 hours, for 4 out of every 6 hours an inhibitory concentration would not be maintained. Dr. Pizzo pointed out that this problem can be overcome by administering the drug on a continuous infusion schedule. He noted that in this study, steady-state AZT concentrations were maintained above the inhibitory concentration even at the lowest dose level. Also, based on the steady-state profile, the continuous infusion schedule demonstrated approximately a 25 percent CSF-to-plasma ratio.

Dr. Pizzo then described an unanticipated result of this Phase I study, that is, the striking clinical effects, particularly for children who had evidence of neurodevelopmental abnormalities. Almost every child improved, either subjectively in terms of improved affect, activity, or ability to interact, or more objectively in terms of a return or improvement of developmental milestones

or improvements in neurological deficits such as gait and ambulation. Striking improvements in IQ scores were also demonstrated both in children who entered the study with encephalopathy and in those who fell into the normal group, indicating that cognitive impairment is probably an early manifestation of disease in a population of symptomatic children, even when clinical signs of encephalopathy are not present. The IQ scores improved comparably in those children with transfusion-associated disease and those who acquired their disease perinatally. In addition, these improvements were supported by changes in PET and CT scans. However, the level of AZT in the CSF did not correlate with the degree of improvement. Other responses that occurred in children on the continuous infusion study included weight gain, decreased lymphadenopathy and hepatosplenomegaly, decreased immunoglobulin levels, and an increase in CD4 levels.

Dr. Pizzo next reviewed the results of the study of AZT administration on an intermittent or divided daily dosage schedule. In this collaborative study, 35 children were entered, including 16 at the Pediatric Branch who were monitored in the same manner as the patients enrolled in the continuous infusion study. Again, about 40 percent of the overall group had neurodevelopmental abnormalities. Pharmacokinetic evaluations in this study revealed the same profile as in the continuous infusion study. Nonetheless, improvements in developmental and motor milestones were seen, though in a smaller percentage of patients than in the continuous infusion study. However, there were no changes in the serial IQ scores in the NCI group of 16 patients at 3 or 6 months.

Dr. Pizzo noted that the striking contrast between the results of the serial IQ testing in the continuous infusion and intermittent dose study raises several important questions, including whether the improved neurodevelopmental function observed in these studies is perhaps due to the better response of children compared with adults, or whether it might be related to the steady-state pharmacokinetic profiles, at least in the continuous infusion study. He raised the possibility that, at least in the CNS, the results reflected an effect of AZT, not as an antiretroviral agent, but as a nucleoside influencing other neurotransmitters. He informed the Board that, because these data apply to adults as well as children, a prospective randomized trial will be initiated in cooperation with the National Institute on Aging (NIA) to evaluate the effects, as measured by changes in various neurodevelopmental parameters, of a continuous infusion schedule versus an oral intermittent schedule and/or either an oral sustained-release formulation or a subcutaneous route of administration.

Dr. Pizzo further pointed out that the limitations of AZT therapy should also be recognized. In addition to the short half-life of AZT, these studies also showed variability among patients in the steady-state data. Thus, the potential need for individual patient dose adjustments and monitoring must be considered. Dr. Pizzo added that AZT toxicity is associated with dose and duration of therapy. The major toxicity experienced is hematologic toxicity, including red cell depletion requiring transfusions, and dose- and time-related neutropenias, which are ultimately dose limiting. However, based upon the steady-state kinetics in these studies, neutropenia occurs more often at levels above 3.5 μM as compared to levels below 3.5 μM, and methods may be developed for maintaining steady-state concentrations below that toxic level.

Dr. Pizzo stated that further studies have been designed to maximize the efficacy and minimize the toxicity associated with AZT and other antiretroviral agents. Approaches include combining or alternating AZT with other agents such as dideoxycytidine (ddC), granulocyte macrophage colony-stimulating factor (GM-CSF), as well as evaluating other agents that have different or minimal toxicities and efficacy or that, like CD4, may have different mechanisms of action. The Pediatric Branch recently completed a Phase I study of ddC in the pediatric population. To date, four dose levels ranging from 0.015 to 0.04 mg/kg every 6 hours for 8

weeks have been evaluated in 15 children. Antiretroviral activity of ddC was evidenced by decreases in p24 antigen levels in seven of the nine children who had elevated levels before ddC therapy. Nine of the 15 children had increments in their CD4 number. Three children who had evidence of encephalopathic changes improved, although changes in IQ scores could not be demonstrated in this 8-week study. The toxicity of ddC was relatively minimal and included mouth sores, rashes, and one case of pain in the hands and feet that was probably not related to peripheral neuropathy.

Dr. Pizzo reported that another study is being conducted to evaluate ddC in conjunction with AZT to attempt to maximize the benefits of both agents. In this study, AZT is administered for 3 weeks and then stopped for 1 week during which ddC is administered, with recurring cycles thereafter. Thus far, 10 patients are enrolled in the study, and the results in terms of preservation of drug delivery without modification of schedule are promising up to 28 weeks, the longest time on study.

Turning to other areas of investigation, Dr. Pizzo described a study combining continuous infusion AZT with daily administration of GM-CSF to maximize the efficacy and minimize the toxicity of AZT. This study was initiated on a very small scale, recognizing the potential that GM-CSF may stimulate viral replication but also that, at least *in vitro*, AZT and GM-CSF may have synergistic antiretroviral activity. Thus far, the first and only child on study has shown a good response based on improved laboratory values and a complete reversal of neurodevelopmental abnormalities.

Dr. Pizzo also briefly described new studies of dideoxyinosine (ddI), a reverse transcriptase inhibitor that appears to accumulate intracellularly, and of soluble CD4, a genetically engineered molecule that has a high affinity to the gp120 glycoprotein which is involved in HIV binding to CD4 cells. He noted that a protocol is being considered to evaluate whether CD4 given during delivery and the first few days of life can act chemoprophylactically to prevent transmission of HIV.

Dr. Pizzo concluded his presentation by expressing his view that the Pediatric Branch program within the NCI will continue to serve largely as a pilot center to evaluate novel strategies that may be studied on a wider scale by NIAID and the National Institute of Child Health and Human Development. He emphasized not only the importance of such collaborative investigation, but also the importance of recognizing and overcoming the many limitations to making new treatments available quickly. He pointed out that not only are regulatory issues and the concept of using experimental agents in young children involved but also many problems exist with funding clinical programs and ultimately the provision of care for these patients, many of whom have lives already disrupted by poverty.

The following points were raised in discussion:

- The probability of an HIV-positive mother infecting her child is estimated at 30 to 50 percent.

- It is not known whether AZT, would affect IQs of uninfected children, but the fact that AZT seems to bring about some reversal of dementia is an important area of research being actively pursued by NIA and others.

- AIDS dementia in children is reversible, which is not true of most chronic dementias, including neuroencephalopathy in leukemic children.

- NIAID will conduct a study on administration of AZT to HIV-infected women during their last trimester of pregnancy. A collaborative effort among NCI, Children's Hospital, the University of Maryland, and Walter Reed will study CD4 therapy in the last trimester of pregnancy.

- Regulatory considerations are especially important in pediatric therapeutic trials. Not including children below age 2 in therapeutic trials could result in delays in AIDS research as most children with AIDS are younger than 2.

- Studies of pediatric AIDS within the Clinical Oncology Program have been supported by AIDS monies, although some money and personnel from NCI have contributed to the research.

- Most of the pediatric AIDS studies have been conducted on an outpatient basis to avoid interfering with the pediatric oncology studies.

X. NEW BUSINESS--DR. DAVID KORN

FORMAT FOR NCAB MEETINGS

As a first item of new business, Dr. Korn introduced for discussion the issue of NCAB meeting format. He explained that the issue had been raised by a number of Board members, and he asked Dr. David Bragg to begin the discussion.

Dr. Bragg reviewed current scheduling structure--four meetings a year amounting to 14 to 21 working days, of which 3 days are devoted to grant review. He proposed that 1) the number of meetings be reduced to three by eliminating the program review meeting and presenting portions of that review at each of the three remaining meetings; 2) the grant review process be compressed; 3) the number of scientific presentations be limited and a different mechanism for presenting science be added that is geared more to the interests of practicing physicians (e.g., a review, on a rotational basis, of the state of the art and future directions of each subspecialty represented on the Board); and 4) adjustments be considered that would permit greater input by interested members in the priority discussions of issues that confront the Board, which often occur in subcommittee meetings rather than plenary sessions.

In discussion, the following points were made:

- Four meetings per year of the NCAB are a statutory requirement.

- The portion of the meeting time devoted to grant review, which is a major statutory obligation of the NCAB, has been steadily decreasing. Fairness to investigators whose grants are under review and adequate commitment of the Board to its part in the dual review process should be the paramount considerations in any attempt to compress further the grant review process.

- The end-of-the-year program review meeting was devised to provide the Board with an opportunity to oversee the spectrum of NCI activities, including intramural research, as mandated, by hearing reports from the divisions and their Boards of Scientific Counselors.

- To support the dual responsibilities of NCAB for advocacy of NCI programs and advising on policy, the Board should spend more time in discussion to reach consensus than in receiving information; broader plenary discussion of issues would capitalize on the diverse subspecialties represented on the Board.

- The change to a 2-day meeting is essential, and the agenda should be developed accordingly.

- Considerations for improving meetings include better planning of agendas, state-of-the-art reviews of scientific topics, grouping of scientific presentations with introductory explanation of why they are being presented, presentations with direct relevance to policy issues confronting NCI, and presentations on controversial issues with both sides being represented.

- Consideration should be given to the scheduling needs of the subcommittees; alternative days of the week (i.e., other than Monday and Tuesday) may be more adaptable to a 2-day format.

- Overviews of the extramural program, such as those presented on the biological carcinogenesis and epidemiology programs, will continue to be scheduled for the closed session, subject to time available.

- The role of lay representatives on the Board is to ensure that the values of the public at large are represented in the actions of the Board.

Dr. Broder stressed NCI's willingness to consider the Board's suggestions and make changes in the format of the meetings. He pointed out that science is at the core of all NCI activities; topics chosen for presentation at Board meetings represent recurrent themes and inform, in the technical sense of the word, everything that is done at every session. These themes are integral parts of some cancer mission and are issues about which the Board needs to be briefed before they become regulatory or policy issues.

Following the discussion, Dr. Howard Temin moved that a subcommittee be formed to develop suggestions for improving the Board meeting format. The motion was seconded by Mrs. Irene Pollin and approved. Dr. Korn invited those interested in serving on the subcommittee (to be empaneled as a Working Group of the Agenda Subcommittee and chaired by Dr. Bragg, with Dr. Paulette Gray as Executive Secretary) to so inform Mrs. Bynum.

LETTER TO THE PRESIDENT

Introducing the next item of new business, Dr. Korn reminded the Board that a suggestion had been made at the December meeting to send a letter to the President calling attention to the Cancer Program and some of its accomplishments and problems.

Such a letter was drafted for Dr. Korn's signature and was delivered to the White House. A second letter with Dr. Korn's signature emphasizing the findings of the public participation hearings, as well as a copy of the report itself, was sent to the White House.

APPROVAL OF DECEMBER MEETING MINUTES

The minutes of the December 5-6, 1988, meeting were approved as presented.

XI. 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 1,423 applications were reviewed, requesting support in the amount of $218,256,179. Of these, 1,280 were recommended for funding at a total cost of $162,249,415.

XII. WELCOME FROM THE OFFICE OF THE DIRECTOR, NIH--DR. WILLIAM RAUB

Dr. Raub welcomed the Board on behalf of Dr. James Wyngaarden and expressed delight and confidence in the appointment of Dr. Broder as the new Director of the NCI. He then outlined some upcoming issues and controversies that will affect the NIH, beginning with a discussion of the budget debates. Commenting that he did not expect dramatic changes by the new Administration in the budget put forward by President Reagan, he described several priority decisions that will affect the NIH and the NCI in particular. He stated that in the non-AIDS area of the NIH budget, the proposed increase from $6.54 billion to $6.77 billion represents an increment of $234 million for an overall growth of 3.6 percent. The increment for basic research represents a 6.6 percent increase, with a projected 5 percent increase for research training and a 2.6 percent increase for intramural research.

Dr. Raub noted that these increments represent part of a larger theme expressed by President Reagan, which he expects to be reiterated by President Bush, that Federal expenditures for basic research and associated activities are absolutely critical in that there are few if any other organizations capable of making an impact in those categories. Implicit in this theme is a likely heightened reliance on the private sector for its role in targeted research and development, as well as application of research results in the private sector. Dr. Raub stated that it is not clear how this dichotomy will play out in the biomedical research area in that the private sector has not traditionally played a primary role in the applied area of the NIH budget, such as large-scale clinical trials and research centers.

Next, Dr. Raub pointed out that the President's budget emphasizes several special program priorities outside the AIDS area. One is the human genome project with a proposal to spend $100 million over and above the collective NIH funding for sequencing associated with particular protein products. Dr. Raub explained that this effort is being carried out by a new office within the NIH Director's Office, the Office of Human Genome Research, headed by Dr. James Watson.

Another special program priority is the establishment of the thirteenth Institute at NIH, the National Institute of Deafness and Other Communicative Disorders (NIDCD), which is being created mainly by a focus on research that had been part of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) program. The increment of funds for the new NIDCD will be approximately 6 percent.

Turning to the budget for AIDS research, Dr. Raub remarked that support for anti-AIDS efforts is clearly dominant in the overall budgeting for the NIH. The expected growth between FY89 and FY90 based on the President's budget is $149 million, which for NIH is half of the total increment requested for the U.S. Public Health Service. Therefore, the total growth for NIH from FY89 to the President's proposed budget for FY90 is $383 million.

Dr. Raub expressed the opinion that the primary overriding concern with the priorities that have been proposed is the continued pressure with respect to the level of the NIH work force. He explained that the budget proposal for FY90 is an increment of 107 FTEs for the AIDS area,

offset by a proposed decrement of 145 FTEs in all other areas, for a balance of minus 38. He added that the proposed pay raise for the Congress will presumably be voted down, which will cause continued difficulty in recruitment and retention of the NIH staff, especially senior scientists. Dr. Raub noted that the NIH senior scientist work force declined 28 percent over the previous decade and that during that period there had not been a single recruitment into the NIH at the senior scientist level. The senior positions, therefore, have been filled from within the NIH by promising younger scientists. Dr. Raub expressed concern over the possible consequences of this decline on the capability and capacity of future research at the NIH. He stated that, assuming the proposed pay raise is not successful, the NIH will reemphasize the special pay system that was proposed in 1988.

Dr. Raub concluded his presentation by noting further areas of expected controversy: the use of fetal tissue in transplantation research in particular and in research in general; research related to gene therapy; and the issue of the use of animals for laboratory experimentation. He emphasized that the NIH has a major role in promoting appropriate use of laboratory animals and also in educating the scientific community at large and the public about the importance of these issues.

The ensuing discussion focused on the following issues:

- To emphasize the leadership role of the NIH in educating the public about the importance of the use of animals in biomedical research, an effective communications strategy should be organized and the NIH advisory board should be requested to offer a resolution in support of the use of animals in research as the NCAB and boards of other NIH Institutes have done.

- The continued focus of the Office of Management and Budget on the research project grant category of the budget and the cumulative restriction of funding in other areas over the last several years have not taken into account the uniqueness of the centers program in cancer treatment research.

- Senior staff recruitment is also difficult at institutions other than the NIH. However, the ability to attract and train capable young investigators who later become senior staff can also be seen as an opportunity. At the NIH, approximately 1 in 10 of these investigators remains at the NIH while the others move on to other positions. Although the rate of those leaving the NIH has been uncomfortably higher than usual in recent years, those individuals who move on to other opportunities can often be effective spokespersons for the NIH.

XIII. REPORT OF THE SUBCOMMITTEE ON CANCER CENTERS--DR. JOHN DURANT

Dr. Durant reported that the main concern at the subcommittee meeting was the development of a funding plan for the cancer centers to be presented to Dr. Broder. He stressed that there are only about $17 million to fund the competing cancer centers, which have a combined recommended funding level of $25 million. The $17 million would cover approximately 12 competing renewals and 2 new centers at 85 percent of their recommended budget, and would leave approximately 5 centers without money. If the centers were funded at recommended levels, only 8 of these would be funded. Dr. Durant referred to a suggestion to fund all 17 competing cancer centers at an even lower budget. He said that this action would reduce each recommended budget by 32 percent. The subcommittee decided to recommend that

the cancer centers be funded at 85 percent of the recommended levels and to anticipate the loss of some centers.

Dr. Durant noted that 20 percent of the funds for the cancer centers goes to the 14 or 15 basic science centers. These centers usually receive better priority scores than the other cancer centers perhaps because their activities are quite focused, but they are not tied to the funding of other basic science research. Dr. Durant described a suggestion made by Dr. Broder to move the basic science centers out of the clinical/comprehensive center line and tie their funding increases in some way to increases in basic science funding. This administrative change would allow the activities in the other cancer centers to be considered independently from the activities in the basic science centers. Dr. Durant said the subcommittee believes that this suggestion is worthy of consideration.

Dr. Durant stated that some of the questions raised at the workshop last summer about increasing the responsibilities of comprehensive cancer centers were predicated on the potential for obtaining more funding, which is not applicable to the current financial environment. He next referred to a study on the cancer centers by the Institute of Medicine that was commissioned by Congress and will probably be completed by March 31, 1989. Mr. McGeary, study director from the Institute of Medicine, was unable to discuss details about the study at the subcommittee meeting because IOM committee action is not complete. Dr. Durant suggested that the subcommittee assist the NCI in strategic planning for the Cancer Centers Program to provide recommendations for Dr. Broder. An interim subcommittee meeting will be scheduled to discuss this suggestion. The subcommittee will also discuss the appropriate administrative location for the management of the cancer centers.

Dr. Durant informed the Board that a list of nominations for an ad hoc advisory committee of cancer center directors has been compiled. He explained that, with the help of the subcommittee, these consultants will advise the Director of the National Cancer Institute on issues related to cancer centers. The 11 nominees represent each of the four types of centers. Dr. Durant said that each of these nominees will be contacted to find out if they are willing to serve on the committee prior to putting their names on a ballot.

Dr. Durant concluded his presentation by announcing that Dr. Peter Greenwald is interested in receiving suggestions for potential candidates to replace Dr. Robert Young as the associate director of the Cancer Centers Program.

XIV. REPORT OF THE SUBCOMMITTEE ON AIDS--DR. HOWARD TEMIN

Dr. Temin reported that the first part of the subcommittee meeting was spent reviewing the status of AIDS RFAs and RFPs being developed by DCT and DCE, the details of which were distributed. Following this, Dr. Bruce Chabner presented a report concerning the transfer of the present NCI AIDS drug screen to the NIAID. Dr. Temin explained that Drs. DeVita and Anthony Fauci had agreed upon this transfer; however, under a new agreement being drafted, both Institutes had agreed that the drug screen should remain in the NCI.

Dr. Temin stated that Dr. Maryann Roper provided an update on the AIDS FTEs. In the fall of 1988, the NCAB requested that NIH give 130 of the 200 new AIDS FTEs to the NCI. The NCI received 43 of those 200 FTEs, the NIAID received 49, the Clinical Center received 30, and the rest were distributed. The DCT AIDS drug screen received 25 of NCI's 43 FTEs. The FY90 budget adds 107 AIDS FTEs and subtracts 145 non-AIDS FTEs from NIH. NCI will receive 32 AIDS FTEs and will lose 28 cancer FTEs. Dr. Temin explained that this reduction in non-AIDS

FTEs at NIH is part of the OMB Management Improvement Initiative. He reminded the Board that in 1988 Congress restored cancer FTEs to NCI, and he moved that the Board should again make a request to Congress to restore the 28 cancer FTEs to the budget.

In discussing the motion, Ms. Brown asked if any of the AIDS positions are actually doing cancer research and if there is going to be a problem with identifying which people are doing cancer research and which people are doing AIDS research. Dr. Broder stated that FTEs assigned to AIDS positions do AIDS work and FTEs assigned to cancer positions do cancer work. The motion to make a request to Congress was unanimously accepted. Mrs. Bynum was asked to draft the letter with the help of Dr. Erwin Bettinghaus.

XV. SUBCOMMITTEE ON PLANNING AND BUDGET--DR. LOUISE C. STRONG

Dr. Strong stated that the Subcommittee on Planning and Budget focused on budgetary concerns that were brought up in Dr. Broder's report to the Board. The committee reiterated the importance of basic research as the highest funding priority.

Other issues discussed included:

- Problem with the centers budget, i.e., how to regroup the centers and possibly achieve additional funding and whether to fund at full recommended levels or some lesser percent to try to fund more centers. The determination was to assume funding at 85 percent of recommended levels.

- The need to make sure the missions of some of NCI's programs (e.g., clinical cooperative groups, cancer centers, cancer prevention and control programs) are understood in Congress.

- The lack of construction funds in the FY89 budget for maintaining the buildings at the Frederick Cancer Research Center.

- Level of funding between the R01/P01 pool and the intramural research program and the effort to keep these on a par. It was noted that the extramural and intramural research programs have not kept the same pace; however, mandated salary increases and the contribution to the NIH Management Fund have resulted in a slightly higher rate of increase in the intramural program in the current year.

- Reduction in research management and support lines, which will affect cancer communication and information activities that are vital to the cancer program.

Dr. Strong said the committee also discussed Dr. Broder's upcoming meeting with Congress to present and defend the President's budget. It is unclear if there will be any major changes in the new budget from President Bush or if Congress will make any major changes.

In a discussion of the bypass budget that followed the subcommittee report, the possibility of including a minimum status quo section as well as a technical needs section was brought up. Dr. Broder stressed the need to keep the bypass budget free of any considerations except the technical, scientific, and clinical needs of the Institute as mandated. He pointed out that the status quo is not technical needs.

XVI. UNFINISHED BUSINESS

Followup information items to be provided to the Board include:

- Report on the effect of changing paylines on the proportion of FIRST (First Independent Research Support and Transition) awards paid.
- Report on research needs in breast cancer, prepared by Dr. Ken McCartney for the DCPC Board of Scientific Counselors, as a followup to the Women's Health Trial's discontinuation. This report will be mailed to the Board and discussed at the May 1989 meeting.
- List of grants for which funding was affected by the change from priority scores to percentile scoring.

Mrs. Bynum reminded the Board that several members have indicated an interest in discussing the scoring of P01s at a future meeting. She then notified members that they would be asked to indicate any change in their review assignment preferences as a preliminary step to modifying the list of review assignments. It was agreed that copies of rebuttal letters from the appropriate programs will be sent to Board members who have review responsibilities for those programs.

XVII. ADJOURNMENT

There being no further business, the 69th meeting of the National Cancer Advisory Board was adjourned at 3:30 p.m. on Tuesday, February 7, 1989.

APR 17 1989

Date

David Korn, M.D.