Department of Health and Human Services

Public Health Service

National Institutes of Health

National Cancer Institute

National Cancer Advisory Board

Summary of Meeting
December 5-6, 1988
Building 31, Conference Room 6
National Institutes of Health
Bethesda, Maryland

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The National Cancer Advisory Board (NCAB) reconvened for its 68th regular meeting at 8:30 a.m., December 5, 1988, 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 (absent)
Dr. Phillip Frost
Mr. Louis V. Gerstner, Jr.
Dr. David Korn
Dr. Walter Lawrence, Jr. (absent)
Dr. Enrico Mihich
Mrs. Irene S. Pollin
Dr. Louise C. Strong
Dr. Louis W. Sullivan
Dr. Howard M. Temin (absent)
Dr. Samuel A. Wells

President's Cancer Panel

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

Ex Officio Members

Dr. David Rall, NIEHS
Dr. Richard Greene, VA
Mr. Richard Lemen, NIOSH
Captain Bimal Ghosh, DOD
Dr. John Johnson, FDA
Dr. James Robertson, DOE
Dr. Murray Cohen, CPSC

Members, Executive Committee, National Cancer Institute, NIH

Dr. Alan S. Rabson, Acting 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. Ihor Masnyk, Acting Director, Division of Cancer Biology and Diagnosis
Executive Secretary, Ms. Iris Schneider, Assistant Director for Program Operations and Planning

Liaison Representatives

Dr. Hugh Barber, Director, Department of Obstetrics and Gynecology, Lenox Hill Hospital, New York, New York, representing the Society of Gynecologic Oncologists.

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

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

Ms. Margaret Foti, Executive Director, American Association for Cancer Research, Philadelphia, Pennsylvania, representing the American Association for Cancer Research.

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.

Ms. Elaine Locke, Associate Director for Practice Administration, American College of Obstetricians and Gynecologists, Washington, D.C., representing the American College of Obstetricians and Gynecologists for Dr. Warren H. Pearse.

Ms. Delores Espinoza, President-elect, Oncology Nursing Society, Cambridge, Massachusetts, representing the Oncology Nursing Society for Ms. Deborah K. Mayer.

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. Gerald Murphy, Senior Vice President of Medical Affairs, Atlanta, Georgia, American Cancer Society.

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

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

Chairmen, Boards of Scientific Counselors, National Cancer Institute

Division of Cancer Etiology--Dr. Hilary Koprowski, Director, Wistar Institute of Anatomy and Biology, Philadelphia, Pennsylvania.

Division of Cancer Prevention and Control--Dr. Paul F. Engstrom, Vice President for Cancer Control, Fox Chase Cancer Center, Philadelphia, Pennsylvania.

Division of Cancer Biology and Diagnosis--Dr. Arnold J. Levine, Chairman and Professor, Department of Molecular Biology, Princeton University, Princeton, New Jersey.

Division of Cancer Treatment--Dr. John E. Niederhuber, Professor of Surgery, Division of Surgical Oncology, Johns Hopkins University School of Medicine, Baltimore, Maryland.

Frederick Cancer Research Facility--Dr. Dante G. Scarpelli, Chairman, Department of Pathology, Northwestern University Medical School, Chicago, Illinois.

In addition to NCI staff members, meeting participants, and guests, a total of 28 registered members of the public attended the meeting.

I. Call to Order, Opening Remarks, and Consideration of September 26-28, 1988, NCAB Meeting Minutes--Dr. David Korn

Dr. Korn, Chairman, called the 68th meeting of the National Cancer Advisory Board to order and welcomed Board members, the President's Cancer Panel, liaison representatives, guests, staff of the National Cancer Institute (NCI), Chairpersons of the divisions' Boards of Scientific Counselors, and members of the public. He announced that the December NCAB meeting comprises an overview of the Institute's programs and does not entail grant review. 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 September meeting minutes was postponed until the Tuesday afternoon session.

In concluding his opening remarks, Dr. Korn offered for the Board's consideration the following resolution in honor of Dr. Gertrude B. Elion, NCAB member, who was chosen to receive the 1988 Nobel Prize for Medicine:

Whereas Gertrude B. Elion has devoted her life to biomedical science; and

Whereas she and her collaborators brought the dawning of a new era in cancer treatment with the discovery of thioguanine and 6-mercaptopurine; and

Whereas her discovery among other achievements gave new tools to clinicians to fight gout, malaria, autoimmune disorders, cardiovascular disease, ulcers, and organ transplant rejection, and broke the barrier of treatment of viral infections, thereby laying the groundwork for the first effective treatment for AIDS; and

Whereas not even the Nobel Prize, the highest of scientific honors, will offer the full recognition she merits for having challenged the most formidable of diseases and aided millions of people across the world, who will continue to benefit from her work for years to come; and

Whereas her achievements provide special encouragement to women in biomedical science; and

Whereas she has served the National Cancer Program with dedication as part of the National Cancer Advisory Board: Be it therefore

Resolved, That the National Cancer Advisory Board rejoices in the bright reflected glow and offers its warmest congratulations to Gertrude B. Elion on the occasion of her receiving the Nobel Prize for Medicine.

The resolution was approved by acclamation.

II. Future Meeting Dates

Dr. Korn called the Board members' attention to the following confirmed meeting dates: February 6-8, 1989; 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 for 1990 are October 1-3 and December 3-5.

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

Dr. Hammer began his report by congratulating Dr. Elion, on behalf of the President's Cancer Panel, for the well-deserved, great honor bestowed on her.

Dr. Hammer reported that the Panel held its final meeting for the year at NIH, where reports were heard from NCI Acting Director Dr. Alan S. Rabson and his staff. Dr. Hammer stated that the Panel was encouraged to hear that the hiring freeze at the NCI has been modified but said the staffing situation continues to be disturbing in that only one person can be hired for every two who leave NCI. He expressed the hope that there will be further modifications in the new year to ease the strain on many programs. Other reports heard by the Panel included those of Dr. Michael Lotze (latest developments with tumor-infiltrating lymphocytes [TIL]), Dr. Steven Rosenberg (combining interleukin-2 [IL-2] with other biological response modifiers such as alpha-interferon, monoclonal antibodies, and tumor necrosis factor), and Dr. Nancy Jenkins (use of transgenic mice in cancer research), as well as reports on latest developments in cytotoxic agents, experiments with the drug suramin, oncogenes and growth factors, and monoclonal antibodies. Finally, Dr. Hammer noted the report on the status of biotechnology in the food supply, which was presented by Dr. Peter Greenwald, Director, Division of Cancer Prevention and Control (DCPC), indicating that genetic alteration of animals to reduce fats and other changes that may come from emerging technologies may one day offer alternatives to trying to change peoples' eating habits to reduce cancer incidence.

Dr. Hammer reported that he and Drs. William Longmire and John Montgomery have been working on the Panel plans for 1989, which, he said, would probably follow the usual pattern of visiting cancer centers throughout the country for the majority of meetings. He noted that the committee, which the Panel had established at the request of President-elect George Bush to review current procedures for approval of new cancer and AIDS drugs, will hold an organizational meeting at NCI on January 4, and he invited interested Board members to attend. He listed the committee members as follows: Dr. Louis Lasagna of Tufts University (Chairperson), Dr. Emil Frei, Dr. Samuel Hellman, Dr. Thomas Merigan, Dr. Charles Leighton, Dr. Elion, Dr. Theodore Cooper, Dr. Henry Pitot, Mr. Peter Barton Hutt, and Dr. Elliott Stonehill (Executive Secretary). Dr. Hammer said the committee will probably require a year to complete the thorough review, but the hope and expectations are that positive suggestions for improvements will result. He invited comments and suggestions from Board members.

In regard to the recent reauthorization of the National Cancer Act, Dr. Hammer expressed dissatisfaction that once again reauthorization was approved for only a 2-year period and noted the need for the cancer community to make an even stronger case for at least a 5-year period when the process begins again in 1990.

Dr. Hammer announced that he would be making a special award of $200,000 to Dr. Rosenberg in recognition of his innovative work in adoptive immunotherapy. He commented on the international acclaim accorded Dr. Rosenberg in November when he was awarded the Griffuel Prize by the French Association for Research, adding that Dr. Rosenberg joined the distinguished company of Dr. Vincent DeVita, Dr. Howard Temin, and the late Dr. Henry Kaplan, previous recipients of the Griffuel Prize. Noting that Dr. Rosenberg had also received the Hammer Award in 1985 for his work with lymphokine-activated killer (LAK) cells and IL-2, Dr. Hammer said the new award acknowledges the continuing research in adoptive

immunotherapy, generally, and the new therapy involving TILs and IL-2, in particular. He pointed out the great potential of adoptive immunotherapy in the future of cancer therapy when added to the traditional treatment modalities (surgery, radiation, and chemotherapy). He said Dr. Rosenberg's paper on the new technology has been accepted for publication by the *New England Journal of Medicine.*

Turning next to an update on the Stop Cancer Project, Dr. Hammer reported that he, Mrs. Helene Brown, Dr. Korn, and Dr. Rabson had been in discussion since the September NCAB meeting and had arrived at an agreement regarding NCI's acceptance of funds from the Project. He noted that the letter of agreement signed by himself and Drs. Korn and Rabson had been distributed to the Board. The Stop Cancer Project was successfully inaugurated in October at a gala concert and dinner. Dr. Hammer said $12.5 million had been raised to date, largely from corporate donors but also including individual donations that had been sent in response to Dr. Hammer's appearance on the Today Show and a Cable News Network program. Dr. Hammer expressed the hope that this initial amount would be matched by Congress soon so that a total of $25 million would be available to fund the research, especially clinical research, of many more qualified scientists than the present NCI appropriation can cover, and he said that this is the purpose of the Stop Cancer Project. In closing, Dr. Hammer stressed the need to raise the goals of the National Cancer Program for the year 2000 higher, to include a **cure** for **all** of the millions who will be afflicted, and he expressed his determination to work with the Panel, Board, and public to that end.

In the discussion, Board members expressed appreciation for Dr. Hammer's interest and effort in this fundraising project.

IV. NCI Director's Report--Dr. Alan S. Rabson

In beginning his report, Dr. Rabson added his congratulations to Dr. Elion on her receipt of the Nobel Prize and to Dr. Rosenberg on his receipt of the Hammer Award.

Dr. Rabson announced the departures of Dr. Robert Young, former Chief of the Medicine Branch and current Chief of the Centers Program, to become Director of the Fox Chase Medical Center, and Dr. Paul C. Rambaut, Deputy Director of DEA, to become Deputy Assistant Secretary General for Scientific and Environmental Affairs at NATO headquarters in Brussels, Belgium.

Regarding the FY 1989 budget, Dr. Rabson stated that the NCI appropriation of $1.571 billion was not reduced by the Gramm-Rudman review on October 15. He noted, however, that all agencies receiving AIDS funding were assessed 0.8 percent of their AIDS budgets to provide the $15 million needed by the Federal government to provide AZT over the next 6 months for individuals who cannot afford the drug; NCI's share totaled $1.013 million.

Dr. Rabson reported that a 2 percent reduction in noncompeting grants would be required to maintain the desired number of grants in FY 1989 rather than the 5 percent believed necessary at the time of the September NCAB meeting; the 10 percent overall reduction projected at that time for competing grants, however, remained unchanged.

Turning next to a discussion of full-time equivalents (FTE) and the NCI staffing situation, Dr. Rabson reported that the hiring freeze had been lifted; NCI has received 43 AIDS and 15 non-AIDS FTEs of the 350 new positions (200, AIDS; 150, non-AIDS) allocated to NIH by Congress. With the new positions, the NCI ceiling is now 2,150. Dr. Rabson stated that while the

new ceiling can be achieved under the 1 for 2 hiring ratio that is in effect, it is 400 positions lower than the operating level of several years ago and will impose considerable hardship on many programs whose responsibilities have increased during that time.

Dr. Rabson outlined the provisions of the National Cancer Act as they relate to the organization and operation of the NCI, noting in particular the presidentially appointed Board, which meets four times a year (three meetings for grant review, the fourth for program review), compared with the Councils of the other Institutes, which meet three times a year. He explained that a key part of the program review would be the presentations on each of the five divisions and the Frederick Cancer Research Facility (FCRF) made by the Directors, who would review organization, scientific highlights, managerial initiatives, and budget, and the Chairpersons of the Boards of Scientific Counselors (BSC), who would present summaries of site visits to the intramural laboratories and of RFAs, RFPs, and program announcements that were reviewed as concepts. The BSC Chairpersons would also present overviews of divisional operations. In reviewing the NCI table of organization, Dr. Rabson noted the three-member President's Cancer Panel, which provides management oversight, and the NCAB, which is legally mandated to provide a second review of all grants as well as program review and assistance in setting policy. He noted further that the FCRF functions like one of the divisions even though it is organizationally located in the Office of the Director, and that the other offices that report directly to the Director include the Offices of Program Operations and Planning (Ms. Iris Schneider, Associate Director [AD]), Cancer Communications (Mr. J. Paul Van Nevel, AD), International Affairs (Dr. Federico Welsch, AD), and Administrative Management (Mr. Philip Amoruso, AD). The five divisions are the Divisions of Cancer Etiology (Dr. Richard Adamson, Director), Cancer Biology and Diagnosis (Dr. Rabson, Director), Cancer Treatment (Dr. Bruce Chabner, Director), Cancer Prevention and Control (Dr. Greenwald, Director), and Extramural Activities (Mrs. Bynum, Director). Dr. Rabson described the Executive Committee, which comprises the NCI Director and all division Directors, as the central point of management, meeting weekly to discuss management problems and make corporate decisions. Finally, he noted that, in accordance with NIH policy of separating program and review functions, the DEA has the responsibility of providing for peer review of all grants and contracts that are delegated to NCI by the Division of Research Grants of the NIH.

Turning next to a review of the NCI budget on which the divisional programs are based, Dr. Rabson stated that actual expenditures for FY 1988 totaled $1,468.4 billion and that Congress has appropriated $1,571.5 billion for FY 1989 (including $123.777 million for AIDS less the $1.013 million assessment for AZT distribution), an overall increase for NCI of $103 million ($70 million for cancer, $33 million for AIDS). Dr. Rabson stated that the major portion of the NCI increase ($58 million) was allocated to the research projects pool, an 8.8 percent increase over FY 1988, leaving other program areas relatively unchanged or, in the case of the centers program, showing a slight decrease. He noted that even with the increase in funds allocated to the grants program, 726 competing grants, or 25 percent of those approved, would be funded in FY 1989, compared with 979 (36 percent) in FY 1988, although the total of funded grants will increase from 3,057 to about 3,100 in the same time period because the number of noncompeting grants increased by 300.

Dr. Rabson pointed out that cancer prevention, which is specifically allocated by Congress, would receive a 6.3 percent increase ($74 million compared with $69 million in FY 1988), whereas the intramural research budget increased by only 2.4 percent, not counting AIDS funds.

Dr. Rabson stated that the level budget for funding mechanisms would create particular hardships for the National Research Service awards (NRSA), which represent the funding

devoted to training the next generation of scientists. He said NCI had received permission to increase the predoctoral stipend from $6,000 to $8,000 and the postdoctoral stipend from an average $22,000 to $25,000. Dr. Rabson explained that legislative policy stipulates that at least 15 percent of the training funds go into individual fellowships (T32s) to avoid a concentration in institutional grants (F32s). The FY 1989 appropriations allocate $32 million for training ($3.9 million for T32s, $28.1 million for F32s) compared with $31.9 million in FY 1988 ($3.2 million for T32s, $28.7 million for F32s). The level budget combined with the increased stipends could necessitate a reduction of approximately 156 in the number of trainees that can be funded (1,456 in FY 1988, 1,300 in FY 1989). Dr. Rabson said that these possible reductions would be a serious problem for all Institutes and that NIH is looking for ways to generate additional money for training. He said the Directors would discuss the topic at their next meeting and would work toward a consistent policy for all Institutes.

Regarding reauthorization of the National Cancer Act, Dr. Rabson compared the actual provisions of the legislation with the list of recommendations developed by NCAB and the Panel, which included a 5-year reauthorization period, optimal funding levels as set forth in the President's bypass budget, appropriation of funds directly to the Institutes, and official recognition of BSCs as the bodies that conduct the statutorily required review of NCI's intramural programs. He pointed out that none of these recommendations was included in the Omnibus Health Extension Act of 1988.

In the discussion, the following points were made:

- The impact of the level FY 1989 budget will be felt equally by the intramural research, cancer centers, and training programs.

- The addition of AIDS funds to the intramural program budget will make operations more reasonable, but cancer research will suffer.

- Even with the addition of funds for AIDS research, a number of cancer centers may have to be closed and/or grants negotiated at reductions from recommended levels.

- Submitting a second bypass budget, which would reflect the funding needed to maintain the programs at the current level, might create more confusion and would probably not be any more effective than a clear presentation of current services requirements in the NCI budget request.

- The increase in AIDS research money in the intramural program will have an impact on the space available for cancer research, but the gravity of the AIDS situation makes it necessary to fit AIDS clinical and drug screening work within the available space.

V. Division of Extramural Activities Program Review--Mrs. Barbara S. Bynum

Mrs. Bynum, DEA Director, began by reviewing the DEA organizational chart, explaining that the DEA Office of the Director includes Dr. Rambaut, Deputy Director, and Dr. Vincent T. Oliverio, Associate Director, in addition to herself. Dr. Oliverio is responsible for coordinating NCI's participation in all those NIH-wide programs that involve each of the Institutes, including activities such as the Small Business Innovation Research (SBIR) Program, as well as for preparing materials from the administrative offices of the other NCI divisions for the NCAB program review meetings. Dr. Rambaut, who is leaving his position in early 1989, as mentioned by Dr. Rabson, has been instrumental in optimizing the DEA's use of contemporary

technology in managing its workload and has been deeply involved in issues related to the peer-review process, particularly those associated with program project grants. Mrs. Bynum also commended Dr. Rambaut for his management over the previous 18 months of the U.S.-U.S.S.R. Joint Cancer Treatment Program, on behalf of NCI's Office of International Affairs. Under this agreement, NCI and its counterpart Soviet organization, the All Union Cancer Research Center in Moscow, function as coordinating centers for a bilateral research program involving institutions throughout both countries.

Mrs. Bynum went on to describe the Administrative Management and Planning Branch, headed by Mr. Stephen M. Hazen, which has responsibility for the division's operational support and financial management. The recent change in the branch title to include the word Planning was intended to emphasize the expanded role of this branch in planning, designing, and implementing information and data management systems for the DEA. Through the Committee Management Office and the Scientific Review and Evaluation Awards Office of this branch, all logistical support for the NCAB is provided via the NCAB Committee Management Officer, Mrs. Winifred Lumsden. The management of all advisory committees, including the BSCs, is also within the purview of the Committee Management Office.

Next, Mrs. Bynum introduced Mr. Harry Y. Canter, head of the DEA Research Analysis and Evaluation Branch, which is the official centralized source of scientific information on NCI-supported research projects. This branch analyzes and indexes the content of all grants and contracts awarded by NCI, as well as intramural research projects, utilizing a computer database called GENIUS for storage and retrieval of this information. Mrs. Bynum noted that Mr. Canter is also the DEA representative for the Operating Committee of the newly reorganized Organ Systems Program.

Mrs. Bynum went on to describe the Contracts Review Branch, headed by Dr. David L. Joftes, noting that several years previously the responsibility for evaluation of contract proposals had been removed from the purview of the programmatic divisions of the NCI and placed in the DEA as this branch. She stated that the peer-review process developed by Dr. Joftes and his staff for contract review since that time had become the "gold standard" for the NIH. She commented that NCI has the largest R&D contract program of any of the Institutes and had awarded approximately $200 million of support in FY 1988. The DEA Contracts Review Branch works closely with the Research Contracts Branch in the Office of Administrative Management and has developed an interactive tracking system so that the status of proposals can be determined at all times. Of the overall procurement process, that component which is the Contract Review Branch's responsibility is now routinely completed within 75 days from the time proposals are received through final report preparation and submission.

The Grants Review Branch, headed by Dr. Robert F. Browning, is the largest branch of DEA and has three sections: Prevention, Epidemiology and Control Review Section (Chief, Dr. Carolyn Strete), Research Resources Review Section (Chief, Dr. John Abrell), and Research Program Review Section (Chief, Dr. Robert Hammond). Mrs. Bynum stated that the new one-tiered review procedures for the program project applications approved by the Board the previous year will be implemented for the applications assigned for Board review at the May 1989 meeting, and she said that the new procedures will be carefully monitored and evaluated at the end of 3 years as agreed. She noted that the NIH also requested such an evaluation and that NCI's Planning Office and Dr. Browning's staff were developing a conjoint approach to the evaluation. She reported that the Grants Review Branch reviews approximately 1,000 applications each year, utilizing 13 executive secretaries and their staff, and that during 1988, the branch managed 100 site visits, reviewed requests for $1.15 billion, and enlisted the

services of peer reviewers at a rate equivalent to 1,350 consultant visits. She emphasized the importance of continued recruitment of well-trained scientists to the branch's staff to perform quality peer review of grants for scientific merit and listed the names of several scientists who had joined the branch over the previous year.

Mrs. Bynum then described the functions of the newest DEA branch, the Review Logistics Branch, which encompasses the activities of the Referral Office run by Mr. Herman Fox, the Distribution Unit run by Mrs. Helen Martin, and the Special Review Office. This branch is intended to pursue implementation of more efficient procedures for tracking and distribution of applications and proposals and to provide support for the other two Branches responsible for the initial merit review. She announced that Dr. Paulette Gray had recently been selected as chief of this new branch.

Mrs. Bynum explained that the final component of the DEA, the Comprehensive Minority Biomedical Program (CMBP), directed by Dr. Lemuel Evans, was established by the NCI to broaden participation by minorities in cancer-related research and training activities. The CMBP is assisted in its activities by the Minority Advisory Committee, which includes program staff from all of the divisions of the NCI.

Further, Mrs. Bynum explained that the CMBP effort includes cofunding arrangements between the NCI and the Minority Biomedical Research Support (MBRS) Program of the Division of Research Resources and the Minority Access to Research Careers (MARC) Program of the National Institute of General Medical Sciences. The CMBP also supports special activities, such as the Minority Investigator Supplement, which provides supplemental funds to NCI grantees for the specific purpose of including minority researchers in their projects. CMBP contributes through the Minority Satellite Supplement to the support of the NCI's clinical cooperative groups to enable inclusion of minority patients and to encourage participation in NCI clinical trials by their physicians. In addition, support is provided to young minority investigators and students to enable them to attend meetings of the American Association for Cancer Research and the American Society for Clinical Oncology. Mrs. Bynum noted that the contract solicitation for cancer prevention awareness using the historical black colleges as resources, approved by the Board the previous year, was currently pending negotiation of one or more awards. In addition, recommendations for the Minority Enhancement Awards to cancer centers to facilitate cancer control efforts in minority populations will be brought before the Board for final review at the February 1989 meeting.

Turning to a description of the DEA budget, Mrs. Bynum illustrated that it comprises three categories: the CMBP budget; costs for scientific review and evaluation of grant applications and contract proposals; and in-house costs for salaries, travel, and supplies. She pointed out that DEA has about 90 staff members. She noted that the sum of all extramural awards, grants, and contracts made by the NCI in FY 1988 was $1.117 billion and that the cost of review by DEA was $10.102 million. She commented that the fraction of each dollar awarded that was spent on effective quality control by DEA was well spent.

To conclude the DEA program review, Mrs. Bynum explained that in the absence of its own Board of Scientific Counselors, the DEA relies on the NCAB Subcommittee on OD Contracts to perform the function of concept review for its solicitations via RFAs and RFPs. In the past year, that Subcommittee, chaired by Dr. Phillip Frost, approved four DEA concepts, including three for support and ADP services and one for the centers' supplement RFA mentioned previously.

As an introduction to the presentation by Dr. Georgette Dent, a recipient of a Minority Investigator Supplement award, Mrs. Bynum further explained that this support program was initiated by the NCI in 1983 and stated that 49 of these awards have been made to date. She noted that the Minority Investigator Supplement will soon be announced as an NIH-wide mechanism for use by all the Institutes. Dr. Dent has pursued her research in the laboratory of Dr. Joe Grisham, Professor and Chair of Pathology at the University of North Carolina, Chapel Hill, and was appointed to her present tenure track position as Assistant Professor of Pathology at the University of North Carolina School of Medicine in July 1988.

VI. Flow Cytometric Correlation of the c-*myc* Oncogene and Cell Cycle Kinetics in HL-60 Leukemia--Dr. Georgette Dent

Dr. Dent stated that the purpose of her project was to develop a flow cytometric technique to measure oncogene expression, DNA content, and monocyte-granulocyte differentiation in HL-60 cells during maturation induction. As background, she explained that in normal hematopoiesis, the majority of hematopoietic cells are terminally differentiated cells, and only a small percentage of cells, the stem cell compartment, has infinite proliferative potential. In leukemia, the relationship between the stem cell compartment and the terminally differentiated compartment is dissociated, and there is an increase in the stem cell compartment and a decrease in the terminally differentiated compartment.

Dr. Dent stated that the HL-60 promyelocytic leukemia cell line model, developed by Dr. Robert Gallo 10 years previously, exists in culture as granular promyelocytes and myeloblasts. The HL-60 cells can be induced by many agents to differentiate into either monocyte- or granulocyte-like cells. Thus, in Dr. Dent's study, two specific maturation inducers, dimethylsulfoxide (DMSO) and cytosine arabinoside (Ara-C), were chosen to investigate cell cycle kinetics in HL-60 cells. Ara-C was chosen because it is one of the more effective and relatively nontoxic agents in the treatment of acute myelogenous leukemia, and there is some anecdotal evidence that low doses of Ara-C may induce differentiation in patients. DMSO, a very toxic drug with no therapeutic value in leukemia, served as a contrast to Ara-C in terms of its kinetics. In this type of model, the untreated HL-60 cells parallel acute myelocytic leukemia in which there is a large stem cell compartment and a very small compartment of terminally differentiated cells; in the induced cell state, an approximation of normal hematopoiesis can be created.

Dr. Dent further explained that in this study c-*myc* oncoprotein was evaluated because it has been implicated in carcinogenesis and appears to have an important role in cell cycle kinetics. Low levels of this oncogene are expressed in lymphocytes and fibroblasts, and when these cells are induced to divide, the levels of this oncogene increase. In HL-60 cells, the c-*myc* oncogene is amplified approximately 32-fold. When these cells are induced to differentiate, the levels of c-*myc* mRNA in protein decrease.

In this study, Northern and slot blots of mRNA isolated from HL-60 cells in the control state and after maturation induction with Ara-C and DMSO showed that the c-*myc* mRNA levels decreased to approximately 20 percent of normal in the DMSO-treated cells and to about 16 percent of normal in the Ara-C-treated cells. The slots were hybridized to actin mRNA. With Ara-C, the cells were stopped in cycle; the DNA cycle was slowed, but the cells continued to produce mRNA and protein at a near-normal rate so that the cells became very large. Thus, the mRNA had to be normalized to actin.

Dr. Dent illustrated flow cytometric contour plots that were obtained using this method. The c-*myc* protein was visualized using a monoclonal antibody label. Again, with Ara-C, the HL-60 cells were slowed in cycle, and there was a reduction in S-phase progression; the increased population of HL-60 cells in the G_1 phase expressed a decreased amount of c-*myc* protein. With DMSO, the HL-60 cells were virtually stopped in G_1 and expressed a decreased amount of c-*myc* protein.

To investigate the relationship between the c-*myc* protein and differentiation, Dr. Dent explained that they looked at the cell surface marker OKM1, which increases as HL-60 cells are induced to differentiate and double stained with propidriem iodide to reveal DNA content. Cells that express increased amounts of OKM1 are in G_1. Thus, this was considered further evidence that the c-*myc* protein may be involved in the transition that cells undergo from the G_0 quiescent state to the G_1 state in which cells are cycling.

In conclusion, Dr. Dent stated that this technique may represent a method for studying patients with leukemia and will allow further study of the molecular biology of the c-*myc* and other oncoproteins, as well as cell cycle kinetics and maturation induction.

VII. Division of Cancer Etiology (DCE) Program Review--Dr. Richard Adamson

Dr. Adamson began his presentation by describing the responsibilities and organization of the Division of Cancer Etiology. He stated that the division supports both intramural laboratories and extramural programs to pursue research on cancer causation and basic research on cancer prevention. The DCE has two advisory committees: the DCE Board of Scientific Counselors and the NCI Executive Committee. In the DCE Office of the Director, Dr. Susan Seiber serves as Deputy Director and Dr. Elizabeth Weisburger as Assistant Director for Chemical Carcinogenesis. The division includes the Administrative Management Branch, headed by Mr. Mark Kochevar, and three programs: the Biological Carcinogenesis Program (Dr. Edward Tabor, AD), the Chemical and Physical Carcinogenesis Program (Dr. Adamson, Acting AD), and the Epidemiology and Biostatistics Program (Dr. Joseph Fraumeni, AD).

Dr. Adamson briefly described each Program. He explained that the Biological Carcinogenesis Program includes six intramural laboratories and one extramural branch, the Biological Carcinogenesis Branch (Dr. Jack Gruber, Chief), which supports studies on the etiologic role of biological factors and cofactors in cancer and is responsible for managing the extramural resource contracts for biological products. Dr. Adamson noted that speakers from two of this program's intramural laboratories--Dr. Stuart Aaronson, Chief of the Laboratory of Cellular and Molecular Biology, and Dr. Gallo, Chief of the Laboratory of Tumor Cell Biology--would follow his presentation.

Dr. Adamson then outlined the structure of the Chemical and Physical Carcinogenesis Program, which includes eight intramural laboratories and two extramural branches. He stated that the extramural Chemical and Physical Carcinogenesis Branch (Dr. David Longfellow, Chief) is responsible for administering the grant program and for maintaining resource contracts for providing chemical carcinogens and their metabolites as well as compounds for chemoprevention studies. The Radiation Effects Branch (Dr. Bruce Wachholz, Chief) administers a grant and contract program focusing on studies of the biological and health effects of exposure to radiation. Dr. Adamson noted that both of these branches reviewed their programs at the February and May 1987 meetings of the NCAB Subcommittee on Environmental Carcinogenesis.

In detailing the structure of the Epidemiology and Biostatistics Program, Dr. Adamson listed the five branches and explained that the Extramural Programs Branch administers the grants and contract support in epidemiology and related activities. He reminded the Board that Dr. Fraumeni presented a review of the entire Epidemiology and Biostatistics Program at the May 1988 meeting of the Subcommittee on Environmental Carcinogenesis. In addition, at the September 1988 Board meeting, Dr. Fraumeni and the five branch Chiefs reviewed their programs in closed session.

Dr. Adamson then went on to describe scientific highlights for each of the Program areas. Findings from studies of the Biological Carcinogenesis Program showed that:

- Mice transgenic for HIV-1 gene develop lesions resembling Kaposi's sarcoma.
- There are growth factors that can support growth of endothelial cells from AIDS patients with Kaposi's sarcoma.
- Abnormal expression of growth factors or their receptors is implicated in many human malignancies.

Dr. Adamson explained that in a joint study between investigators at the University of California and investigators from the Laboratory of Molecular Virology, one of the genes from the HIV virus, the *tat* gene, was used to establish transgenic mice lines. At 12 to 18 months, approximately 15 percent of the male mice developed skin tumors resembling Kaposi's sarcoma. Notably, only male mice developed these lesions. (Drs. Aaronson and Gallo elaborated on the latter two highlights in their presentations.)

For the Chemical and Physical Carcinogenesis Program, Dr. Adamson listed three highlights and described each briefly. Studies supported by this Program showed that:

- 13-cis retinoic acid prevents new skin cancers in xeroderma pigmentosum patients.
- A tobacco-specific nitrosamine induces pancreatic and lung tumors in animals.
- A mutagenic heterocyclic amine (IQ) found in cooked meats induces tumors in nonhuman primates.

The first finding resulted from a 3-year controlled prospective study of high-dose (2 mg/kg/day) 13-cis retinoic acid administration in xeroderma pigmentosum patients and established the feasibility of chemoprophylaxis of skin cancer. The second finding was based on a study of a tobacco-specific nitrosamine called NNK, which was administered to rats and shown to be a potent carcinogen, producing both lung and pancreatic tumors and providing the first experimental evidence of pancreatic tumor induction by a constituent of tobacco smoke. The third finding, that a heterocyclic amine, 2-amino-3-methylimidazol-4,5-quinoline (IQ), found in cooked meats induces tumors in nonhuman primates, is based on studies of IQ administration in cynomolgus monkeys, following earlier studies in Japan on rodents. Dr. Adamson stated that the quantitative determination of various heterocyclic amines is being developed further but that the data available thus far indicate that the intake of heterocyclic amines by humans is approximately 100 ng/day.

Dr. Adamson next listed three scientific highlights from Epidemiology and Biostatistics Program studies indicating that:

- Vegetables of the Allium class (e.g., garlic, onion, chives) protect against stomach cancer.

- New risk models suggest that radon may contribute to 10 percent of all U.S. lung cancers.

- The decline in immunity of HIV-positive male hemophiliacs is associated with increased infectivity to female sexual partners.

He expanded briefly on each finding, noting first that additional studies are under way to try to validate the study in China showing that there was a significant reduction in risk of developing stomach cancer with increasing consumption of Allium vegetables. In relation to the second finding, Dr. Adamson noted that the risk model indicating that radon may contribute to 10 percent of all U.S. lung cancers is based on high-dose exposure information from uranium miners. Therefore, more studies are under way in Missouri and New Jersey to attempt to determine what the actual exposure to radon in the United States contributes to risk of lung cancer. Dr. Adamson commented that the third highlight summarizes data that suggest that heterosexual transmission of HIV can occur during routine vaginal intercourse, but it usually does not occur until the hemophiliac has severe immune deficiency late in the course of HIV infection when T-cell helper cells are depleted.

Dr. Adamson also outlined four managerial initiatives that the Division undertook during the last year:

- The Epidemiology and Biostatistics Program initiated a training program for pre- and postdoctoral fellows in cancer epidemiology, which will support approximately 10 fellows each year.

- In the spring of 1988, construction of a centralized animal holding facility was completed. The facility was built to meet the standards of the NIH Guide for the Care and Use of Laboratory Animals and is being managed by the NCI Office of Laboratory Animal Science.

- Also in spring 1988, the DCE Epidemiology Program and extramural management staff relocated to the newly leased Executive Plaza office complex along with NCI contracts and grants management staff and staffs of other divisions.

- The DCE continued to support EEO objectives through various administrative activities, including promoting minority and women's participation in the division's summer student research training program and postdoctoral fellowships.

Turning to the subject of funding for new RFAs and the DCE budget, Dr. Adamson listed the four new RFAs, one of which was assigned to the DCE from the Organ Systems Program and three of which resulted from workshops sponsored by DCE. He noted that one RFA, Epidemiological Studies of HIV-Associated Malignancies, which was discussed with the NCAB AIDS Subcommittee, was reissued recently. In addition, in 1988 DCE funded one cooperative agreement entitled Development, Validation, and Application of Biochemical Markers of Human Exposure and Susceptibility for Use in Epidemiological Studies.

To conclude his presentation, Dr. Adamson explained the DCE budget, both overall and then broken out into cancer and AIDS funding. He stated that the overall DCE budget increased 8.7 percent, from $296 million for FY 1988 to $322 million for FY 1989. Funding for grants increased by 9.2 percent, for contracts by 4.3 percent, for RFAs and cooperative agreements by 17 percent, and for in-house costs by 7.5 percent (compared with 2.4 percent for the entire NCI intramural program). Of these increases, the cancer portion of the budget increased 8.2 percent for grants, 3.5 percent for RFAs and cooperative agreements, 2.4 percent for in-house activities, and 2 percent for contracts. The overall increase for the cancer portion of the budget was 6.4 percent. Dr. Adamson pointed out that the relatively small increase for cancer RFAs was attributed to the fact that both the Biological Carcinogenesis and Epidemiology Branches have RFAs on HIV.

Within the DCE AIDS budget, Dr. Adamson emphasized that the base cooperative agreement increased to $2.5 million, which is responsible for the large overall increase of 17.9 percent in the division budget for RFAs and cooperative agreements. The AIDS budget for grants increased 47 percent and for contracts 9.4 percent.

When the budget is broken out by four programs--the three DCE programs and one on nutrition for Congressional interest--Dr. Adamson noted that each will increase in FY 1989. The Biological Carcinogenesis Program will have the largest increases, particularly due to the increase in grant monies for AIDS activities.

Dr. Adamson concluded by commending the DCE BSC for its efforts and contributions over the past year.

Report of the DCE Board of Scientific Counselors--Dr. Hilary Koprowski

Dr. Koprowski briefly reviewed the history of the DCE BSC, stating that the Board was established in 1978 and had held 26 meetings to date. He stressed that the BSC members consider their collaboration with Dr. Adamson to be excellent and feel that the division functions well under his leadership.

Dr. Koprowski explained that the Board serves four primary functions: concept review of contracts, RFAs, cooperative agreements, and interagency agreements; budgetary advice on concepts and laboratory costs; site visits to intramural laboratories; and participation in special *ad hoc* subcommittees in areas of importance.

Dr. Koprowski noted that the BSC holds three meetings each year. An indepth review of the budget for the division takes place at the fall meeting, a report on intramural laboratories at the spring meeting, and concept review at the winter meeting. The specialties of the Board members, including viral oncology, chemical and radiation carcinogenesis, genetics, biostatistics, and epidemiology, reflect the activities of the division.

Dr. Koprowski presented listings of the intramural site visits conducted by the Board members and other specialists, beginning with the first site visit in October 1987 to the Laboratory of Tumor Virus Biology. Other site visits were to the Biostatistics Branch, the Environmental Epidemiology Branch, and the Laboratory of Cellular and Molecular Biology. Dr. Koprowski explained that the chairman of each site visit is responsible for collecting opinions of members of the site visit team and for presenting the results at a closed session meeting of the Board. After discussion, the recommendations of the site visit team are then reported to

Dr. Adamson. Within a year of the site visit, the Board is informed about implementation of the suggestions.

To conclude his presentation, Dr. Koprowski summarized the concepts and budgets presented to the Board in FY 1988. He noted that the Epidemiology and Biostatistics Branch operates the largest number of contracts within the Division, and therefore, the BSC reviews more concepts for this program than the others.

The following points were raised in discussion after Drs. Adamson's and Koprowski's presentations:

- NCI maintains an overview of intramural as well as extramural and private research so that unnecessary duplication of research effort can be avoided and priorities can be set for intramural research. The Institute also interacts with industry, professional organizations such as the Society of Toxicology, the American Association for Cancer Research, and others, and there is Departmental coordination by the DHHS Committee to Coordinate Environmental Health and Related Programs. Other coordination with various agencies is accomplished by several means, including membership on the NCAB.

- Studies are under way in New Jersey in an area called the Reading Prong and in an area of Missouri with high radon levels, in which the actual radon levels in houses are being measured so that it can be determined whether the high dose to low dose extrapolations from the miner studies apply to risks from actual housing situations.

- The heterocyclic amines are potent mutagens and potent carcinogens in rodents and from preliminary data in nonhuman primates, and further studies of the effects of lower doses of these compounds are under way. Humans are exposed to these compounds when they eat meat cooked at high temperatures, especially with charcoal cooking and pan frying.

- The training program for pre- and postdoctoral fellows in cancer epidemiology is individually tailored to each fellow who is selected.

VIII. Oncogenes, Growth Factors, and Cancer--Dr. Stuart Aaronson

Dr. Aaronson said he would discuss aberrations in genes that are important in growth factor-triggered normal cell proliferation, in particular, the genes that code for growth factors or their receptors. He suggested that someday it may be possible to use knowledge about growth factors to develop better methods of cancer treatment.

Referring to studies of retroviruses, Dr. Aaronson said it had been learned that captured cellular genes encode normal cellular proteins that function in growth factor-activated pathways. The first match between an oncogene and normal protein was the *sis* oncogene and platelet-derived growth factor (PDGF). Subsequently, relationships were documented between oncogenes and activated forms of genes encoding growth factor receptors. Over the past 5 years, some of the genes captured by retroviruses have been found to be intimately involved in the origin of human cancers, completely independent of any retrovirus involvement.

Dr. Aaronson pointed out that the v-*sis* gene is closely related to the PDGF-B gene, a growth factor normally present in platelets and important for normal wound healing. He said that the genes for the A and B chains of PDGF can exist in three different isoforms: as

homodimers of the A or B chain and as a heterodimer involving both chains. The *sis* oncogene product, which forms a B chain homodimer, has all the properties of PDGF. These properties include triggering the PDGF receptor on the cell surface, activating cell proliferation, and causing transformation in culture of those cell types that possess the appropriate receptor.

To determine whether the normal human gene for PDGF-B expressed in a normal animal induces tumors, Dr. Aaronson said that animals were inoculated with a PDGF-B chain encoding retroviral construct. The animals developed tumors at the site of inoculation, but only in cell types that possess the appropriate receptor for the gene. Dr. Aaronson said these studies have indicated that overexpression of the growth factor in the animal can act as the initiating step for the development of malignancy. In humans, no expression of the growth factor is seen in fibroblasts or normal glial cells, but at least 60 to 80 percent of fibrosarcomas and glioblastomas examined express the transcript and the protein form of the growth factor.

Although these genes are important for normal growth and development, Dr. Aaronson said the development of neoplasia seems to require that the growth factor, to trigger the receptor in the cell, must get to the cell surface. Therefore, this provides a target at the cell surface that may permit the modulation of growth and interfere with the development of malignancy. For example, certain drugs such as suramin can strip growth factors from their receptors and reduce the growth of transformed cells.

Dr. Aaronson emphasized that even though a cell has receptors for a growth factor, expression of growth factor may not always trigger malignancy. He described a transfection experiment in which the DNA for either PDGF-B or PDGF-A was added to fibroblasts using the same promoter to obtain the same level of expression. The PDGF-A chain was found to be much less active than the PDGF-B in causing malignant transformation. In studying differences between the two proteins, it was found that the PDGF-A chain is much better secreted, thus effectively lowering the concentration of the product at the cell surface where the receptor is triggered. The A chain was also found to have less mitogenic activity than the B chain.

Dr. Aaronson said that other growth factors can be expressed in cells that possess a moderate number of the appropriate receptors without inducing abnormal growth. He stated that there appears to be some critical threshold number of receptors that must be activated by the growth factor to induce the development of malignancy. Dr. Aaronson showed a slide of a typical growth factor receptor, noting the outside part or the ligand binding domain, the transmembrane domain that goes through the cell membrane, and the tyrosine kinase domain, the site of the special activity of growth factor receptors, which is thought to link them to signal transduction pathways within the cell. He stated that recently a human gene had been found that is structurally related to the genes of growth factor receptors. This new gene was found to be most closely related to the PDGF receptor than to the others, and its expression in normal tissue paralleled that of the known PDGF receptor. Dr. Aaronson said a gene for a second PDGF receptor had been discovered, and in a cell that only expresses the new receptor, all three forms of PDGF can trigger tyrosine phosphorylation. The first known PDGF receptor is triggered by the B chain homodimer and to a much lesser extent by the AB heterodimer. Dr. Aaronson said these findings indicate a network of three ligands for two receptors. He also pointed out that the forms of PDGF that stimulate the new receptor seem likely to be important in the development of arteriosclerotic heart disease and arthritis.

Dr. Aaronson next discussed receptor genes related to the EGF receptor, which is triggered by both EGF- and the TGF-alpha protein. A gene related to the EGF receptor has been found to be amplified in a human breast cancer. It has been suggested that this gene, termed *erb*-B-2,

may be a predictor of breast cancer, and, in fact, as many as 20 or 30 percent of some carcinomas have been found to have amplification and/or overexpression of the *erb*-B-2 or EGF receptor genes. In the presence of a promoter, the murine retroviral LTR, the *erb*-B-2 gene is overexpressed 50- to 100-fold and becomes a potent transforming gene. Dr. Aaronson said the cells transformed by this gene are as malignant as any cell type ever tested in the model system. However, when the level of expression is decreased by 5- to 10-fold, there is no evidence of transforming activity. In contrast, the EGF receptor in the presence of a promoter and expressed at high levels shows no evidence of transforming activity, except when a growth factor is added to the cells. Dr. Aaronson said that in human tumors, overexpression of both the EGF receptor and its cognate growth factor are required for these genes to have a role in human malignancy.

In conclusion, Dr. Aaronson emphasized that conditions under which growth factors are abnormally expressed and where cells possess the cognate receptors may often have a role in malignancy. Because drugs can be targeted to surface proteins overexpressed by cells, this may represent an important treatment modality. If the interaction of the growth factor with the receptor can be intercepted, this may make it possible to stop the action of overexpressed growth factors.

In discussion, Dr. Aaronson said that no case has yet been observed in which a metastatic breast carcinoma has overexpression of *erb*-B-2 but the primary tumor does not. He said the overexpression is probably a step in the progression of tumors, earlier than metastasis, but not necessarily the first step. Dr. Aaronson agreed that it might be useful to study PDGF with respect to the differential evolution of wound healing, keloids, and fibrosarcomas.

IX. New Clues About Kaposi's Sarcoma--Dr. Robert Gallo

Dr. Gallo began by recognizing the contributions of coworkers in his laboratory involved in the research he would present: Drs. Shuji Nakamura, Zaki Salahuddin, Peter Biberfeld, and Barbara Ensoli.

Referring to Dr. Aaronson's presentation, Dr. Gallo stated that there is general agreement that the most important properties of tumor cells are that they are blocked in differentiation and become immortalized and that they possess signals to trigger mitosis. A virus can infect a cell and directly convert the cell into an abnormal cell that contains viral genes. When malignancy occurs, all the progeny of the original cell will harbor the viral sequences at exactly the same place in exactly the same chromosome. These cells are clonal derivatives of the original cell, and Dr. Gallo said, all human cancer is believed to be clonal. He stated that theoretically, a virus also can have an indirect role in tumor formation: a virus infects a cell but does not make it a cancer cell; rather, that infected cell by some mechanism produces an effect on another cell. The possible mechanisms of this effect include activation of a cellular gene for growth factors in the first cell that augments the proliferation of another cell, or in B-cell tumors, chronic antigenic stimulation, where the viral proteins become a growth factor for producing B cell proliferation. Dr. Gallo explained that increased proliferation over many years in a target B cell increases the probability of that cell undergoing a malignant conversion. He suggested that Kaposi's sarcoma is an example of a tumor virus playing an indirect role in malignancy.

Dr. Gallo next discussed the mechanisms by which retroviruses can produce a cancer. The most common mechanism is believed to be insertional mutagenesis in which viral genes are integrated near a cellular gene important to the proliferation of the particular target cell. A rare mechanism is the transduction of a cellular proto-oncogene. The retrovirus picks up the proto-oncogene and reinserts it at an abnormal place, or in an abnormal copy number, or with an

abnormal regulator sequence, and the gene can be expressed in high amounts with an altered protein. Dr. Gallo said that although this mechanism appears to occur rarely, it can produce a malignancy within a few weeks or months. A third mechanism is transactivation, in which the human leukemia virus HTLV-I and probably also HTLV-II integrate anywhere in the cell and activate the IL-2 receptor and possibly also the expression of IL-2. Dr. Gallo explained that this can occur because HTLV-I and HTLV-II carry extra genes at the 3' end of the viral genome, and at least one of these genes, the *tax* gene, makes a protein that can lead to the activation of cellular genes as well as viral genes. When the gene for the IL-2 receptor is turned on, the cell cannot be down regulated.

Dr. Gallo said there is evidence that retroviruses also may increase the probability of malignancy by the indirect mechanism of chronic antigenic stimulation. For example, people infected with the HTLV-I virus shortly after birth in endemic areas of the world might have lifetime stimulation of some target B cells that respond to the virus. There is an increased risk of B-cell leukemia with HTLV-I infection, but the virus is in the T cell. Epidemiologic studies have demonstrated that B-cell leukemias are clonal and make one type of antibody that is directed to the HTLV-I protein. Dr. Gallo said this protein then acts as a growth factor with a chronic growth-promoting effect.

Dr. Gallo then turned to discussion of Kaposi's sarcoma as an example of HIV having an indirect role in malignancy. He first pointed out that some forms of Kaposi's sarcoma are not associated with HIV and have some other initiating mechanism that remains unknown. Dr. Gallo noted the characteristic multiple red skin lesions of Kaposi's sarcoma as well as internal lesions, all associated with blood vessel proliferation, sometimes hemorrhage and edema. The tumor cell is thought to be an abnormal endothelial cell, but there is no agreement on whether it is vascular or lymphatic in origin. Dr. Gallo said that if the tumor occurs in multiple sites because of independent transformations, it is unlike any other human cancer. He also noted Drs. Rabson's and Costa's hypothesis that Kaposi's sarcoma may not be a true malignancy. Possible reasons supporting that hypothesis include the pathology of the tumor (it looks like granulation tissue in the early phases of a scar) and its multifocal nature. These observations combined with the epidemiologic findings that males are afflicted more than females and that homosexual males are afflicted much more than other HIV-infected persons stimulated Dr. Gallo and his colleagues to a more intensive study of this neoplasia and, in particular, to look for another virus.

Dr. Gallo said there was early speculation, now thought to be unconfirmed, that the cytomegalovirus (CMV) was involved. With or without CMV, another prevailing opinion was that people with HIV infection do not have immune surveillance, but Dr. Gallo pointed out that failure of immune surveillance does not automatically lead to malignancy. In addition, Kaposi's sarcoma can be the presenting abnormality in persons with HIV infection, before the development of detectable immune deterioration. Efforts to identify known viruses from Kaposi biopsy tissue were unsuccessful, so efforts were next undertaken to grow the cells to try to isolate a new virus. However, Dr. Gallo said, the cells proved very difficult to grow, even with various growth factors. Finally, various sources of conditioned media were tested, and as he and his coworkers described in a recent issue of *Science*, spindle cells were successfully grown for periods of time up to a year or longer. (Spindle cells in Kaposi's sarcoma are believed to be the real tumor cells.) Dr. Gallo referred to the cultured cells as Kaposi's sarcoma-derived endothelial-like cells (KSEL), or alternatively as the cultured spindle cells. The conditioned medium is from a human retrovirus-infected T4 cell (HTLV-II infected T4 lymphocyte conditioned medium). Dr. Gallo explained that all human retrovirus-infected cells release a growth factor, and a clone (number 38) of one HTLV-II transformed T4 cell line was found to release the most. Use of HIV-infected cells results in some cell killing and more associated

contaminated molecules, so that even though this would theoretically be the best choice for obtaining the factor if the factor were to be relevant to the pathogenesis of Kaposi's sarcoma, the factor was easier to obtain from the number 38 cells. Dr. Gallo said the growth factor appears to be biochemically and biologically novel and will be named when the gene is cloned and purified or the protein is purified and its immunoassay sequence determined.

In describing the Kaposi's spindle cells that are being grown, Dr. Gallo said they have been successfully cloned, and they appear to be pure populations of mesenchymal cells probably abnormal endothelial cells--but the latter specification is still not certain. Moreover, if they are endothelial, Dr. Gallo said it is still not known whether their lineage is lymphatic or vascular. Once the spindle cells are growing, they in turn release growth factors of several kinds, one or more of which produces growth of blood vessels. When the cultured spindle cells are inoculated into nude mice, more than 90 percent developed lesions within 10 days, which pathologically look like early Kaposi's sarcoma. Dr. Gallo pointed out that surprisingly and of interest, the cells were found to be of mouse origin, entirely dependent on the presence of the inoculated cultured human spindle cells. Thus, the human cells must be releasing some factors with biological activities. In fact, these cells were found to make growth-promoting factors for normal fibroblasts and endothelial cells (paracrine effects) and for themselves (autocrine effects), and they release a factor having IL-1-like activity and granulocyte-monocyte, colony-stimulating factors. They also release chemotactic and chemoinvasive factors for normal endothelial cells, for normal fibroblasts, and for the Kaposi's cells. As noted already, they have neoangiogenic activity *in vitro* and *in vivo*.

To explain these activities, Dr. Gallo said the cells growing in culture were examined by Northern blot analysis for different mRNAs of known cytokines. The Kaposi's sarcoma cells express much basic fibroblast growth factor, much IL-1-beta, and some GM-CSF, compared with none in normal endothelial cells, and equivalently express TFG-beta and PDGF. Similarly, the proteins expressed by the Kaposi's sarcoma cells include much basic fibroblast growth factor and IL-1, and they appear to be involved in the continuation of cell growth. In studies using specific antibodies against these growth factors, growth of the Kaposi's sarcoma cells in the conditioned medium was inhibited.

Dr. Gallo then summarized the current understanding of the development of Kaposi's sarcoma. HIV infects macrophages and CD4 positive T lymphocytes, and from the work of G. Jay et al., evidence is available in mice that suggests that the *tat* gene of HIV turns on one or more cell genes that may lead to Kaposi's sarcoma. He speculated that one of these was probably the new growth factor that he and his group used to initiate growth of the spindle cells. The growth factor acts on the target endothelial cells, and eventually they become chronically activated (the spindle cell) and produce their own growth factors, including chemotactic and chemoinvasive factors, IL-1, angiogenic factors, and basic fibroblast growth factor, which can affect proliferation of other endothelial cells and other fibroblasts and also promote their own proliferation. Dr. Gallo said the experiments offer no obvious explanation of why Kaposi's sarcoma occurs so frequently in homosexual men, but he pointed out that it appears to be declining, along with other types of infections, in some homosexual populations. He speculated that HIV infection, plus antigenic stimulation of the T cell by other infections that are known to make the viral genes become active, increases the probability that high concentrations of the "new" growth factor will be produced. Dr. Gallo said this theory is also in keeping with the hypothesis that Kaposi's sarcoma may not be a true malignancy and is supported by reported spontaneous regressions of Kaposi's sarcoma. He said current efforts are aimed at developing an experimental chemotherapeutic program to interfere with the interactions of the growth factors

and receptors. In concluding his remarks, Dr. Gallo asserted that the next step is the development of a radioimmunochemical assay for the novel growth factor.

In discussion, Dr. Gallo indicated that although there has been progress in developing treatment for AIDS, it is impossible to predict when a cure will be found.

X. Division of Cancer Prevention and Control (DCPC) Program Review--
Dr. Peter Greenwald

Dr. Greenwald stated that the primary aim and mission of the Division of Cancer Prevention and Control is the development of cancer prevention and control strategies that will lead to lower cancer incidence and mortality rates across the country. He expressed the view that the division continues to make progress toward that aim despite fairly severe FTE and budget problems. Dr. Greenwald cited as examples of this progress the growing cancer prevention research effort, including more investigator-initiated research, involvement of major cancer research centers in cancer control research, and the establishment of community-based interventions and research networks with the potential to reach minority populations as well as the general public. He noted the complementary public information activities of the Office of Cancer Communications and pointed out the improvement in some national statistics, including the decline in lung cancer incidence in males and indications that use of mammography is increasing.

In describing the organization of the division, Dr. Greenwald identified within the Office of the Director, the Smoking, Tobacco, and Cancer Program, headed by Dr. Joseph Cullen; the Administrative Office, headed by Mr. Nick Olympio; the Surveillance and Operations Research Branch, headed by Dr. Edward Sondik; and the Biometry Branch, headed by Dr. David Byar. The three divisional programs, each with a number of branches, are the Cancer Prevention Research Program, headed by Dr. Dan Nixon; the Centers and Community Oncology Program, with Dr. Don Fox as Acting Director; and the Cancer Control Science Program, with Dr. Sondik as Acting Director. Dr. Greenwald emphasized the importance of studies on the relationship between diet and cancer, and he mentioned the frustrations associated with establishing the Laboratory for Nutrition and Cancer Research.

Dr. Greenwald said DCPC's actual 1988 budget was $276 million. Cancer prevention and control, a designated line item, accounts for about one-quarter of the DCPC budget and about 4.7 percent of NCI's budget. Major budget items include the training program in the Cancer Control Science Program and the cancer centers in the Centers and Community Oncology Program. Dr. Greenwald pointed out that the cancer prevention and control portion received about a 6 percent increase in the 1989 budget with the rest of the budget remaining essentially level.

Dr. Greenwald began his presentation of the scientific highlights by describing activities of the Smoking, Tobacco, and Cancer Program. He noted the evolution of research, in parallel with the cancer control phases, from early emphasis on etiology of smoking and lung cancer to research on applications to projects that affect the population. Studies in progress involve 10 million people in 30 states and more than 200 communities and have multiplier effects. These projects include the Community Intervention Trial for Heavy Smokers, called COMMIT, involving 11 different communities and 11 controls, and the American Stop Smoking Intervention Study (ASSIST), a national demonstration project to be conducted with the American Cancer Society in 20 states and involving 50 million people. A manual for physicians was completed and will be distributed to 100,000 physicians as the basis for a national training program for physicians to help their patients stop smoking. A guidelines document for public schools,

"Essential Elements of School-Based Smoking Prevention Programs," was completed and will be distributed to 25,000 school administrators and curriculum specialists.

Among the highlights of the Cancer Prevention Research Program, Dr. Greenwald noted the establishment of the nutrition laboratory and the need to build that program. He mentioned efforts in chemoprevention to identify potential preventive agents and decide which ones should be taken into preclinical and potentially into clinical prevention research. Twenty-four chemoprevention trials are in progress, as well as studies on the physiology and chemistry of dietary fat and fiber. A pilot study was completed in Yunan, China, that demonstrated the feasibility of conducting a large-scale chemoprevention trial among tin miners to prevent lung cancer. Studies are planned on how changes in the food supply, which may result from new biotechnologies, might affect cancer risk.

Dr. Greenwald identified participation in the NCAB's National Black Leadership Initiative on Cancer as one of the Cancer Control Science Program's highlights. Planning has begun to develop a Hispanic Cancer Control Initiative. The NCI/Giant Food Project will be completed in February 1989, and efforts will be made to apply the findings about buying behavior to food markets across the country. A set of nutrition guidelines for screening, counseling, and monitoring of the diet and cancer risk status of patients was developed jointly with the Office of Cancer Communications for physician use and will be distributed in FY 1989.

Within the Centers and Community Oncology Program, Dr. Greenwald noted that four new centers had been funded in 1988: Colorado, Pittsburgh, Michigan, and the consortium of Drew, Meharry, and Morehouse. The NCI Working Guidelines for Early Detection were endorsed by a number of health professional organizations; these were jointly developed with the American Cancer Society. A National Educational Cancer Plan for Melanoma is being developed with the American Cancer Society and the American Association of Dermatologists. The Community Clinical Oncology Program (CCOP) was expanded to include clinical trials in cancer prevention and control, as well as treatment, and accrual to both kinds of trials has been good.

Briefly citing a few highlights of the Surveillance and Biometry Program, Dr. Greenwald pointed out that Dr. Larry Kessler would give a presentation on the report "Measurement of Progress Against Cancer." He indicated that information is being collected not only on cancer incidence, survival, and mortality, but also on such factors as smoking rate and diet.

In concluding his presentation of program highlights, Dr. Greenwald remarked that most of the DCPC staff has moved to a new building that is quite close to the NIH campus. He also commented on a study done in the DCBD Dermatology Branch, which produced the first report of a chemoprevention trial where a change in cancer incidence was the endpoint. Five patients with xeroderma pigmentosum, a condition involving defective DNA repair and high occurrence of skin cancer, were orally administered 13-cis-retinoic acid for two years. During that period, the number of skin tumors decreased, probably indicating a reduced incidence or a delay in onset, or both.

To illustrate the changes in the food supply that may result from biotechnology, Dr. Greenwald discussed two fat substitutes, Simplesse, a protein made by the Nutrasweet Company, and Olestra, a sucrose polyester made by Procter and Gamble. He suggested that although there are uncertainties about these products, the use of fat substitutes in cooking could substantially reduce dietary fat intake as well as calories. Other changes that may affect cancer incidence include the widespread use of microwave ovens and the associated use of convenience and fast foods; the grazing phenomenon, meaning that people eat small amounts all day long; the

move from commodities to processed foods; and increased demand for foods that meet health guidelines. Dr. Greenwald reiterated the need for the nutrition laboratory and prevention trials to build a solid research base for studying the impact of such changes.

Before introducing Dr. Paul F. Engstrom, Chairman of the DCPC BSC, Dr. Greenwald noted the death of Dr. Tim Talbot on November 7, 1988. Dr. Talbot, who was a major leader in the development of cancer centers, founded the Fox Chase Cancer Center and served on the Pennsylvania Governor's Task Force on Cancer Control from 1974 to 1978. Dr. Greenwald also mentioned that Dr. Young, who had headed the CCOP, would be the new director of Fox Chase and that Dr. Engstrom was Vice President for Cancer Control at Fox Chase.

Report of the DCPC Board of Scientific Counselors--Dr. Paul F. Engstrom

Dr. Engstrom began by pointing out that five members of the DCPC Board are involved in cancer centers, and others provide expertise in nutrition and various cancer prevention issues. In discussing the Board's contributions to DCPC programs, Dr. Engstrom said that in the area of nutrition and chemoprevention, the Board has taken a strong role in emphasizing the scientific basis of chemoprevention. The Board reviewed and renewed the Nutrition Intervention Studies in Linxian, China, on esophageal cancer, which involve use of vitamin preparations to attempt to reverse esophageal dysplasia. Dr. Engstrom noted the Board's strong support for the nutrition research laboratory, including the appeal to Dr. Hammer for assistance in overcoming some of the obstacles to staffing the lab. He also recalled the Board's decision to disapprove the full implementation of the Women's Health Trial and its endorsement of NCI's dietary recommendations on fat and fiber.

Dr. Engstrom said the Board endorsed some major concepts in the area of cancer control science. One project is a tie-in between NCI and state health departments to encourage the use of data in state registries to help plan and construct interventions that can meet the needs in various states. Dr. Engstrom said the Board found the original concept of Prescribe for Health too general and not likely to meet the goal of involving practicing physicians in screening, detection, and prevention. The new RFA is expected to be released within 6 months.

Board activities related to the Centers and Community Oncology Program included the endorsement and budget increase for the Minority Enhancement Award and endorsement of a training program for cancer control investigators. Dr. Engstrom pointed out that over the past 3 years, the Board has strongly recommended that construction funds for cancer centers be included in the budget. Referring to preliminary findings from the Cancer Centers Subcommittee, Dr. Engstrom said that the Board suggests that if increased funds become available, cancer control activities, such as the Cancer Information Service, and education of health professionals in the community should be a responsibility of a comprehensive cancer center. Other major concepts approved by the Board included the COMMIT trial, which will test a method for reaching hard-to-reach, high-risk smokers, and the ASSIST trial, aimed at decreasing smoking throughout the country.

Dr. Engstrom also mentioned several divisional reports that came to the Board, including the various guidelines documents cited by Dr. Greenwald. He noted the new guidelines for the Clinical Investigation Grant (K08) Program, which will essentially replace the Physician-Scientist Grant (K11) Program. The K08 awards are intended to encourage newly trained physicians to develop research interests and skills in basic and applied science relevant to cancer and increase the number of cancer physician-scientists specializing in areas such as diagnostic and therapeutic radiology, preventive oncology, epidemiology, nutrition, and primary care. Dr. Engstrom said

the Board also received the report of the *ad hoc* review committee for the Surveillance, Epidemiology, and End Results (SEER) Program. The Board agreed with the committee's recommendations that the program be expanded to increase its usefulness in tracking the year 2000 goals and in tracking the effectiveness of the CCOP in diffusing cancer information in surrounding communities.

In conclusion, Dr. Engstrom expressed the Board's overall enthusiasm for many of the division's programs and support for Dr. Greenwald and the staff.

The following points were raised in discussion:

- NCI engages in much strategic planning before undertaking large-scale human intervention trials and considers coordination with other agencies, but this has been difficult to implement.

- Including disease endpoints other than cancer in human intervention trials at times may be important, but also could compromise the quality of the trials and may increase the size and costs of the trials.

- The NIH Committee on Disease Prevention and Health Promotion provides a forum for discussing collaborative activities.

- Hiring of a director for the nutrition laboratory has been hampered by the limited available space (3,000 square feet at Frederick) and lack of staff positions.

XI. Smoking and Public Health--Dr. Kenneth Warner

To establish the context for his presentation, Dr. Warner began by suggesting that future historians would evaluate smoking and health as one of the most important and interesting stories of the 20th century. Its importance relates to the associated unparalleled amount of morbidity, disability, and mortality, and its interest relates to the incredible adoption of smoking behavior during the first half of the century and the equally fascinating rejection of that behavior during the second half of the century.

Dr. Warner said he would focus on the rejection of smoking, noting first that this phenomenon is unevenly distributed across socioeconomic groups. As an example, Dr. Warner said that 30 years ago, the majority of physicians smoked, whereas today smoking prevalence is only about 8 percent among physicians. Prevalence of smoking among college graduates has decreased from 34 percent in 1966 to 16 percent in 1987. In contrast, among Americans who do not have college diplomas, smoking prevalence is virtually unchanged: 37 percent in 1966 and 36 percent in 1987. Dr. Warner asserted that although everyone knows that smoking is hazardous, a large number of Americans have a superficial appreciation of the nature of the hazard.

To illustrate his assertions, Dr. Warner pointed out that teenagers almost uniformly identify illegal drugs as the agents that cause the most deaths among Americans, but in reality, cigarettes kill 100 times as many people each year as all illegal drugs combined. In the 1984 Prevention Index survey, experts identified smoking as the Nation's number 1 health priority, while the lay public identified smoking as number 10 on the list. The public ranked home fires, which kill fewer than 6,000 people a year, as number 4. Smoking kills between 300,000 and 400,000 people a year and causes probably 30 percent of home fires.

Dr. Warner contended that although knowledge may be superficial, there has been enough dissemination of information and enough social change to produce substantial behavioral change. He cited the decrease in smoking prevalence among males from 50+ percent in the mid-1960s to 32 percent in 1987, and in females, from 33+ percent to about 27 percent. In terms of peak smoking prevalence, the decrease has been more dramatic: 70 percent of men born between 1911 and 1930 were smokers at the age of peak prevalence, compared with 42 percent of men born between 1951 and 1960. Based on preliminary data from the 1987 Health Interview Survey (HIS), the prevalence may have dropped as low as 30 to 32 percent among those born between 1961 and 1970.

By projecting the experience of earlier cohorts onto later cohorts, Dr. Warner illustrated what the situation would be today without all the information dissemination and social changes that have occurred. He suggested that smoking would have decreased among males but not nearly as much as what has occurred, but among females, prevalence would have continued to increase. The net result is that tens of millions of people who would be smoking today are not as a consequence of the antismoking campaign.

Using per capita cigarette consumption as an indicator, Dr. Warner showed that after World War II every decrease in consumption is associated with some major smoking and health event. These events included publication of articles in *Reader's Digest* in the late 1950s; the first Surgeon General's Report in 1964; the Federal Communications Commission (FCC) requirement, starting in 1967, that the media donate 1 minute for antismoking messages for every 3 minutes of smoking advertising; the removal of smoking ads from radio and television in 1971; and the nonsmokers' rights movement, starting in about 1973. Dr. Warner also noted the strong statistical correlation between the number of new state laws restricting smoking in public places and per capita cigarette consumption.

Dr. Warner next described the mortality benefit by estimating that through 1978, 200,000 premature deaths have been postponed or avoided because of the antismoking campaign, and by extending the estimate through 1985, the total would be several hundred thousand deaths. He stated that each of the deaths averted represents two decades of life expectancy and pointed out that one out of every three or four smokers will lose 20 or more years of life. Dr. Warner suggested that this gain in life expectancy is one of the greatest public health accomplishments in history. He added, however, that premature deaths were not postponed or avoided for many millions of people.

Dr. Warner then turned to discussion of some related policy issues. Referring to the tobacco subsidy, he pointed out that in addition to price support, the Government pays farmers who hold allotments to grow tobacco. Dr. Warner said that if subsidies were eliminated, the price of tobacco would fall slightly, as would the price of cigarettes, and because people are somewhat responsive to price, cigarette consumption would increase. He also noted the indirect effect of the political power created by the farm interest groups and allotment holders. Dr. Warner said he suspected that the tobacco lobby has helped to sustain consumption.

Dr. Warner identified excise taxation as another important policy tool and cited estimates that a 10 percent price increase would decrease cigarette consumption by about 4 percent. That decrease would be mostly in prevalence, not daily consumption. For teenagers, a 10 percent price increase would result in an 8 to 14 percent decrease in consumption, again mostly in prevalence. When Congress was considering whether to maintain the temporary doubling of the Federal cigarette excise tax, Dr. Warner said that he calculated that if the tax was allowed to lapse, resulting in an 8-cent decrease in cost, 2 million people would have been enticed to smoke.

Further, he found an inverse correlation between age and price responsiveness, with the youngest ages being most price responsive, and he underscored the importance of that finding to prevention.

As an emerging issue, Dr. Warner cited the fact that there are fewer state laws restricting children's access to cigarettes today than there were in 1964 at the time of the first Surgeon General's Report. Those laws that do exist are almost uniformly not enforced. Dr. Warner said a second issue is the exportation of America's lung cancer epidemic abroad, particularly to Asia and the Third World. He noted efforts to remove trade tariffs and remove restrictions on cigarette advertising. In Japan, he said cigarette advertising, disproportionately for American cigarettes, has increased to 10 to 20 percent of all television advertising, and according to the latest prevalence studies, Japanese girls and young women are smoking, which historically has not occurred.

In concluding his presentation, Dr. Warner addressed the important emerging issue of alternative nicotine delivery systems (ANDS) and described various products. For example, a smokeless cigarette was developed consisting of a hollow tube containing some material impregnated with nicotine; a person sucks on the tube and inhales the vapors. FDA declared this a drug delivery device subject to the usual safety and efficacy requirements, and it is now off the market. Candy or gum containing tobacco and providing 1 mg of nicotine was labeled an adulterated food product by FDA and is also off the market. A creamy snuff product, in the form of toothpaste, that is rubbed on the gums remains on the market. This product carries the following warning: "Caution, those who are not used to the effects of nicotine should start with a small quantity of this product." Dr. Warner said the most important ANDS is the "cleaner smoke" cigarette developed by R.J. Reynolds. The patent describes the product as a drug delivery device and mentions that other drugs besides nicotine could be delivered through the device. Dr. Warner speculated that crack and cocaine could be among the other drugs. He suggested that this device would encourage smoking because it would provide an alternative to quitting smoking and because it does not emit much visible smoke, its use might be permitted in offices. In addition, such a product might have considerable appeal to former smokers.

A question was raised in discussion about the economic impact of smoking and associated morbidity on the business community. Dr. Warner acknowledged that research was being done in this area, but cautioned that much of the benefit to be derived from the avoidance of smoking is in the future, which for businesses might mean higher costs in terms of pensions and secondary health care. Another question related to a national excise tax on cigarettes, and Dr. Warner noted the recent 25-cent increase in California. He said a national excise tax is a possibility as a deficit reduction measure. With respect to the California tax, it was pointed out that although the tobacco lobby spent a great deal of money, the antismoking forces won by 2 to 1 in the state referendum. The $600 million in revenues expected to be generated by the tax will be used for health services, health education, and medical research.

XII. Measures of Progress Against Cancer--Dr. Larry Kessler

Dr. Kessler provided information on the report "Measures of Progress Against Cancer," requested by the Senate Appropriations Committee. As requested by the Committee, NCI convened an extramural committe of experts, chaired by Dr. Lester Breslow, to write the report, with support provided primarily from the DCPC Surveillance Program under the direction of Dr. Sondik. The committee was charged with recommending how to assess which measures are the most appropriate for progress in cancer. The committee determined this assessment should address the direct measures of cancer incidence, survival, and mortality, and the many different

types of cancer, the multiple risk factors, the barriers to prevention, screening, and treatment, and the assessment of progress in basic and clinical research.

To address these issues, Dr. Kessler said the committee developed a framework related to the way the disease progresses through the population that included interventions such as prevention, detection, screening, diagnosis and treatment, management, including rehabilitation and continuing care, and the ultimate outcomes of cancer and noncancer deaths. He cited examples of measures related to interventions and risk factor measures, such as smoking rates, alcohol consumption, or occupational exposure, and knowledge, attitudes and practices related to cancer. For early detection, measures may include incidence rates of cancer as well as the use of Pap smears and mammography. Measures relevant to diagnosis and treatment may include the number of patients on protocols and patterns of care. Patient management measures might include survival rates, quality of life, and psychosocial measures. Dr. Kessler emphasized that the committee considered it important to include both noncancer and cancer deaths in the overall context of measuring progress.

Dr. Kessler identified some of the issues addressed by the committee in three major areas as follows:

- Data collection
  --coverage issues, e.g., the breadth of the SEER program and coverage of minorities
  --frequency of collection

- Reporting
  --extent of reports
  --frequency
  --method of presentation

- Analysis
  --use and emphasis of various measures
  --interpretation of statistics

He also selected several conclusions of the committee to report to the Board. First, the committee found that the ultimate measure of cancer is how it affects people in their lifetimes. It is critical to address both specific cancers and total cancer, using measures of mortality, incidence, and survival. Dr. Kessler cited examples to substantiate the committee's conclusions that mortality as the ultimate measure is not sufficient. Mortality from prostate cancer was essentially unchanged from 1950 to 1985, but incidence rose dramatically, perhaps indicating an increase in morbidity in this disease. Mortality from colorectal cancer has declined since after World War II through 1985, although recent data suggest a significant increase in incidence, raising the possibility that there have been large gains in survival, perhaps coupled with problems related to prevention or early detection.

Dr. Kessler reported that the committee's second set of conclusions was that two sets of measures are necessary to define progress in cancer. These are the direct measures of impact on people, e.g., incidence, survival, mortality, new cases, length of life with disease, and deaths from cancer, and indirect measures that portend significant future impacts, such as smoking, screening rates, and clinical trial accrual. The committee suggested that the importance of these indirect measures is linking them with their eventual impact on the direct measures. For example, decreases in smoking will turn into decreases in cancer incidence and, ultimately,

decreases in mortality. The projected effects of changes need to be based on data and linked with actual experiences, where possible.

Turning to the recommendations, Dr. Kessler said the committee urged NCI to produce a comprehensive reporting document on a periodic basis to cover the many aspects of the cancer program and synthesize the information. He noted that the expansion of the Annual Cancer Statistics Review last year represented one step toward that recommendation and was used extensively by the committee in its deliberations. Dr. Kessler stated that the committee also recommended monitoring changes in treatment and access to care. The SEER-based patterns of care studies that have been initiated should assist in determining whether state-of-the-art therapy is being widely used.

Another committee recommendation cited by Dr. Kessler was that cancer control trends and their impact should be reported. It is expected that the 1987 HIS cancer supplement will address this issue, at least in part. Other committee recommendations related to reporting on progress in basic and clinical research. Dr. Kessler noted the committee's view of the importance of linking basic research to overall cancer progress. Another committee recommendation was for more basic statistical and epidemiologic research. Finally, Dr. Kessler said that the committee recommended extending the population base and expanding collaboration for the purpose of collecting cancer-related and cancer control data. This recommendation is addressed in part by the review of the SEER program and the plan for the 1992 HIS.

In response to a question about followup of the committee's report, Dr. Greenwald said that the plan for the Surveillance Program is based, in part, on the report. Different types of information will be included in the Annual Cancer Statistics Report, and information will also be reported periodically from the patterns of care studies.

XIII. Organ Systems Annual Report--Dr. James Karr

Dr. Karr began by expressing pride in the accomplishments of the Organ Systems Program (OSP) in the first 4 years of its existence and concern about some of the plans for the program's restructuring. In reviewing progress at the time of the 1987 report, he noted that the group had registered a successful year, having received BSC approval for 7 concepts for an overall total of 12 RFAs and 8 program announcements. He added that the numbers of initiatives ready for potential development, planned workshops, working group meetings, subcommittee activities, and publications in preparation were sufficient at that time to sustain the momentum that had been building over the first 3 years of the program. Dr. Karr noted that the program entered a transition period when the recommendations were made to disperse the OSP's grant portfolio, phase out the external Organ Systems Coordinating Center (OSCC), and internalize all OSCC activities by July 31, 1989.

Before addressing the past year's accomplishments and future plans, Dr. Karr presented insights and background on developments during the transition period that have contributed to the status of the Organ Systems Program. He noted that the strength and success of the OSP has resided in the working groups, which had functioned with a degree of flexibility and autonomy for setting programs and agendas. The OSCC provided support to the groups. Dr. Karr stated that the working groups were informed in February 1988 that they would be chartered to ensure their stability and to give them official status that would permit their access to actual grant progress reports. Plans to charter the working groups were confirmed in a special communication in March and were cancelled 1 month later. Dr. Karr added that there was concern that the working groups would be able to function only as *ad hoc* advisory groups and that losing the

ability to generate agenda items could change the dynamics, cohesiveness, and diversity of the working groups. Another concern was that recruitment has been nonexistent during the transition period, while the definition, composition, tenure, and role of the new working groups are being developed. He observed that the former practice of replacing up to five working group members each year had ensured the diversity and infusion of new ideas. He said that an added concern voiced by the groups was that the future appointments would be controlled by NCI.

Dr. Karr noted that keeping the biomedical community informed of organ systems activities, as required in the cooperative agreement, had been accomplished through the organ systems newsletter, which gave the program clear visibility and identity to the more than 8,000 subscribers. He stated that the OSCC was advised by NCI officials to stop publishing this newsletter. He was also advised that the working groups may not be able to sustain the current level of book and journal publication.

Dr. Karr said another concern related to communication to the groups on progress made toward achieving the goals of the original concepts. Five collaborative networks of investigators were formed in response to organ systems RFAs. In the transition period, network activities and meetings are limited to NCI staff, and progress reporting to working groups has been varied. He cited as examples the fact that the working groups received no information from the large bowel network and that the OSCC's facilitating role was eliminated from the prostate and two bladder cancer networks. Dr. Karr emphasized that to maintain the interest of the working groups, there is a need to keep them well informed on the progress of the research their ideas originated. He added that the groups should also receive comprehensive reports on all other NCI-sponsored research if they are being asked to identify gap areas.

Regarding workshops and conferences, which had been principal annual activities of the working groups, Dr. Karr stated that the prostate working group had recently been informed that R13 grant applications would have to be developed to fund future workshops after the OSCC grant expires and that the group could apply to other agencies for funds needed that are in excess of the customary $10,000 ceiling on the grants. He noted that this ruling places control of workshop funding almost entirely in NCI. He said there is also uncertainty among the groups about the process or mechanisms for obtaining workshop funding.

Dr. Karr reported that during the transition period, the groups have been presented with a paradox in that the charge at the outset was to develop new initiatives to compete in the marketplace of ideas for BSC approval of a concept destined for RFA or program announcement development, whereas they are now being told that the program cannot be concept driven. He suggested that the success of the organ systems RFAs during the first 3 years, as exemplified by the rapid rise in dollar amounts, had reportedly led to budgetary and priority dilemmas for the NCI and that this was a primary reason for restructuring the OSP.

Dr. Karr listed as a final concern the level of NCI's commitment to the organ systems concept. He said that at a meeting with the NCI Director earlier in the year two factors were emphasized as critical to the future of the OSP: support from NCI's leadership, to the extent of moving the program into the Director's office, and assurance of adequate staff to fill the void left when the OSCC contract ends. Dr. Karr noted that even though the amount available for the outside contractor is $120,000 more than the total direct and indirect costs of the OSCC award, the services received will exclude the scientific professional input that was provided full time by the OSCC. He pointed out that support will be provided on a task-driven basis, as needed, and he expressed the opinion that the contract staff would probably have no knowledge regarding the history, continuity, or mission of the program.

For these reasons, Dr. Karr said the working groups were less spontaneous and enthusiastic than formerly, and the perception was that their vigorous involvement in generating a broad spectrum of activities catalyzed the changes to the program that were occurring. Dr. Karr said that in the transition meetings, OSP and NCI staff have discussed the problems at length and resolved a number of points, but serious problems remain, although he acknowledged that the NCI officials in charge of the program are fully supportive and are concerned that it succeed.

Turning next to a summary of accomplishments and future plans for each of the seven working groups, Dr. Karr noted that, collectively, the cancers their programs represent cover 40 percent of the annual cancer mortality and 50 percent of new cancer cases.

Dr. Karr reported that the Bladder Working Group held a DNA workshop in January, which evolved to include all solid tumors and became a joint endeavor of all the groups. At a June working group meeting with outside consultants and NCI program representatives, discussions began that culminated in plans made at a November meeting for a workshop in 1989 on the molecular biology of normal and abnormal urethial cells and their response to carcinogens and metabolites in urine.

The Breast Working Group submitted two concepts to NCI for processing and BSC review. The group is awaiting publication of a program announcement on markers for subclinical metastasis, which was approved the previous year, and has planned a workshop in the spring of 1989 on progestin action and receptors.

Dr. Karr said the relatively new Central Nervous System Working Group has identified as top priority the development of molecular probes for classification of astrocytomas. A concept on this topic was received by NCI for processing in February, approved in June, and published as an RFA 3 months later. A workshop on radiation biology in December 1987 led to development of a concept on radiation damage, which is scheduled for review at the upcoming DCT retreat. A workshop on imaging is planned for 1989, and there is interest in developing another on monoclonal antibodies.

The Large Bowel Working Group, which has been working with NCI for several years on a conservative treatment concept, has progressed to the point of agreeing on a Phase II treatment protocol involving local resection and 5-FU and radiation therapy. The protocol is being presented by NCI to the clinical cooperative groups as a possible intergroup study. Dr. Karr said the proceedings of a polyps workshop were well received, and a June 1989 workshop on dysplasia and cancer in colitis is planned, the latter to be cosponsored by the National Ileitis Foundation.

Of two workshops held by the Pancreas Working Group during the year, the first provided a forum for scientists to define the antigens of pancreatic tumors and apply them to diagnosis and therapy; the second addressed growth and differentiation of pancreatic cancer. Abstracts and summaries of these workshops will be published in *Pancreas*. Plans for the coming year include a small workshop on surgical versus nonsurgical palliation of obstructive jaundice and a study of the basic enervation and neural endocrinology of the exocrine pancreas as it relates to pain.

The Prostate Working Group held two workshops during the year, one that addressed diagnostic markers and quantitative assessment of bony metastasis and another that focused on the use of sonography in staging and monitoring treatment responses. Dr. Karr said NCI's proposed prostate cancer screening project was presented for critique at the first workshop and may be an example of how future working groups may function in an advisory role. The second workshop was cosponsored by the National Science Foundation and the Japan Society for

Promotion of Science and may be a prototype for finding supplemental support for future workshops. Proceedings of two prior prostate workshops have been published, and those of the two latest workshops are planned for publication in 1989. Dr. Karr said the committee reports on staging, grading, and response criteria in the reporting of clinical data have been published and that four standing subcommittees continue to work toward improvement and standardization of these measures. He added that committee reports were applauded locally and abroad and are being formally presented to the American Urological Association and various clinical cooperative groups. Another highlight of the year was the prostate carcinogenesis concept, which recently received BSC approval as an RFA; the concept on prostatic involution, which was approved the previous year as a program announcement, has not yet been published.

The Upper Aerodigestive Working Group submitted an initiative on magnetic resonance imaging (MRI) for processing. The concept's objective is to explore recent technological advances that would reduce the cost of MRI and improve detection of subclinical disease. Workshops on drug resistance and speech rehabilitation were held; the proceedings of the latter will be published as a supplement to the journal *Head and Neck Surgery*. Future activities include development of an initiative on genetic determinants in head and neck cancer to be published as a program announcement, a working group meeting to be held in conjunction with a workshop on chemoprevention (March 1989), and work on two other topics that were submitted to NCI the previous year.

In summary, Dr. Karr said the working groups received BSC approval for two concepts, held nine workshops, eight working group meetings, and generated seven publications, including three books. For 1989, development of concepts remains questionable (four of the seven groups have no plans), seven workshops are planned, three publications are in process, and five subcommittee and two full working group meetings are scheduled. Dr. Karr noted that there has been a decline in overall organ systems activity and new idea generation when 1988 activities in all categories are compared with the 1987 report.

In concluding his report, Dr. Karr stated, on behalf of the OSCC, that it had been a privilege to serve the working groups, which he termed valuable resources. He expressed the view that the groups want to continue their association with the OSP, but to continue a strong commitment of time and effort, they will require a clear delineation of the restructured program in terms of their roles and responsibilities, measurable and realistic goals, and endpoints for evaluation. Dr. Karr expressed the opinion that the Organ Systems Program could continue to play an important role in solid tumor research with strong commitments from working groups, strong support throughout NCI (possibly operating out of the Office of the Director), and adequate organ systems staffing headed by Drs. Chiarodo and Brian Kimes.

XIV. Transition Status Report on Organ Systems Program--Dr. Brian Kimes

Dr. Kimes began by emphasizing the enthusiasm that has been generated for the Organ Systems Program throughout the NCI. He acknowledged that problems remain but pointed out that they have been assessed openly and the conclusions reached will expand the sphere of the program and give an organ systems perspective across all programs that will benefit the Institute as a whole.

Dr. Kimes stated that NCI was building on some of the successes of the OSCC and incorporating them in a positive way. He listed positive outcomes of the transition period as follows:

- With the absence of portfolios, the OSP will have an advisory role across all programs of the Institute.

- Divisional program staff members will have greater opportunity to be exposed to disease-oriented issues and to interact across divisions and programs as a result of the relocation and consolidation of all divisional staff in the new building. OSP staff, in turn, can become more involved in the disease-oriented problems faced by NCI.

- NCI program staff will be invited to Organ Systems Committee meetings to discuss ways to make the OSP work optimally.

- To clearly and consistently communicate the objectives of the OSP to extramural staff, Chiefs of Program Directors meetings will be held to which all NCI program staff will be invited.

- Dialogues have already begun between NCI staff and working group members at subcommittee meetings where NCI and working group priorities are being meshed to produce realistic plans of action.

- In presentations to divisional Boards of Scientific Counselors, Dr. Kimes has been explaining how the OSP will operate and what roles the BSC will have in the operation. An attempt will be made to involve BSCs at very early stages of concept development.

- The emphasis in the restructuring process will be on complementing rather than competing with the existing program advisory structures of the divisions by encouraging interaction among the advisory groups and OSP working groups.

- Organ systems staff will be encouraged to follow the divisional priority setting processes to keep informed of divisional priorities in the organ systems areas.

Dr. Kimes stated that the task of identifying problem areas has been accomplished in extensive and constructive discussions with Dr. Karr and the OSCC staff, and he expressed confidence that the problems would be solved in the ensuing 6 months. He listed the following as focuses of the joint effort:

- Promoting the new concept for the OSP among working group members.

- Encouraging maximum use by NCI program staff of advice from experts who are members of the working groups.

- Promoting gradual changes in the planning and conduct of working group meetings and workshops through greater interaction between program staff and working group members.

- Promoting cooperation in defining priorities and developing concepts, especially in times of lower budgets.

Dr. Kimes suggested that there would be reservations on all sides until a program is constructed that can be accepted generally, but he cited some examples of the transition process in operation that promise success of the philosophy underlying the program, as follows:

- The collaborative effort of NCI staff, the OSCC, and working group members was successful in bringing the CNS concept on molecular probes for classification of astrocytomas to publication as an RFA in less than a year.

- The individual pilot studies by working group members were stimulated by Large Bowel Working Group discussions on a protocol for conservative surgical therapy, and now there is a good possibility that this concept will be tested further in one or more of DCT's Clinical Cooperative Groups. Dr. Kimes said this is an example of how working group initiatives can be pursued within the existing NCI resources rather than through the development of new RFA and/or RFP initiatives.

Dr. Kimes concurred with Dr. Karr's suggestion that the working groups should receive progress reports from the networks formed in response to organ systems RFAs and pointed out that at its next meeting, the Bladder Working Group will become involved in finding ways to approach the flow cytometry network more effectively.

Dr. Kimes listed as an accomplishment of the transition period the speed with which the project plan for the support contract RFP was completed. He said the RFP would probably be published within the month and would be widely competitive in order to identify the best people to provide support to the working groups. He acknowledged that dispelling the reservations of some working groups and reorienting them to interact with the NCI would be major tasks. He said NCI recognizes the value of bringing new people into the working groups and at the same time maintaining the stability of the working group concept. Dr. Kimes said that future productivity of the program will prove its value and that the NCAB will be asked to evaluate the program in coming years as it has evaluated the current change. He noted that evaluation of the new working groups' performance will be more difficult than in the former concept-driven system where the numbers of concepts, initiatives, RFAs, program announcements, and workshops were measurable outcomes, and he solicited suggestions from the Board. He emphasized that working groups will continue to deal with concepts and will continue to provide multidimensional and multidisciplinary input into disease-oriented research and that there are many ways to evaluate success other than numbers.

Dr. Kimes pointed out the difficulty at the present time for any of the programs to consider initiatives that require set-aside money, and he noted the percentage of R01s projected to be funded in FY 1989 compared with the FY 1988 figure. He added that the reorganization of the Organ Systems Program was an attempt to utilize the existing budget more creatively.

Dr. Kimes stated that a document proposing guidelines for selecting new members was being reviewed by the Executive Committee. He emphasized that after observing patterns of productivity in the existing groups, the NCI Organ Systems Committee proposed that the working groups have cores of 8 to 10 regular members supplemented by 5 to 6 *ad hoc* members. He added that the guidelines as proposed are experimental and are an attempt to find better ways of generating ideas. Regarding the purpose and method of operations statement, Dr. Kimes noted that it will be developed as an operational document to help NCI staff understand the role of OSP and recognize the possibilities for help in managing their programs. He added that it would also define the roles of the NCAB and BSCs.

Dr. Kimes concluded that the reorganized Organ System Program will actually be more complex in that it will crosscut all divisions and encourage interaction at every level, and he expressed the opinion that it would provide a solid base of research for the National Cancer Institute.

In response to the observation that it was understood that NCI was committed to chartering the working groups, Dr. Kimes explained that this was not a viable option for NCI at this point. He pointed out that the *ad hoc* structure permits flexibility in developing working groups with the greatest scientific diversity at any given time. Moreover, NCI would be losing the resources of recognized experts needed to serve as study section members, etc., if the working groups were hartered because of the NIH prohibition against dual membership on chartered committees.

Regarding the decision to discontinue publication of the organ systems newsletter, Dr. Kimes said the Executive Committee was not certain that funds would be available over the long run to continue publication. He added that NCI will use the OSCC database in the future to accomplish many of the goals of the newsletter. He pointed out that the *Cancer Letter* already publishes OSP concept announcements and special communiques and has a very broad audience of biomedical cancer researchers.

Other points made in the discussion included the following:

- The working groups require clarification of their roles in the restructured Organ Systems Program.

- The decrease from 36 percent in FY 1988 to 25 percent in FY 1989 of approved grants that are funded reflects only competing grants; the total number of grants funded increased from FY 1988 to FY 1989, but outyear commitments to noncompeting grants and OIGs and MERIT awards absorb much of the FY 1989 budget increase.

- It is too early to judge whether the changes in the OSP have increased the effectiveness of the program.

- It may be useful for the working groups to meet with the NCAB Subcommittee on the Organ Systems Program to more directly air some of their concerns.

In conclusion, Dr. Kimes stated that it is standard NCI procedure to prepare a detailed internal document that clearly defines the operation of a new program, and from this comprehensive document, an abstracted version is then prepared for distribution to the community. He said guidelines would be developed for this program according to NCI procedures and pointed out that the new guidelines would not take effect until the Organ Systems Committee and program staff assume management from the OSCC.

XV. Division of Cancer Biology and Diagnosis (DCBD) Program Review--Dr. Alan S. Rabson

Dr. Rabson said that the programs of the Division of Cancer Biology and Diagnosis involve all the basic sciences of cancer biology and cancer immunology and their application to the diagnosis of cancer. The Office of the Director includes the Deputy Director, Dr. Ihor Masnyk; the Planning and Analysis Branch, headed by Ms. Susan Ficker; and the Administrative Office, headed by Mr. Larry Willhite. The division's programs are the Extramural Research Program, headed by Dr. Kimes and including branches on cancer biology, immunology, and diagnosis, and the Intramural Research Program, which encompasses 13 laboratories. Dr. Rabson highlighted the following research activities of the intramural laboratories:

- Laboratory of Molecular Biology (Dr. Ira Pastan, Chief)--immunotoxins and oncotoxins as applied to cancer research; molecular approaches to multidrug resistance; fibronectin and matrix proteins; regulation of bacterial genes.

- Laboratory of Biochemistry (Dr. Claude Klee, Acting Chief)--repetitive DNA; calcium binding proteins involved in cell growth, metabolism, and regulation; genetics of the protein metallothionein; gene expression in Drosophilia.

- Laboratory of Mathematical Biology (Dr. Jacob Maizel, Chief)--applications of computer technology to biomedical research, including studies of RNA structure and protein folding.

- Laboratory of Genetics (Dr. Michael Potter, Chief)--plasmacytoma resistance genes; IL-6; antibody structures.

- Metabolism Branch (Dr. Thomas Waldmann, Chief)--IL-2 receptor; control of gene expression in lymphoid cells; mechanisms of T cell activities.

- Laboratory of Cellular Oncology (Dr. Douglas Lowy, Chief)--*ras*-oncogene studies; papillomaviruses.

- Dermatology Branch (Dr. Steven Katz, Chief)--immunodermatology.

- Laboratory of Pathology (Dr. Lance Liotta, Chief)--metastasis research; use of antibodies to the laminin receptor to target drugs to cancer cells; cloning of gene for type IV collagenase; drug inhibition of the autocrine motility factor; identification of the NM23 metastasis suppressor gene.

- Immunology Branch (Dr. David Sachs, Chief)--transplantation biology.

- Laboratory of Immunology (Dr. Tibor Borsis, Chief)--complement research and study of deletion of portions of chromosome 3 in lung and renal cancers.

- Laboratory of Tumor Immunology and Biology (Dr. Jeffrey Schlom, Chief)--application of monoclonal antibodies to the diagnosis and treatment of cancer; molecular genetics of breast cancer.

- Laboratory of Cell Biology (Dr. Lloyd Law, Chief)--tumor antigens; heat shock proteins; regulation of class I histocompatibility genes.

- Experimental Immunology Branch (Dr. Al Singer, Chief)--T-cell lymphocyte differentiation; lymphocyte-mediated cytotoxicity; antigen-independent T-cell adhesion.

Dr. Rabson referred Board members to the Board books for a full listing of the scientific highlights of the extramural program and proceeded to discuss one of the activities in detail. Dr. Irving Weissman, at Stanford, has isolated individual murine bone marrow hematopoietic stem cells and used them to reconstitute all immune cells in lethally irradiated mice. The system for doing this involves a fluorescent-activated cell sorter to select out of bone marrow those cells that have differentiation markers. As selection continues, the resulting cell populations have increasing numbers of very primitive stem cells. Finally, using monoclonal antibody selection, Dr. Weissman can purify the true hematopoietic stem cell and has shown that as few as 40 of these cells put into a lethally irradiated mouse can completely reconstitute the immune system and the whole blood system. Dr. Rabson suggested that if this finding could be applied to humans, it would have a major impact on bone marrow transplantation. He also noted a recently reported study by Dr. Weissman's group in which human fetal liver, thymus, and lymph node cells were

engrafted into severe combined immunodeficiency (SCID) mice to produce an animal model in which to study the human immune system. Dr. Rabson pointed out that other researchers in DCBD's extramural program developed the SCID mouse and identified a missing enzyme that is involved in differentiation of cells of the immune system. The SCID mouse with human lymphoid cells may be useful for studying HIV because the mouse has human T cells. Dr. Rabson said another group of researchers has used white cells from adult humans to get similar reconstitution.

Turning to a discussion of the budget, Dr. Rabson said the total estimated FY 1989 budget is $316 million, of which $51 million is for the intramural program, representing a 4 percent increase. The budget for competitive grants is estimated at $253 million. Overall, the DCBD budget will increase by 15.2 percent in 1989.

Report of the DCBD Board of Scientific Counselors--Dr. Arnold J. Levine

Dr. Levine said he would discuss some of the issues that came before the DCBD Board and the 1988 site visits, as well as present the scientific research of Dr. Lou Staudt, a young investigator in the division. Dr. Levine began by noting that the Board members represent a variety of scientific disciplines and bring expertise in scientific administration.

Dr. Levine cited the Cooperative Human Tissue Network as a new initiative in the division. The purpose of the network is to supply researchers around the country with high-quality, well-characterized samples of human tumors and human cancers, including rare cancers. The network has three major divisions: the southwest division, centered at the University of Alabama in Birmingham; the midwest division, located at Ohio State University in Columbus; and the eastern division, located at the National Disease Research Interchange in Philadelphia at the University of Pennsylvania Hospital. Dr. Levine said it was hoped that the tissue network would contribute to a uniform diagnostic system and uniform specimen preparation and help to reduce biohazards through quality control. He noted that with the development of the polymerase chain reaction, genes can be selectively replicated, which has speeded up dramatically the process of analyzing oncogenes in human tumors. The Human Cooperative Tissue Network provides a means of maximizing that technological breakthrough by providing high-quality tissue samples. Dr. Levine stated that demand for tissues has grown exponentially, with the network currently sending more than 600 samples a month to laboratories all over the United States.

Dr. Levine next described the Board's involvement in the Organ Systems Program. He said that people working in the OSP were invited to address the Board, and they raised the following points about the value of the organ systems approach: communication is improved among individuals with diverse scientific background; training is facilitated in a diverse environment; and funding can be targeted to solving problems. Dr. Levine also voiced the view that science progresses through investigator-initiated ideas and cited as an example the recent development by two laboratories, not part of the OSP, of a transgenic mouse carrying an oncogene that, when expressed in the pancreas, gives rise to pancreatic cancer. He said the DCBD Board discussed at length the philosophy of funding research to achieve the best results.

In turning to the subject of site visits, Dr. Levine said 3 or 4 of the 13 laboratories are visited each year. Those visited in 1988 were the Dermatology Branch, Laboratory of Immunobiology, and the Immunology Branch. Dr. Levine said the site visits were all excellent, and he underscored the high level of excitement at which the intramural scientists are working.

Before describing the research being conducted by Dr. Staudt, Dr. Levine pointed to the importance of NCI being able to attract extremely capable young scientists. He also noted that scientific information often comes from totally unexpected places and that the more information that is obtained, the more apparent is the unity of life processes. As background, Dr. Levine recalled the biotechnology revolution of the 1970s and the cloning of genes and oncogenes. During the 1980s, much progress has been made in elucidating the function of oncogenes and understanding how the function becomes abnormal when there are mutations. For example, some oncogenes have been found to be altered growth factors, some are receptors for growth factors, and some oncogenes are involved in the transmission of the signal from the receptor to the nucleus. Dr. Levine said that within the past year, another function of oncogenes has been identified--the regulation of gene expression, a process called transcription or mRNA production. Of the 3 billion bits of information or chemical signals in the nucleus of a human cell, only 1 percent is expressed in any cell. Proteins or transcription factors bind to sequences of information and turn them on; other proteins turn off the information. It has also been learned that these transcription factors that control the information can be oncogenes.

Dr. Levine said that Dr. Staudt, who works in the Metabolism Branch, has an M.D. and Ph.D. from the University of Pennsylvania, where he studied the response of humans and animals to foreign antigens. He then went to the Whitehead Institute at MIT, where he discovered a transcription factor responsible for making B cells produce a particular antibody. Dr. Staudt then cloned and sequenced the gene for the transcription factor and compared it with genes in the central computer. He learned that it recognizes signals found elsewhere, including the homeobox signal first described in Drosophilia and which plays a fundamental role in the organization of the fruitfly. Dr. Levine documented the evolutionary relatedness between the genes that control master switches in development of fruitflies and the transcription factors that control lymphoid development in humans. He noted that Dr. Staudt's research would be published in a forthcoming issue of *Cell*.

The following points were raised in discussion of Dr. Rabson's and Dr. Levine's presentations:

- The impact of the product of multidrug resistance genes on several carcinogens involved in liver carcinogenesis is under investigation.

- Consideration will be given to including a person from a proprietary private laboratory on the DCBD Board.

- The DCBD Board reviewed eight concepts during the year, including several related to the OSP.

XVI. Multichain IL-2 Receptor: From the Gene to the Bedside--Dr. Thomas Waldmann

Dr. Waldmann described the T cell as the pivotal cell in the immune system, which when it functions protects us from an array of assaults, but when it fails leaves us vulnerable to an array of diseases, including AIDS and neoplasias of the immune system. The T cell also plays a pivotal regulatory role in the control of the action of other cells of the immune and hematopoietic system and is a cytotoxic cell in its own right. Dr. Waldmann explained that to perform all these functions, the T cell must change from a resting to an activated state, which requires two sets of signals from independent receptors on the cell surface to the nucleus. The first set of signals is mediated by an appropriately processed antigen interacting with the heterodimer T-cell receptor that senses foreign substances in the environment and, with associated molecules, signals the

nucleus to prepare for the second phase of events. Dr. Waldmann said this part of the system provides specificity. In the context of macrophage-derived IL-1 and IL-6 molecules, the second phase of events involves turning on of a gene for IL-2, originally called T-cell growth factor, which to function must interact with high-affinity receptors on cell surfaces. Dr. Waldmann pointed out that resting T cells require the interaction of the antigen with its receptor, thus stimulating the lymphokine and its IL-2 receptor. Interrupting the production of IL-2, or the induction of its receptor, or the interaction of IL-2 with its receptor will shut off T-cell-mediated events.

Dr. Waldmann said that to study the IL-2 receptor, hybridoma technology was used to prepare an IgG 2A monoclonal antibody in the mouse. This antibody interacts with one of the major constituents of the receptor, a 55-kilodalton molecule that binds IL-2. Dr. Waldmann said the antibody has been used for several purposes: to define the structure of the receptor, to molecularly clone the gene encoding it, to define the functions that require IL-2 to recognize its receptor, and especially to define abnormal expression of this receptor in neoplasia and autoimmune disease. In addition, these basic insights were used to develop an IL-2 receptor-directed approach to immunotherapy based on the fact that resting cells, including T cells, do not have this receptor, yet certain malignant cells do.

As background, Dr. Waldmann explained that the antibody was used to deduce the amino acid sequence of the 55-kilodalton *tac* peptide in the receptor. He described it as a classical protein that goes across the membrane, and he noted that IL-2 and the IL-2 receptor are, in part, regulated by an enhancer sequence almost identical to that of HIV. Both bind a protein, NF kappa B, involved in controlling immunoglobulin expression. Dr. Waldmann said early problems in the studies were related to the facts that there are high and low affinity forms of the IL-2 binding peptide and there seemed to be no way of signaling to the nucleus from its receptor because initially it did not express any *tac* peptide. Also, it was found that cell lines such as MLA-144 expressed large numbers of IL-2 binding sites but did not express the *tac* peptide. By using radiolabeled IL-2 in crosslinking studies to define the size of the peptide of the cells that could bind to IL-2 but did not have *tac*, Dr. Waldmann said a novel 75-kilodalton IL-2 binding peptide was discovered. Cells that express both the *tac* and 75-kilodalton peptide generate the high affinity receptors used by activated T cells.

Dr. Waldmann said that the 75-kilodalton peptide is the receptor on large granular lymphocytes initially and alone is sufficient for IL-2 to work, but IL-2 must be present in concentrations far higher than those found in biological fluids. The *tac* peptide receptor cannot alone signal the nucleus but complements the 75-kilodalton receptor and rapidly binds and releases IL-2. Dr. Waldmann said that the coordinate receptors together have very rapid uptake and very slow release of IL-2, and because affinity is determined by the ratio of the dissociation and association constants, the coordinate receptors have a 2 to 3 log greater affinity than either of them alone. Using site-directed mutagenesis, it was found that amino acids 9 through 20 are involved in binding the 75-kilodalton peptide and that amino acids 33 to 54 are involved in binding the *tac* peptide. Dr. Waldmann said that recently a third IL-2 protein had been defined. Functionally, this means that site-directed mutagenesis of IL-2 can be made to generate a molecule that is different from the natural parent molecule. The new molecule could bind to one but not all of the receptors, for example, the receptor on lymphokine-activated killer cells, without simultaneously binding to activated T cells.

The multichain IL-2 receptor can act on many types of cells, and Dr. Waldmann noted that activated B-cells, activated monocytes, and granulocytes display this growth factor receptor. In addition, a released smaller form of the receptor, which is still capable of binding IL-2, goes into

biological fluids, including serum and urine. By defining the level of the receptor with a simple ELISA technique, it is possible to infer the state of activation of T cells, wherever they are in the body. Dr. Waldmann stated that the normal level is very low, 2 logs higher in adult T-cell leukemia, caused by HTLV-1, and considerably higher in Sezary leukemia mycosis fungoides. Measurement of the receptor is useful for gauging the efficacy of therapy, evaluating patients' prognoses, and helping in diagnosis. Dr. Waldmann added that it also provides a way to identify patients who are candidates for IL-2 receptor-directed therapy.

Dr. Waldmann recalled that the rationale for the therapy is that resting cells do not display the receptor, so that if receptor-bearing cells were killed there would be a high level of specificity. Tumor cells with excessive receptor expression include T cells, B cells, Reed-Sternberg cells of Hodgkin's disease, and chronic and acute granulocytic leukemia cells. The receptor is aberrantly expressed in an array of autoimmune diseases where T-cells participate in the autoimmune phenomenon. In addition, in allograft rejection, the T cells of the host recognize the foreign transplantation antigen of the organ, become activated, display the *tac* peptide, and participate in organ rejection. Therefore, Dr. Waldmann summarized that the goal of IL-2 receptor therapy is to treat certain forms of lymphoid neoplasia and autoimmune disease, prevent allograft rejection, and treat graft-versus-host disease.

Dr. Waldmann focused next on adult T-cell leukemia, to which anti-*tac* was made. The disease, which has a mean survival of 20 weeks, involves malignant cells infiltrating the skin, lungs, and liver; hypercalcemia; and a cellular immunodeficiency similar to that in AIDS. It is clustered familially and geographically and transmitted like the AIDS virus. The etiologic factor is HTLV-1, which also causes a demyelinating disease called tropical spastic paraparesis. The cells infected with the virus constitutively express the *tac* peptide. Dr. Waldmann suggested that this constant association between the virus and receptor expression occurs because the retrovirus has a 42-kilodalton protein, known as *tax*, which acts on the enhancer repeat sequence to turn on the virus and also activates NF kappa b, which activates the IL-2 and IL-2 receptor genes and also HIV.

Dr. Waldmann identified the *tac* peptide as the target for immunotherapy. One approach using unmodified anti-*tac* monoclonal antibodies has been used in 10 patients with adult T-cell leukemia. None of the patients have had complications, and they have not made antibodies to the monoclonal antibody. Three of the patients went into remission, passing 1, 5, and 11 months, as assessed by disappearance of skin lesions and leukemic cells; however, all relapsed and were given chemotherapy. Dr. Waldmann said that HTLV-1 integrates into the nucleus and sets up an autocrine IL-2/IL-2 receptor system, which means that the anti-*tac* antibodies are effective. At some point, however, chromosomal aberrations may provide a cell with an independent signal so that it no longer requires IL-2. The cell continues to display the IL-2 receptor but it is autonomous, at which point anti-*tac* is no longer effective. Dr. Waldmann noted that unmodified anti-*tac* is being used in an organ transplantation protocol. Anti-*tac* blocks IL-2 from recognizing a foreign transplantation antigen and prevents the generation of killer cells. In a Phase III trial of immunosuppression of patients receiving allografts, those who received anti-*tac*, in addition to the conventional immunosuppression, have had a statistically significant reduction in graft rejection episodes with no added complications.

Another therapeutic approach involves chelates of anti-*tac*. Anti-*tac* is used to deliver alpha-emitting isotopes like bismuth-212 and beta-emitting isotopes like ^{90}yttrium to tumor cells, with modest damage to other cells. In a monkey xenograft transplant model, prolonged survival of the xenografts was achieved with a tight chelate of ^{90}yttrium and anti-*tac*. The approach has been applied to the development of agents to treat patients with adult T-cell leukemia.

Dr. Waldmann pointed out that another approach is to make chimeric antibodies. Monoclonal antibodies are mouse protein to which humans make antibodies, and they tend to work poorly in human effector systems. Therefore, hybrid molecules are made at the DNA level, which retain some of the mouse molecules and include human IgG1 or IgG3 kappa monoclonal antibody. Dr. Waldmann said that these proteins are much less immunogenic, and human immunotherapeutic studies should begin as soon as enough of the molecules can be obtained and chelated to the alpha-emitting isotopes. The chimeric antibodies have specificity and affinity for binding to the *tac* peptide, and they function *in vitro* to inhibit IL-2 dependent proliferation of lymphocytes.

In summary, Dr. Waldmann stated that the pivotal role of the T cell involves the interaction of appropriately processed and presented antigen with a specific T-cell receptor on the cell surface. The interaction induces the cells to turn on a number of host genes required for T-cell function, including the gene for IL-2, the 15-kilodalton gene on chromosome 4, and the gene for the inducible 55-kilodalton *tac* peptide from chromosome 10. At least two peptides involved in this growth factor receptor binding to different parts of the IL-2 molecule have been defined. The *tac* peptide also exists in the serum and can be used as a marker of lymphocyte activation. Resting cells do not display the *tac* peptide, while certain tumor cells, notably, those associated with HTLV-1 do, as well as T cells mediating certain forms of autoimmune disorder and allograft rejection. Therapeutic approaches are aimed at exploiting this difference between normal and disease cells.

The following points were raised in discussion:

- Vigorous chemotherapy along with anti-*tac* chelated to isotopes may provide an improved approach for treating T-cell leukemia.

- Research is in progress on the development of resistance by variants that have mutated in the epitope and is focusing on events that occur within the karyotype.

- It is not known what the next step may be in the permanent differentiation of lymphocytes.

- A problem has not yet been seen with later damage to the immune system following anti-*tac* therapy.

XVII. Novel Therapeutic Agents Created by the Fusion of Toxin and Cell-Targeting Genes--Dr. Ira Pastan

Dr. Pastan said he would discuss the use of a bacterial toxin to create cell-specific cytotoxic agents for cancer treatment. The pseudomonas exotoxin, which is made and secreted by an ordinary soil organism, is a single chain protein toxin of 66,000 molecular weight that acts to inhibit protein synthesis in cells. When protein synthesis stops, the cell cannot reverse the inhibition and it dies. Dr. Pastan said the important point is that a single molecule of the toxin in the cytosol will cause the cell to die. However, during endocytosis very few molecules are translocated into the cytosol, because most of them are degraded in the lysosomes, a mechanism that serves to protect against toxins. Efforts to develop therapeutic agents have been directed at increasing the specificity of the toxin so that it binds only to particular cells and increasing the efficiency of translocation into the cytosol.

Dr. Pastan pointed out that the first efforts were to simply chemically couple the toxin to an antibody as a 1:1 conjugate. Models chosen for study were ovarian cancer and adult T-cell leukemia. The OVB3 antibody was developed and has been found to react with more than 30 adenocarcinomas of the ovary, as well as some normal tissues, particularly breast, thyroid, and pancreatic acinar cells. Dr. Pastan stated that the antigen has not yet been identified. Using a nude mouse model, treatment with OVB3-PE on days 5, 6, and 7 after injection of ovarian cancer cells resulted in some mice living more than 275 days, compared with the median survival of 40 days in the control group. In mice, doses of 5 to 50 μg/kg are therapeutic, but doses of about 100 μg/kg are lethal. Treatment of patients has produced intra-abdominal pain at higher doses.

In describing the three-dimensional structure of pseudomonas exotoxin, Dr. Pastan identified three domains having the following functions: cell binding, membrane penetration or translocation, and ADP-ribosylating or cell killing. Domain 1 causes the toxin to bind to all types of cells. By deleting domain 1, nonspecific cell killing was decreased several hundred-fold. Dr. Pastan said this principle was applied to developing conjugates to antibodies to attack the IL-2 receptor in adult T-cell leukemia. With Dr. Waldmann, a molecule has been engineered that includes, in the following sequence, antibody, translocating domain, and ADP-ribosylating domain. Dr. Pastan said this molecule is very active and has low nonspecific toxicity, and efforts are in progress to develop enough of this agent for a patient trial.

Chimeric toxins have been developed in *E. coli* by fusing cDNAs encoding growth factors to a modified pseudomonas exotoxin gene. Dr. Pastan cited as an example IL-2-PE40 in which the IL-2 is present in place of the recognition domain. In an adult T-cell leukemia cell line, 5 ng/ml is the toxic dose, while other cell lines that do not have the IL-2 receptors can tolerate more than 2 μg of IL-2-PE40. In a mouse cardiac allograft model, survival of the allograft was increased with increasing amounts of IL-2-PE40. Dr. Pastan said these results are encouraging because treatment was at concentrations expected to be efficacious against leukemia cells.

In addition, Dr. Pastan said other molecules have been created focused at other cancers that overproduce receptors, which probably function as oncogenes. For example, the EGF receptor is overexpressed in several cancer cells and when introduced by transfection or infection into normal cells can cause cancer to form. Therefore, the cloned pseudomonas exotoxin gene was attached to the gene encoding the growth factor TGF-alpha to make a recombinant chimeric protein called TGF-alpha PE40. Dr. Pastan noted that TGF-alpha binds to epidermal growth factor receptors, enters the cell, and kills it. Cell lines with amplified EGF receptor gene are very selectively killed by the TGF-alpha PE40, which is being developed for Phase I trials.

Dr. Pastan next described the development, in collaboration with NIAID, of a reagent targeted at cells infected with HIV. Infection occurs when the gp120 protein on the surface of HIV binds to the CD4 protein on the T cell. When the cell is infected, it makes a lot of virus. Therefore, a cloned portion of CD4 was attached to the PE toxin, which was expected to bind to gp120 on HIV-infected cells, enter the cells, and kill them. Dr. Pastan summarized studies that showed that the CD4 chimeric toxin kills T cells infected with HIV-1 with an ID_{50} of less than 1 ng/ml. He said it is hoped that this reagent will be developed for preclinical and perhaps clinical testing in AIDS.

Dr. Pastan said it is also possible to remove the constant region of antibodies and replace them with portions of the toxin, either in animal cell expression systems or in *E. coli*. In summary, he noted that the agents he discussed, perhaps appropriately called oncotoxins, can be

used to target cells bearing specific receptors. He stated that additional work is needed to improve the efficiency of the translocation step and test the agents in Phase I trials.

XVIII. Report of the National Black Leadership Initiative on Cancer--Dr. Louis Sullivan

Dr. Sullivan began by stating that the National Black Leadership Initiative on Cancer (NBLIC) represents NCI's first attempt to reach out in an organized and structured way to the black population throughout the country. He added that the Initiative has succeeded in mobilizing a significant segment of the Nation's black leadership to address the problem of the disproportionate burden of cancer in the U.S. black population.

Dr. Sullivan recalled that the Initiative originated from a discussion at the October 1986 NCAB meeting, when concern was expressed about tobacco and liquor advertisements targeting blacks and about the high rates of cancer among blacks. A national planning committee was established to develop a plan of operation to enlist the participation of the black business community and to increase awareness that the black population has a higher incidence of cancer and poorer survival than the white population. This committee included Dr. Claudia Baquet, Chief of NCI's Special Populations Branch; Mr. William Allison, a vice president of the Coca Cola Company in Atlanta; Mr. John Cox, vice president of Delta Airlines; Mr. Collier St. Clair, vice president of Equitable Life Insurance Company; and Dr. Dorcas Bowles, at that time, acting president of Atlanta University. An operational plan was developed by the committee and presented to the NCAB for approval in September 1987 and included the following statement of purpose:

> The National Black Leadership Initiative on Cancer will develop a plan for the national mobilization of the nation's black leadership to support the year 2000 goal of the NCI and to involve the Black community in this effort. Various facets will include leaders of political, religious, business, health and medical, civic and social organizations. The hope is to create a network of concerned and active Black leaders throughout the country to help organize, implement, and support cancer prevention programs.

Dr. Sullivan added that it was also hoped that the Initiative would encourage blacks to identify sources of support for their organizations and institutions other than the tobacco and liquor industries on which they are so heavily dependent.

Dr. Sullivan said that the Association of Minority Health Professions Schools, which includes the Morehouse School of Medicine, the Meharry School of Medicine, the Charles R. Drew Medical School, the Veterinary Medical School at Tuskegee University, and the colleges of pharmacy at Texas Southern University, Xavier University, and Florida A&M University, joined the Initiative as cosponsors with the NCAB to help carry out the NBLIC goals. The National Medical Association (NMA) has entered into an agreement with the Office of Cancer Communications in which the OCC will provide pamphlets and brochures for the NMA physicians' meetings to assist in the education and dissemination of information targeting the black community.

Dr. Sullivan explained that to achieve the goals of the NBLIC, regional meetings took place in six U.S. cities with large black populations: Atlanta, Los Angeles, Chicago, New York, Washington, D.C., and Houston. He noted the support of NCI for these meetings through the official greetings from Dr. DeVita, Dr. Rabson, or Dr. Roper at each meeting. He also

acknowledged support from Board members, Dr. Korn, Dr. Hammer, and Mrs. Brown. At each meeting, Dr. Baquet or Mrs. Bynum gave a presentation on facts about cancer in blacks. Next, Dr. Baquet or Dr. Greenwald provided specific details on risk factor reduction and cancer prevention and control strategies that could be adopted by the black population. The participants responded to these presentations with their own ideas about what blacks could do to reduce the risks of cancer. The meetings then broke up into working group sessions that were structured to allow each participant the opportunity to offer ideas on spreading the message throughout the black community. Finally, the concluding session of the 2-day meetings provided a summary of the recommendations of the working group sessions and a discussion of what the next steps in the community and Nation should be.

Dr. Sullivan pointed out that the proceedings were available from each of the regional meetings and from a summary meeting of regional chairpersons that was held on October 11, 1988, at NIH in Bethesda. He summarized the major themes of each meeting. At the Atlanta meeting (November 20, 1987), participants focused on ways to make the black community aware of the problem; at the Los Angeles meeting (March 10-11, 1988), participants focused on approaches and solutions to the problem; at the Chicago meeting (May 16-17, 1988), participants emphasized the need to recognize stratification in the black community and expressed an urgency to move quickly to implement the Initiative. Participants at the New York meeting (June 23-24, 1988) focused on the factors that make blacks different with respect to cancer, including inadequate access to information and to screening, diagnosis, and treatment services; illiteracy and cultural differences; and heavy tobacco usage. Participants at the Washington, D.C., meeting (September 13-14, 1988) emphasized developing a regional cooperative approach for reaching the black population, and at the Houston meeting (September 29-30, 1988), participants recommended that advocacy groups be established to provide informed advice to legislators.

Dr. Sullivan announced that, to date, Diahann Carroll, Marla Gibbs, Dionne Warwick, and Phylicia Rashad have made public service announcements on breast cancer, diet, smoking, the need for early detection, and other concerns of the NBLIC, and these videotapes were shown at the regional meetings. The tapes are available to community organizations for their use, free of charge.

Dr. Sullivan stated that members of the press attended several of the NBLIC meetings and that articles about the meetings appeared in local newspapers and magazines. He noted that an article in *Jet* magazine generated 250 written inquiries to NCI, and he added that many people involved with the NBLIC continue to receive requests for interviews and information. He commented that it was gratifying to receive official recognition of the Initiative in the form of proclamations that were presented at the meetings by mayors, city officials, governors, and state and national legislators.

Dr. Sullivan noted that considerable enthusiasm and many exciting ideas were generated at the meetings. He proposed that to capitalize on the momentum generated and to have optimum continued success, a full-time coordinator be hired for each of the six regions. This person would support the regional planning committee in implementing and sustaining cancer prevention and control activities. Specific duties of the coordinator would be to follow up on recommendations generated by the regional meeting, to maintain contacts throughout the region, to identify local interests and groups who could contribute to cancer control efforts, to identify public and private screening resources, and to work with NCI program staff in the initiation and development of concepts that will lead to competitive funding opportunities. The coordinators would also help to organize and energize local groups and form a network with other regional coordinators to learn from each other. This network would provide feedback to NCI on

information needs and advice on long-range national research programs. The regional committee chairpersons agreed that the focus areas for actions would include (1) health education and promotion, (2) cancer screening and followup, (3) health policy and legislative advocacy, (4) research, (5) training, and (6) media activities. They intend to make maximum use of local resources to reach throughout the black community. They also intend to continue to meet as a group twice a year to review progress and to identify areas requiring action. Dr. Sullivan asked the NCAB for its support in the placement of a coordinator in each region as the next step in the Initiative.

In discussion, Dr. Korn introduced a proposal that Mrs. Bynum, Dr. Sullivan, and he had developed, which recommended that four minority cancer centers--Howard University, Morehouse School of Medicine, Meharry School of Medicine, and Charles R. Drew Medical School--be involved in the regional coordinator program to give the program a base of established structure. While the specific responsibilities of the centers in the program and their relationship to NCI and the NCAB remain to be determined, the basis for the Board's support of this proposal was their feeling that the minority centers were committed to achieving most, if not all, of the NBLIC's objectives and that the centers would provide access to the full array of mechanisms which might support future NBLIC activities. A motion was then made to approve the concept of supporting regional coordinators to continue the efforts of the NBLIC. The motion was unanimously approved. In closing comments, several Board members emphasized the importance of ensuring continued efforts in all six geographic regions defined by the NBLIC.

XIX. Report of the Minority Manpower Development Subcommittee--
Dr. Louis Sullivan

Dr. Sullivan provided the report of the December 5, 1988, meeting of the Board Subcommittee on Minority Manpotwer Development. He reminded the Board that this *ad hoc* subcommittee of Board members and NCI staff had been formed as a result of concerns expressed at the October 1988 NCAB meeting about the lack of compliance with NIH guidelines on minority trainee recruitment for T32 institutional training grants.

Dr. Sullivan reported that at the Subcommittee meeting, Dr. Vincent Cairolli, Chief of the Cancer Training Branch and Executive Secretary of the Subcommittee, summarized the NIH guidelines on encouraging recruitment of minority trainees on T32 grants and presented data showing that most NCI applicants do not present a minority recruitment plan. For example, for the October 1988 grant cycle, only 36 percent of the applications included any plan or discussion of minority recruitment efforts.

Dr. Sullivan stated that the Subcommittee recognized the need to inform applicants of the elements of recruitment plans that have been successful as well as of those that are not likely to be productive. The Subcommittee also discussed the need to encourage programs that will affect minority students early so that the applicant pool can be enlarged.

The Subcommittee recommended that the NCI staff draft a plan that encompasses elements of successful recruitment strategies, coupled with a strongly worded directive that such plans are required in applications and that if they are absent, the application would not be reviewed or funded, similar to the human subjects review requirement. Dr. Sullivan stated that the Subcommittee recommended that a 6- to 8-month warning notice should be given before putting this requirement into effect, so that all grantees will be fully aware of it. The NCI staff was asked to provide a draft of this directive for review by the Subcommittee at the February 1989 NCAB meeting.

The report of the Subcommittee for Minority Manpower Development was unanimously accepted.

XX. Public Participation Hearings Report--Mrs. Helene Brown

Mrs. Brown stated that the comments raised by the Subcommittee on Information and Cancer Control on the first draft of the NCAB Report on the Public Participation Hearings had been incorporated into a second draft, which was mailed to Board members. She asked for any final comments on the document by January 1, 1989, and announced that the final report would be released at a press conference at the NCI in January 1989. She noted that the report includes one general and seven specific recommendations.

In discussion, Dr. Korn suggested that the press conference be coordinated with the February 1989 NCAB meeting and urged all Board members to send any comments on the report before, not after, the press conference. Mrs. Brown expressed her opinion that the items within the report that are probably most newsworthy are the reiteration of the goals for the year 2000 and the fact that the seven specific recommendations carry the proviso, "given the proper support to bring all of this about."

Dr. Roper stated that the NCI Executive Committee had discussed reviewing progress made thus far towards achieving the year 2000 goals and perhaps reassessing the progress that can be made by the year 2000 for a report to the NCAB. Dr. Greenwald emphasized that the goals would not be changed and stated that only some of the information being gathered on questions related to changes in smoking habits and other behavior would be available for a report at the February 1989 Board meeting.

In response to a request for a brief summary of the Public Participation Hearings Report, Mrs. Brown stated that the general recommendation is to gain individual commitments throughout the country. She listed the seven specific recommendations as follows: (1) eliminating tobacco use, (2) expanding access to cancer screening, (3) reaching special populations, (4) engaging the private sector, (5) cooperating with the volunteer organizations and the media, (6) involving the schools, and (7) expanding the role of state and local governments. She further explained that because the Board Subcommittee on Information and Cancer Control is charged with monitoring progress toward the year 2000 goals, it is the Subcommittee's responsibility to release the results of the Public Participation Hearings to the Nation. She stated that the report does provide some specific suggestions under the seven recommendations and emphasized that although resources for cancer control activities exist within the communities and within some of the funding programs, other support is needed. She cited one finding from the hearings that physicians are not recommending mammography and noted that this was specifically addressed in the report of the hearings.

A motion for approval of the NCAB Report on the Public Participation Hearings was seconded and unanimously approved.

XXI. Status of Biological Response Modifiers Program--Dr. Dan Longo

Dr. Longo explained that the Biological Response Modifiers Program (BRMP) is one of five programs in the Division of Cancer Treatment. He stated that the mission of the BRMP is to study the biology of and interaction between host defense and tumors and to develop new treatment strategies that alter the host-tumor relationships in favor of the host.

The BRMP has five components; the Biological Resources Branch (BRB), headed by Dr. Stephen Creekmore, is the extramural component. Dr. Longo emphasized that the BRMP is unique because it is a comprehensive program with both extramural and intramural clinical research and basic research components dedicated to finding new therapies and new strategies for treating cancer using biological modalities.

The intramural program of the BRMP consists of three basic science laboratories and one clinical branch. The Clinical Research Branch, under Dr. Ronald Steis, is the clinical arm; its major focus is studying the physiological consequences of altering host-tumor relationships. The three laboratories have the following primary focuses: cellular aspects of host defense in the Laboratory of Experimental Immunology; cytokines, lymphokines, intracellular signaling, and cell-surface signal transduction in the Laboratory of Molecular Immunoregulation; and biochemistry and molecular biology in the Laboratory of Biochemical Physiology. Dr. Longo emphasized that there is close interaction among the laboratories and the two branches.

The BRB supports Phase I contracts devoted to development of cytokine treatments and monoclonal antibodies. There are also many master agreement holders from whom the BRB seeks innovative ideas for clinical development. The Phase I contracts have two primary missions: (1) to define maximum tolerated dose and schedule of biologicals and (2) to perform immunologic monitoring of patients to define the optimal immunomodulating dose and schedule of biologicals. In addition, there is a large grant program for support of investigator-initiated research and extensive collaboration with private corporations. Examples of preclinical contracts include the BRMP repository of biologicals, a production contract for monoclonal antibodies, and contracts for development of biologicals, such as mouse-human chimeric antibodies, and immunoconjugates, as well as peptides synthesized to contain active components from different genes, antisense oligonucleotides, and oligopeptides. There is also a Preclinical Evaluation Laboratory that focuses on animal modeling of various biological response modifiers. In addition, the BRMP actively supports small business initiatives and uses the SBIR program to support research to establish a monoclonal antibody database, for example.

Dr. Longo provided a flow diagram illustrating how the BRMP develops compounds. Compounds are received for evaluation by BRMP from the pharmaceutical industry, intramural laboratories, and various other sources, including university and independent investigators. The BRB maintains a close working relationship with the Developmental Therapeutics Program through the BRMP/DTP Working Group (BDWG) for preclinical development and with the Cancer Therapy Evaluation Program through the BRMP/CTEP Working Group (BCWG) for clinical development. The two groups decide which biologicals should be pursued in *in vivo* or *in vitro* test systems. Compounds are then taken to the DCT Decision Network for formal consideration for further development.

Dr. Longo stated that overall the BRMP focuses more on drug development than on drug discovery. He provided examples of research supported by the BRMP, including investigations of the features of monoclonal antibodies in terms of their affinity and epitope distribution on tumors and in humans that affect imaging and the effect of the relationships between the radioisotopes and monoclonal antibodies on the biodistribution and handling of antibodies. Dr. Longo reported several other investigations in this area but stated that the use of monoclonal antibodies has presented two problems: these molecules are quickly eliminated from the body because the liver eliminates foreign proteins very effectively; moreover, because these antibodies are foreign proteins, the host often develops an antibody response to them.

Dr. Longo described ongoing work with the drug deoxycoformycin (DCF), which is an adenosine analog capable of killing T cells. This agent produces a selective defect by lowering T4 counts, and almost all antibody responses require T4 cells. Investigations have shown that pretreatment with DCF in mice successfully prevented development of antibodies to a treatment monoclonal antibody. Thus, it may be possible to induce permanent tolerance to the treating molecule and allow treatment with monoclonal antibodies for prolonged periods.

Dr. Longo stated that several other target molecules are also being investigated for tailoring monoclonal antibody therapy. For example, in studies by Dr. Michael Gottesman and coworkers in Dr. Pastan's Laboratory of Molecular Biology, four to eight copies of the MDR gene, which is associated with multidrug resistance, were put into the HT29 colon tumor. These cell lines were tested *in vivo* in the BRMP. In nude mice, the HT29 cells with the MDR gene and the wild type HT29 cells showed similar patterns of response to cyclophosphamide; however, any response to adriamycin was obliterated by the expression of the MDR gene. Dr. Takashi Tsuruo developed a monoclonal antibody called MRK16 to the MDR protein on the surface of cells. The administration of the antibody to an MDR-expressing tumor completely reversed the adriamycin resistance that the MDR mediates. Further experiments are under way to investigate the possibility that this approach might be useful in patients with acquired resistance and also in *de novo* resistance in certain tumor types.

Because chemotherapy produces dose-limiting toxicity in the bone marrow, it is important to understand the cellular basis of hematopoiesis. Dr. Longo briefly described the organization of the stem cell compartment and hematopoiesis, noting that one or more factors are capable of fostering the transition of a cell from multipotential to unipotential in the cell differentiation process to erythrocyte or megakaryocyte lines and to lymphoid or myeloid lines. The system has elements of positive regulation in that the endproduct of hematopoiesis produces many of the factors that are involved in the generation of cells. These factors are being investigated in terms of trying to prevent the toxicity of cancer treatment; however, not all the molecules that are involved in the control of hematopoiesis are as yet known.

Dr. Longo explained that in studies of IL-1, which acts early in progenitor development, pretreatment of mice with IL-1 protects the animals against lethal irradiation. Future clinical trials are planned to evaluate the capacity of IL-1 to protect the marrow against this effect. In addition, a pentopeptide called HP-5 exerts effects on the marrow. When the peptide is allowed to form a cysteine-cysteine homodimer, it has stimulatory effects on colony development and at very low doses exerts a protective effect on the bone marrow, almost comparable to IL-1. This molecule is of special interest because it is active when administered orally.

Further, Dr. Longo explained that there are negative regulatory signals in hematopoiesis. For example, TGF-beta is capable of interfering with the proliferation and expansion of every early precursor cell and all the lymphoid cells. The more mature the myeloid cell, the more refractory the TGF-beta cells become. However, TGF-beta will block any stimulatory effect and antigen responses by T cells or B cells. Thus, it appears that TGF-beta provides an important negative regulatory effect. TGF-beta has been shown to be active in certain primitive leukemias such as the KG1 cell line but not in more mature cell lines such as HL60, which does not express TGF-beta receptors. The ability of various compounds such as the natural product bryostatin to induce TGF-beta receptors on human lymphoid cell lines is being investigated as a possible therapy for refractory lymphomas. TGF-beta receptors would be induced with a compound like bryostatin, followed by administration of TGF-beta, which would produce irreversible proliferation independent of the cytotoxic effects of drugs that are active in lymphoma.

Next, Dr. Longo described several ongoing studies of LAK cells and LAK/IL-2 therapy based on Dr. Rosenberg's early research. He stated that 15 to 30 percent of both melanoma and renal cancer patients respond to LAK/IL-2 therapy. Research has shown that LAK cells may act systemically by producing cytokines that coordinate a multicellular immune response to a tumor. A variety of stimuli are being tested to try to activate the LAK cells to produce more activity, both in terms of lysis and in terms of cytokine production. Alternative LAK cell sources and varying doses and schedules of IL-2 are also being investigated. Because LAK cells seem to travel through the body poorly, depositing the cells directly into the peritoneal cavity in diseases such as colon cancer, ovarian cancer, and peritoneal mesothelioma, in which control of peritoneal disease is a major problem, is being investigated. However, because patients develop serious adhesions that limit the ability to deliver more therapy to the peritoneal cavity, several approaches are currently being tested in animals to attempt to prevent the scarring, which is the end result of the inflammatory response to therapy.

Dr. Longo described observations that resulted from studies by the Cetus Corporation in which patients received IL-2 in various doses and schedules. These studies showed that the response rate to IL-2 alone was high only in the fraction of patients in whom LAK activity was induced in the peripheral blood. Therefore, the BRMP is investigating ways of administering IL-2 that would boost peripheral blood LAK activity. Studies are also planned to investigate effective ways of combining IL-2 and monoclonal antibodies.

In conclusion, Dr. Longo described collaborative studies with DTP using flavone-8-acetic acid (FAA). This compound was found to be less active *in vitro* than *in vivo*, and a biological mechanism of action was suspected. BRMP studies showed that FAA administration in mice resulted in a dramatic increase in the NK activity obtained from the liver cells. Further studies of stage II renal carcinoma in animals using FAA treatment, followed by nephrectomy on day 11 and four doses of IL-2 in two different dosages, showed an unprecedented level of synergy between FAA and IL-2. The animals with stage II renal cancer were not only cured but were also immune to rechallenge from the tumor, suggesting considerable activation of T cells by this combination regimen. The fact that the lower, 10,000-unit dose of IL-2 appeared to be more effective than the 100,000-unit dose also suggests the involvement of T cells because NK or LAK cells usually require higher doses of IL-2. In addition, patients being treated with FAA in a Phase I Study at Walter Reed had increased levels of circulating NK cells in the peripheral blood. Preliminary results of further clinical trials of this agent should be available within about 6 months.

In closing, Dr. Longo expressed the opinion that biological therapy will become an increasingly important component in cancer treatment over the next decade.

In the discussion, Dr. Enrico Mihich asked what targets and mechanisms for entering these targets are being investigated for antisense oligonucleotides. Dr. Longo described briefly several of the preclinical studies of antisense oligonucleotides and stated that all of these experiments focus on the tumor, not the host cells, as the target. In response to another question from Dr. Mihich about priorities in studies of monoclonal antibodies, Dr. Longo described several ongoing studies of the R24 antibody in combination with IL-2 that show promise and are of particular interest. He emphasized that an essential element of BRMP-supported studies is evaluation of biological mechanisms by performing biopsies and immunohistology of tumors both before and after treatment.

XXII. Frederick Cancer Research Facility Program Review--Dr. Werner Kirsten

Dr. Kirsten stated that the Frederick Cancer Research Facility, located about 35 miles northwest of Bethesda, occupies approximately 70 acres of land, which was transferred in 1972 from the U.S. Army's Fort Detrick to NCI. FCRF consists of 70 buildings with a total of 900,000 square feet and 550,000 square feet of usable research space. Dr. Kirsten added that construction of two additional buildings is nearly complete. He described the FCRF as a Government-owned, contractor-operated facility and said that it consists of a blend of research and technical support services. FCRF's only extramural research program is a subcontract with the Primate Research Institute for the development of an AIDS vaccine. Dr. Kirsten explained that FCRF is a part of the Office of the Director of NCI, it is represented on the Executive Committee, and it has a chartered Advisory Committee chaired by Dr. Dante Scarpelli.

Dr. Kirsten stated that the functions of FCRF are provided by five contracts: the Basic Research Program, operated by Bionetics Research, Inc., with Dr. George Vande Woude as principal investigator; the Operations and Technical Support Program, provided by Program Resources, Inc., with Dr. Wayne Gilden as director; the Animal Production Facility, provided by Harlan Sprague Dawley, with Dr. Robert Russell as principal investigator; and the Computer and Library Facilities, operated by Data Management Systems. A number of additional intramural laboratories are also housed at FCRF. These intramural programs include laboratories from the DCPC, DCT, DTP, NIAID, and NINCDS.

Dr. Kirsten listed the seven laboratories that make up the Basic Research Program at FCRF: Eukaryotic Gene Expression, Chromosome Biology, Molecular Mechanisms of Carcinogenesis, Crystallography, Molecular Virology and Carcinogenesis, Chemical and Physical Carcinogenesis, and Mammalian Genetics. Dr. Kirsten added that there is also a main Genetics Laboratory. In noting some of the research projects, Dr. Kirsten described a project in the Genetics Laboratory, in which transgenic mice are used to study HTLV-1 and -2 and developmental defects as they relate to neoplasia. A study of the c-*mos* oncogene, which is not expressed in tumors, has found it to be expressed in low levels in developing gonads and to be essential for germ cell maturation. Another project involves the *met* oncogene, which was first isolated in Dr. Vande Woude's laboratory and found to have a transforming function. Current studies show that *met* is located on chromosome 7, near the suspected site of the cystic fibrosis gene.

Dr. Kirsten stated that several projects within the Basic Research Program are AIDS related. Dr. S. Oroszlan's laboratory has isolated, purified, and chemically produced HIV protease enzymes that are required for the final cleavage of envelope glycoproteins. These enzymes are available in large quantities to be used in drug assays against AIDS. Dr. Steven Hughes' laboratory has generated monoclonal antibodies against reverse transcriptase and against specific regions of reverse transcriptase. These monoclonal antibodies are available for use in drug assays against HIV reverse transcriptase and for crystallographic studies. Dr. George Pavlakis' laboratory has cloned and sequenced the *rev* gene, which is a regulator of HIV protein synthesis.

Dr. Kirsten said that the Operations and Technical Support Program, FCRF's largest contract, provides support for NCI, for NCI-supported grantees, and for other components of NIH. The Natural Products Extraction Laboratory and Repository processes and stores plant and marine specimens for anticancer and anti-AIDS drug screening, and the Fermentation Production Facility houses a variety of research projects for DCT. Several laboratories within the Operations and Technical Support Program participate in clinical monitoring of AIDS patients, provide seroepidemiologic support for human retrovirus research, and participate in research on genetic polymorphism and diseases.

Dr. Kirsten mentioned several AIDS research studies that are under way in the Operations and Technical Support Program. He said that large quantities of HIV and its subviral components, such as envelope glycoproteins, have been produced, and he estimated that 3 g of HIV are stored at FCRF. With investigators in Sweden, an immunostimulatory component has been developed, which is a particularly advantageous adjuvant for vaccine trials. Specific immunoassays for all core and outer HIV proteins are being developed for the vaccine studies. Dr. Kirsten said that the HIV transmembrane protein, which is a likely candidate for vaccine attempts, has been partially purified. Also, a retroviral vector containing the HIV *env* gene and other viral vectors has been constructed, and pure envelope glycoprotein has been produced for these vaccine studies. Studies on a lentivirus isolated from cattle and related to HIV are also under way. Dr. Kirsten concluded his presentation by stating that the material produced at FCRF is being used for the largest single vaccine effort at NIH using chimpanzees.

Report of FCRF Advisory Committee--Dr. Dante Scarpelli

Dr. Scarpelli presented an overview of the FCRF Advisory Committee and identified its four major responsibilities: scientific review of the Basic Research Program laboratories, review of the management of the NCI-FCRF system of contracts, advice on new support efforts for the AIDS shared services, and concept review for recompetition of FCRF contract areas. Outside experts are brought in for review of laboratories, and in some cases, these laboratory reviews have resulted in facility and budgetary changes.

Dr. Scarpelli said that the Laboratory of Chromosome Biology was reviewed in 1986, the Molecular Mechanisms of Carcinogenesis Laboratory was reviewed in 1987, and the Laboratories of Eukaryotic Gene Expression and of Chemical and Physical Carcinogenesis were reviewed in 1988. He mentioned the very favorable review of the Laboratory of Eukaryotic Gene Expression and praised the tremendous amount of interaction among laboratories at FCRF and the supportive environment for postdoctoral students and fellows. The following points were raised in discussion:

- The c-*mos* oncogene is located on chromosome 4 in the mouse; its human homologue is not known.

- AIDS vaccine development is complicated by the fact that HIV is a labile virus and while animals can be temporarily protected against an homologous strain of virus, they are not protected against the heterologous virus that exists naturally.

XXIII. Division of Cancer Treatment Program Review--Dr. Bruce Chabner

In beginning the Division of Cancer Treatment program review, Dr. Chabner stated that it had been an eventful year for the division with many personnel changes. He announced that Dr. Robert Wittes, former Associate Director of CTEP, who had replaced Dr. Gregory Curt as Deputy Director, DCT, was leaving to become vice president of the cancer drug development program at Bristol Myers. He described Dr. Wittes' departure as a great loss for DCT and the NCI, both of which he served in an extraordinary fashion not only in drug development, but also as a leader on some very important issues, including drug approval interactions with the Food and Drug Administration, reimbursement for clinical trials, and reorganization of the clinical cooperative groups. Other major personnel changes were as follows: the appointment of Dr. Michael Friedman to replace Dr. Wittes as Associate Director of CTEP and the appointment of two new assistants in the Office of the Director--Dr. Mace Rothenberg, Special Assistant for

Clinical Affairs, and Dr. Wyndham Wilson, Special Assistant for Pre-Clinical Affairs (to include DCT's AIDS-related activities).

Dr. Chabner listed other key DCT personnel as follows: Mr. Larry Ray, Administrative Officer; Dr. Samuel Broder, Associate Director, Clinical Oncology Program; Dr. Michael Boyd, Associate Director, Developmental Therapeutics Program; Dr. John Antoine, Associate Director, Radiation Research Program; and Dr. Dan Longo, Associate Director, Biological Response Modifiers Program.

Dr. Chabner stated that important changes had taken place in the Clinical Oncology Program during the year, including the consolidation of the Medicine and Clinical Pharmacology Branches under Dr. Charles Myers. He listed other highlights of the COP as follows:

- Medicine Branch (Dr. Charles Myers, Chief)--use of suramin as an antagonist of fibroblast growth factor-related peptides (recent clinical trials of this drug have produced interesting responses in prostate cancer).

- Pediatric Branch (Dr. Philip Pizzo, Chief)--studies relating to the treatment of pediatric AIDS.

- NCI/Navy Medical Oncology Branch (Dr. John Minna, Chief)--research demonstrating the deletion of the RB gene in human lung cancer.

- Radiation Oncology Branch (Dr. Eli Glatstein, Chief)--photodynamic therapy using protoporphyrins and lasers to treat intraperitoneal tumors.

Turning next to the Radiation Research Program (RRP), Dr. Chabner stated that efforts to recruit permanent heads of the Radiotherapy Development Branch (RDB) and the Diagnostic Imaging Research Branch (DIRB) had been unsuccessful to date but that the RRP has continued to move into new areas despite the vacancies (Dr. Frank Mahoney has been Acting Chief of the RDB). RRP research focuses include the continuation of the neutron therapy clinical trials and expansion of efforts in diagnostic imaging through the recently organized Radiologic Diagnostic Oncology Group, which is comparing the efficacy of this technology in treatment of four tumor types.

Personnel changes in the Cancer Therapy Evaluation Program, in addition to Dr. Friedman's appointment to the associate directorship, are Dr. Michael Hawkins' appointment to head the Investigational Drug Branch and Dr. Richard Ungerleider to head the Clinical Investigations Branch.

Dr. Chabner reported that many of the DTP laboratories devoted to preclinical drug development had been site visited during the year and would be discussed by Dr. John Niederhuber; the extramural DTP program would be reviewed by Dr. Michael Boyd.

Turning next to a review of the DCT FY 1989 budget estimates, Dr. Chabner noted that the controllable activities, i.e., the clinical cooperative groups, contracts, and intramural research, that are so important to the division are experiencing either a level budget or a decrease. He pointed out that the increases in the program budgets were accounted for by the expansion of AIDS research or the grants budgets of the various programs. He said the cooperative groups, which are included in the controllable line and do not get the same percentage increase as other grants (9.2 percent), will be particularly affected at a time when they are expanding accrual to

clinical trials. Dr. Chabner stated that the funds to take advantage of the opportunity to emphasize high-priority studies are not available this year. He pointed out that the 22 percent increase in funding for AIDS contracts would not filter into intramural activities.

Report of the DCT Board of Scientific Counselors--Dr. John Niederhuber

Dr. Niederhuber summarized the activities of the Board of Scientific Counselors as reviewing DCT concepts for contracts, RFAs, cooperative agreements, interagency agreements, and program announcements; advising on budgetary issues; performing site visits to the intramural laboratories; and serving on subcommittees. He stated that the BSC has taken quite seriously the task of performing rigorous site visits (similar to those experienced by extramural laborabories) of the intramural laboratories.

Commenting next on the activities of the subcommittees, Dr. Niederhuber stated that the Surgical Oncology Research and Development Subcommittee (SORDS), of which he is a member, was initiated in large part by NCAB member Dr. Samuel Wells and was having an increasing impact on the relationship between surgical oncologists and the DCT. He noted that the scope of membership has been enlarged to include some other disciplines in head and neck and neurologic surgery. He said the director of the American College of Surgeons was invited to attend the second of two meetings held during the year as part of the effort to foster a better relationship between NCI and the community of surgeons.

Dr. Niederhuber pointed out that the BSC has members from the surgical, medical, and radiation oncology community as well as experts in the disciplines of tumor biology, immunology, and molecular genetics, some with significant laboratory expertise also. He noted that the BSC had site visited the Clinical Pharmacology Branch, COP; Laboratory of Biological Chemistry, DTP; Laboratory of Biochemical Pharmacology, DTP; Laboratory of Molecular Immunoregulation, BRMP; and Laboratory of Medicinal Chemistry, DTP.

Commenting first on the review of the Clinical Pharmacology Branch, Dr. Niederhuber stated that the committee, headed by Dr. Yung-chi Cheng, noted significant progress in the 5 years since the last site visit, and he expressed the opinion that the development of a clinical service and clinical research beds had significant impact on the progress. A total of 19 projects, including 12 protocols, were reviewed by the committee, which concluded that the branch was doing excellent work and had clearly benefitted from the leadership of Dr. Myers and the support of Drs. Chabner and Broder.

The second program reviewed was the Laboratory of Biological Chemistry (LBC), under the leadership of Dr. Richard Cysyk. Dr. Niederhuber said the anticancer drug development projects based on targets in the metabolic pathways, especially pyrimidine metabolism, and those directed at targets defined by the increasing knowledge of signal transduction within the tumor cell received very high marks from the site visit committee. He added that concerns were expressed about the degree of originality and innovation in a few of the projects and the lack of focus in several of the projects in the newer areas of research, and that these concerns had been brought to the attention of the staff.

In reviewing the Laboratory of Biochemical Pharmacology (headed by Dr. David Johns), the site visit committee, chaired by Dr. Thomas Frei, commented that the research really encompassed two major programs: one in microtubular studies and their therapeutic implications; the other in AIDS-related nucleosides. Based on the advice of the committee, the microtubular program has been moved to the LBC and the AIDS-related nucleoside work is in the process of

being moved to the Clinical Oncology Program, where it will have more direct interaction with Dr. Broder's program.

Dr. Niederhuber described the Laboratory of Molecular Immunoregulation, headed by Dr. Joost Oppenheim, which was reviewed by a committee chaired by Dr. John Kersey, as a fairly large program (about 50 people) having two research emphases: immunobiology and lymphokines. He said the group had been extremely productive with over 55 publications (11 more in press). Of the 11 projects reviewed, Dr. Niederhuber said the committee commended in particular Dr. Farrar's research in the area of molecular and biochemical events controlled by lymphokines and growth factors and Dr. Ruscetti's work on TGF-beta. Based on the productivity of Dr. Farrar's group, the committee recommended that the DCT consider creating a separate new section under his direction and recruit additional senior scientists. Concerns were expressed about the inadequate space allotment for such a large group and the need for more molecular genetic expertise.

Dr. Niederhuber noted that the Laboratory of Medicinal Chemistry, headed by Dr. John Driscoll, was reviewed by the committee chaired by Dr. Robert Jackson. Two of the projects in synthetic chemistry were cited as very valuable. A new research area, peptide chemistry, was not reviewed during this visit. A general concern was expressed that there was insufficient biological input into program design and data evaluation and that there was a need for earlier biochemical feedback when compounds were being evaluated prior to their submission for screening. In addition, the site visitors recommended acquisition of state-of-the-art equipment, particularly for NMR spectroscopy and computer modeling of agents.

Turning next to the Board's concept review responsibilities, Dr. Niederhuber described action on the concepts presented at the October 1987 (all 9 approved), February 1988 (16 approved; two recommended for consolidation), and June 1988 meetings (2 approved as presented; 1 disapproved, and 1 approved but recommended for release as a program announcement rather than an RFA). Cooperative agreements were approved for National Cooperative Drug Discovery Groups for General Mechanism of Action-Based Anticancer Treatment and National Cooperative Anticancer Model Development Groups.

Dr. Niederhuber listed as highlights from the October 1987 meeting the discussion of plans for the expanded network for high-priority clinical trials following a presentation on that subject by Dr. Wittes, and a session on new drug application approval following presentations by Dr. Frank Young representing the FDA perspective; Dr. Steven Carter, the industrial perspective, and Dr. Marty Abeloff, the FDA Advisory Committee perspective. Responding to the need for further action on the issue of FDA drug approval, the BSC formed the *Ad Hoc* Review Committee for FDA New Drug Approval to formulate a set of recommendations for presentation at the February meeting.

Dr. Niederhuber said a white paper, which listed assumptions for drug approval and outlined approaches to the assessment of net benefit from the standpoint of clinicians dealing with cancer patients, was developed by the *ad hoc* committee. It was enthusiastically approved at the February meeting and forwarded to the FDA as the BSC reaction to the discussions at the October meeting. An immunotherapy update by Dr. Rosenberg and presentation on strategies for identification of new agents for the treatment of AIDS by Dr. Boyd were also February 1988 meeting highlights.

June 1988 meeting highlights included a review of the National Cooperative Drug Discovery Groups and a report from the Subcommittee on Neutron Therapy. Dr. Niederhuber briefly

reviewed the history of the DCT's support of the neutron therapy effort beginning in 1972. The program that has evolved includes ongoing clinical trials at the University of Washington, UCLA, and M.D. Anderson. Dr. Niederhuber stated that the committee believed there was enough preliminary data, especially in the areas of head and neck cancer and prostate cancer, to warrant continued DCT support of the neutron therapy effort, both in followup of patients who have been treated and in continuing to accrue patients in those areas. Whether the areas of lung and other resistant histologies should be included remains to be decided.

Dr. Niederhuber noted that the FDA was encouraged to present a response to the white paper at the June meeting and that Dr. Carl Peck presented general comments on the FDA's position. Dr. Niederhuber stated in summary that the BSC was not satisfied with the FDA's response on what is considered to be a significant problem. He noted that continued input will be possible through the BSC member who is also serving on the committee convened by the President-elect to study the issue.

In response to a question about the need for additional molecular genetic expertise in the Laboratory of Immunoregulation that was recommended by the two latest site visit committees, Dr. Chabner explained that there is considerable involvement with molecular biology in the BRMP as a whole, but the preponderance of talent in that particular laboratory is in protein chemistry and cell biology. Noting that the question was one of balance, Dr. Chabner stated that DCT would probably take the advice of the site visit committee.

Following Dr. Niederhuber's BSC report, Dr. Chabner noted that information on the status of clinical trials accrual had been distributed to NCAB members as requested, and he presented highlights of the clinical trials effort for the year and an update on the AIDS preclinical drug development program. He stated that the accrual effort has resulted in about a 25 percent increase in accrual to Phase III clinical trials in the previous year and a half, but that DCT is faced with the problem of expanding the accrual effort without additional funds beyond the $2.1 million recently allocated by the NCI Executive Committee.

Turning next to the AIDS preclinical drug development program, Dr. Chabner reported that a number of positive compounds have been identified through Dr. Broder's laboratory and the preclinical screen at the FCRF. He stated that many active nucleosides and natural products are being identified by the screening system, and the problem in the future will be in prioritizing the active drugs for further development. He summarized trials of interesting new agents that are under way in the clinical cooperative groups as follows:

- Pentostatin in a comparison study with interferon in patients with hairy cell leukemia appears to produce more complete responses. Trials of combinations of pentostatin and interferon are also under way.

- VM-26, an analog of an already approved drug (VP-16), has been shown to have high activity producing single agent complete responses in childhood monocytic leukemia and has been put into the Group C category because of this activity. Filing for an NDA for this indication is anticipated. VM-26 is also active in relapsed acute lymphocytic leukemia and may become a primary treatment for adult acute lymphocytic leukemia in the future.

- Taxol, an experimental tubulin binding drug that promotes microtubular assembly, is active in ovarian cancer and has shown a 25 percent response rate in previously treated patients in a Johns Hopkins study.

- Fludarabine has been shown to be highly active in the treatment of chronic lymphocytic leukemia, producing responses in the majority of previously treated patients and complete responses in a fraction of them.

- WR 2721, a radioprotective drug that also protects against alkylating injury, has been used with cis-platinum to mitigate renal toxicity, and at high doses, the combination produces a 50 percent response rate in malignant melanoma. The major problem is that it cannot be given on a repeated basis, but it is now in clinical trials with ovarian cancer patients.

- Photodynamic therapy for treating neoplasms is being investigated in the Radiation Oncology Branch using intraperineal light administration. This branch is also studying the use of intravenous iododeoxyuridine with external beam irradiation for undetectable or rapidly recurrent soft tissue sarcomas with a high local control rate.

- Verapamil combined with adriamycin is producing good responses in patients with refractory multiple myeloma who had previously failed adriamycin alone.

- Colony-stimulating factors, which can restore white blood counts, have been shown to shorten the interim of leukopenia during autologous bone marrow transplantation, and they probably can be used to escalate dosage to test the concept of dose intensification in routine chemotherapy.

- TIL cells in combination with IL-2 and cyclophosphamide and IL-2 with interferon are producing interesting leads in immunotherapy.

Dr. Chabner predicted that suramin for the treatment of prostate cancer would be a major story in 1989. Finally, he noted the drugs that were entered in Group C designation during 1989, including ifosfamide, deoxycoformycin, and VM-26.

XXIV. Update on *In-Vitro* Drug Development Screen--Dr. Michael Boyd

Dr. Boyd began his presentation with a brief review of the plans of the Developmental Therapeutics Program to put the status report on the *in vitro* drug screening project in perspective. He stated that the screening project is part of an overall 10-year plan to enhance DTP's focus on new drug discovery through the development and implementation of new screens, the pursuit of a new Natural Products Drug Discovery Program, and the inclusion of new investigator-initiated activities, namely, the National Cooperative Drug Discovery Groups. He noted that the new screening project has been developed and implemented by both intramural NCI staff and contractor staff, principally at the FCRF.

Turning to the status report on the *in vitro* drug development screening project, Dr. Boyd first distinguished between primary and secondary screens. He stated that the important aspect of a primary screen is its capacity for a high flux or high volume of compounds in the initial stage of evaluation. In secondary screens, *in vitro* and/or *in vivo* systems that have a relatively limited throughput are used primarily for confirmation and prioritization of "actives" from the primary screen. He noted that compounds are submitted to the NCI anticancer and AIDS antiviral screening programs from a worldwide diversity of sources and emphasized that the numbers of materials potentially available for screening exceed the DTP anticancer screening capacity, although the AIDS screen is now approaching the capacity to accommodate essentially everything available to that screen. He commented that the new DTP Natural Products Drug

Discovery Program is also a source of a large number of materials for screening. He stated that if 0.5 percent of 10,000 crude extracts screened per year showed interesting patterns of activity, yielding 50 active extracts and averaging 100 fractions per project, the number of fractions necessarily screened per year would be 5,000. Adding this large screening volume to the requirement to accommodate submitted compounds allows an appreciation of the need for a high-capacity, high-flux primary screen.

Next, Dr. Boyd focused on the primary differences between this disease-oriented drug development project and a compound-oriented strategy that NCI pursued for many years. He summarized and illustrated the main features of compound-oriented and disease-oriented strategies, noting that preclinical testing in the compound-oriented model began with a narrow-spectrum primary screen, whereas the disease-oriented model begins with a broad-spectrum screen. The compound-oriented screen previously used by the NCI included an *in vivo* murine P388 leukemia model as the primary screen and an *in vivo* panel of animal tumors and later some human tumor xenografts as the system to determine the spectrum of activity of agents selected initially by the P388 prescreen. Those agents showing potent, broad-spectrum activity were then considered for full preclinical development, INDA submission, and clinical testing. Dr. Boyd pointed out that although this compound-oriented screen allowed evaluation of more than 300,000 unique chemical structures since its inception in 1955 and identification of agents with useful clinical activity in certain cancer patients (especially those with leukemia/lymphoma), little clinical activity had been observed against the most common solid tumors in humans.

Therefore, the goals of a new screening model were to emphasize biological diversity in the primary screen; to allow detection of broad-spectrum as well as disease-specific antitumor activity; to allow highly sensitive, specific bioassay support for detection, isolation, and identification of active trace substances; and to permit more rational interface of the primary screen and preclinical development and prioritization in disease-oriented clinical testing. Dr. Boyd illustrated the *in vitro*-based disease-oriented screening model that was proposed approximately 4 years ago. This model included a broad panel of *in vitro* human tumor cell line panels as the primary screen and *in vivo* test systems using selected sensitive human tumor cell lines for further prioritization and preclinical evaluation and development for clinical testing. He listed the disease-oriented panels of human tumor cell lines and emphasized the magnitude of the laboratory task of the screening project. He pointed out that an input of 10,000 compounds in a 120-cell line panel tested in duplicate at five concentrations of each agent results in a monumental laboratory task.

Next, Dr. Boyd reminded the Board that throughout its development, the DTP screening project has been the subject of considerable scrutiny and oversight by several groups, including the DCT BSC, internal review groups, and particularly an *ad hoc* advisory committee. The role of the *ad hoc* advisory committee has been to review and critique progress; make recommendations in various areas, including scientific and technical, staffing, management, and facilities; and to participate directly in the decision-making process. The committee is chaired by Dr. Kenneth Harrap and includes a cross-section of international experts.

Dr. Boyd then identified the three main areas of development of the screening project. The first--acquisition, characterization, and selection of cell lines--involves ensuring that cell lines are free of contaminating agents and are clearly and confirmably human; a 60-cell line panel is currently available. The second area--development and implementation of automated growth inhibition assays--has focused on evaluation of three different alternatives as endpoint assays. These have included two tetrazolium assays, MTT and XTT, and a sulforhodamine B (SRB) protein staining assay. Dr. Boyd described the advantages and disadvantages of each of the three

assays, beginning with a brief review of the principle of the MTT assay system. He stated that the disadvantages of the MTT assay, the relatively labor-intensive aspiration and solubilization step required because of the formation of an insoluble crystalline material generated by MTT reduction, led to the evaluation of an alternative tetrazolium assay, the XTT assay, which is based on the same principle as the MTT assay but is relatively nonlabor intensive because it does not require an aspiration and solubilization step. Although it is unlikely that XTT will be used in the large-scale anticancer screen, it has proven ideal for the AIDS antiviral screen.

The third area of development has been defining and implementing the requirements of the laboratory computer support system. Dr. Boyd noted that there are two types of computer requirements: one that involves the mainframe system to manage the input of materials into the screening program and the efflux of data and generation of screening information for delivery to suppliers; and the within-the-laboratory requirements for managing the screening process.

Dr. Boyd then summarized key observations from the pilot-scale screening using the tetrazolium assays and illustrated a method of depicting the data from the screen. In this format, the data are arrayed along a central point that represents the mean IC_{50} value calculated for the test across the entire panel of cell lines. A visual impression of the differential effects of a particular agent across cell lines is shown, in that bar graphs project to the right of center for those cell lines relatively more sensitive than the mean and to the left for those relatively less sensitive. Dr. Boyd commented that the patterns are highly characteristic and reproducible for individual agents and suggests that the screen is producing information that is sufficiently reproducible to make it a viable mechanism for analog development or development of agents similar to the types of agents currently available.

At the time when the DTP was almost committed to using the XTT assay in the primary screen, several problems arose. An electron-transfer reagent (PMS) was required with most cell lines making the XTT system more complicated. The very fact that the aspiration step is not required results in a high background and low signal-to-noise ratios in the screen. However, most important, there was erratic occurrence of crystals and conditions promoting crystal formation with the XTT and PMS in the culture wells. Dr. Boyd outlined the approaches to resolve the difficulties with the XTT assay, which included analysis of the crystals and conditions promoting crystal formation, comparison studies with alternate electron carriers, and development of a CO_2-independent culture medium. However, aspects of both the MTT and XTT assays potentially compromising the use of these assays in the high-flux primary anticancer screen (i.e., unstable endpoints and theoretical limitations of metabolic assays) led the DTP to evaluate another, nonmetabolically based assay, the SRB assay. Dr. Boyd listed the features relevant to consideration of this assay in the primary screen noting particularly that it has a fixed endpoint, does not depend on metabolic integrity of the cells, and is more labor intensive but less time critical than the MTT or XTT assays. He noted that several factors were considered in selecting one of the tetrazolium assays versus the SRB assays for the primary screen, and stated that the SRB assay appears to offer greater standardization, reproducibility, and quality control and will enable screening of approximately twice as many compounds in a given amount of time as the time-critical tetrazolium assays.

Dr. Boyd summarized the key assay parameters for use in the actual screening operation to be launched in January 1989. He stated that the screen will include the SRB endpoint assay with CO_2-independent culture medium and that each compound will be tested in duplicate at fivefold and tenfold dilutions against all cell lines in a 60-cell line panel; a relatively short incubation time and relatively high inoculation density will be used. He emphasized that many computer

problems, resulting from antiquated and inadequate hardware and software and insufficient staff, have arisen in the scale-up process and are also being resolved.

Dr. Boyd stated that the first focus for 1989 of the DTP disease-oriented anticancer drug screen is to implement the new, dedicated computer/information technology operations and management at FCRF. Other goals are to operate the primary *in vitro* screen with a 60-cell line panel at a rate equivalent to 20,000 compounds per year, 10,000 synthetic or pure compounds, and 10,000 crude extracts or fractions; continue the development and refinement of the cell line panel, with a goal of 100 to 120 cell lines and 10 to 12 disease-related panels; continue development of the stage II *in vitro* assays; continue development of the counterpart *in vivo* evaluations program; and recruit essential new staff.

Dr. Boyd explained that there will be a major new thrust in the *in vivo* component of the screen. He said that the principal reliance will be upon subcutaneous tumor models and orthotopic models in athymic nude mice. Second, cell lines from the primary screen panel based on demonstrated *in vitro* sensitivity and selectivity will be used. Third, there will be an emphasis on drug effects on fully established growing tumors, for example, growth arrest or lysis rather than an antiproliferative *in vivo* effect. Fourth, there will be close integration with pharmacology and toxicology. Dr. Boyd stated that, most important, each study will be handled as an individualized R&D effort.

Dr. Boyd listed the following reasons for abandoning the P388 *in vivo* primary screen: cost considerations prohibited the operation of two primary screens; feasibility was established for the new cell-line based *in vitro* primary screen; the DTP budget was declining and there was a need to reprogram funds to support implementation of the new screen; the *Ad Hoc* Advisory Committee and DCT BSC recommended the abandonment; and P388 continues to be extensively available and used in both private and commercial laboratories worldwide.

In discussion, a question was raised about the rationale behind the goal of using as many as 120 cell lines or more in the screen. Dr. Boyd said that the new screen evolved from the Lung Cancer Drug Discovery Project and a 30 lung cancer cell line panel to the idea of including multiple panels with multiple members. He explained that the decision on the appropriate number of cell lines for the screen was based on feasibility considerations of statistical requirements for handling the data. Dr. Boyd stated that experts were consulted before a decision was made and emphasized that it is important now to incorporate many and diverse representative lines in the disease panels and proceed with screening operations to accrue a database and experience. He added that it is difficult to make those types of decisions without having some information about how the cell lines respond, and in comparison to one another, to a broad cross-section of drugs.

Another question related to whether all of the known clinically effective anticancer agents were tested in the screen and showed comparable activity profiles. Dr. Boyd said that the patterns of cellular sensitivity obtained with the cell line panel tended to be broadly differential but are characteristic and unique to particular families of agents. Dr. Boyd said it is important to analyze the basis for the differential responsiveness to agents within a disease type because it may have an impact on the way future members of the cell line panels are selected or removed from the panels. He said it is also important to try to understand clinical diversity of response to agents versus cell line diversity response to those same agents.

A concern was raised as to whether a system exists to share data between laboratories so that research is not overly repeated. Dr. Boyd explained that a database is available for anyone who

wants to use it for nondiscreet compounds. However, there is not yet a database for the data being generated now.

It was agreed that Dr. Korn, with input from Drs. Mihich, Montgomery, and Elion, would formulate specific questions on the rationale for the *in vitro* drug screening program and on the results achieved to date.

XXV. New Business

The minutes of the September 26-28, 1988, NCAB meeting were unanimously approved as presented.

Dr. Mihich suggested that the Board, as a body appointed by the President, draft a document to the new President early in 1989 expressing key concerns and needs in the National Cancer Program. He noted the the American Association for Cancer Research had decided to draft a similar document to the President.

Dr. Korn emphasized that such a document needed to be carefully developed and asked that Dr. Mihich prepare a draft document for the February 1989 meeting. A discussion of the document will be included on the agenda for the February 1989 NCAB meeting.

XVI. Adjournment

There being no further business, the 68th meeting of the National Cancer Advisory Board was adjourned at 4:20 p.m. on December 6, 1988.

2/1/89
Date

David Korn, M.D.