National Institutes of Health

National Cancer Institute

NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
November 28-30, 1983
Building 31
Conference Room 6
National Institutes of Health
Bethesda, Maryland

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

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The National Cancer Advisory Board (NCAB) convened its 48th regular meeting at 8:30 a.m., November 28, 1983, in Conference Room 6, C Wing, Building 31, National Institutes of Health (NIH), Bethesda, Maryland. Dr. Tim Lee Carter, Chairman, presided.

Board Members Present

Mr. Richard A. Bloch
Dr. Roswell K. Boutwell
Dr. Ed L. Calhoon
Dr. Tim Lee Carter
Dr. Maureen M. Henderson
Dr. Robert C. Hickey
Dr. Geza J. Jako
Dr. J. Gale Katterhagen
Mrs. Rose Kushner
Ann Landers
Dr. LaSalle D. Leffall
Dr. William E. Powers
Dr. Janet D. Rowley
Mr. Sheldon W. Samuels
Mr. Morris M. Schrier
Dr. Irving J. Selikoff

President's Cancer Panel

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

Ex Officio Members

Dr. Hollis Boren, VA
Dr. Kenneth Bridbord, NIOSH
Dr. Allen Heim, FDA
Dr. Robert E. McGaughy, EPA
Dr. F. Kash Mostofi, DOD
Dr. David P. Rall, NIEHS
Dr. Gordon Wallace, OSTP
Dr. Ralph E. Yodaiken, LABOR

Absent

Dr. Victor Braren
Mrs. Angel Bradley

Liaison Representatives

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

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

Dr. Raymond Lenhard, Jr., Associate Professor of Oncology and Medicine, Johns Hopkins Medical Institute, Baltimore, Maryland, representing the American Society of Clinical Oncology, Inc.

Dr. Stanley Order, Director of Radiation Oncology, Johns Hopkins University, Baltimore, Maryland, representing the American Society of Therapeutics Radiologists.

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

Dr. Paul Sherlock, Chairman, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, New York, representing the American Gastroenterological Association.

Dr. J. W. Thiessen, Acting Deputy Associate Director, Office of Health and Environmental Research, Office of Energy Research, Department of Energy, representing the Department of Energy (for Dr. Charles W. Edington).

Members, Executive Committee, National Cancer Institute

Dr. Vincent T. DeVita, Jr., Director, National Cancer Institute
Dr. Richard H. Adamson, Director, Division of Cancer Cause and Prevention
Mr. Philip D. Amoruso, Executive Officer, National Cancer Institute
Mrs. Barbara S. Bynum, Director, Division of Extramural Activities
Dr. Bruce A. Chabner, Director, Division of Cancer Treatment
Dr. Peter J. Fischinger, Associate Director, National Cancer Institute
Dr. Peter Greenwald, Director, Division of Resources, Centers, and Community Activities
Dr. Jane E. Henney, Deputy Director, National Cancer Institute
Dr. Alan S. Rabson, Director, Division of Cancer Biology and Diagnosis
Ms. Iris Schneider, Director of Staff Operations

In addition to NCI staff members, meeting participants, and guests, a total of 25 registered members of the public attended the meeting.

I. Call to Order--Dr. Tim Lee Carter

Dr. Carter, Chairman, called the meeting to order and welcomed members of the Board, the President's Cancer Panel, liaison representatives, Chairmen of Divisional Boards of Scientific Counselors, staff of the National Cancer Institute (NCI), guests, and members of the public. Dr. Carter welcomed Dr. William Longmire back to the Board following his absence due to illness. Dr. Carter then introduced the liaison representatives.

Procedures for the conduct of Board meetings were reviewed. Members of the public who wished to express their views on any matters discussed by the Board during the meeting were invited to submit their comments in writing to the Executive Secretary of the NCAB within 10 days after the meeting.

II. Future Board Meeting Dates

Future Board meeting dates were confirmed as follows: January 30-February 1, May 14-16, September 24-26, and November 26-28, 1984.

III. Consideration of NCAB Minutes of October 1983

The minutes of the October 1983 meeting of the National Cancer Advisory Board were approved without objection.

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

After welcoming Dr. Longmire back to the Panel and to the Board, Dr. Hammer reported on the third Panel meeting of the year, held at the Memorial Sloan-Kettering Institute in New York on October 12. Dr. Paul Marks hosted the meeting; attendees included Drs. Montgomery, DeVita, Stonehill, Schiaffino, and Mr. Bloch from NCAB. Dr. Joshua Lederberg and Mr. Benno C. Schmidt, former Panel chairmen, were also present.

Discussion focused on the need for long-term stability of NIH grant support to maintain the quality of research programs, e.g., more 5-year grants to individuals were encouraged. The effectiveness of the national biomedical research enterprise is critically dependent on the stability and productivity of major academic research institutions. Questions remain on how to provide long-term stability most effectively.

Other items discussed were: Outstanding Investigator Grant Awards, the composition of peer review panels, the operation of the study sections in the Division of Research Grants, the grant application appeal process, the use of electronic video conference techniques, and other items that could significantly affect the process of supporting the Nation's biomedical research. Dr. Elliot Stonehill is preparing a paper reviewing the various discussions of the peer review system; this paper is expected to form the basis of a suggestion from the Panel to NIH for improving this valuable system.

The Panel also discussed the subject of categorical versus noncategorical research. This subject is being raised because of the National Academy of Sciences' current study of the structure and operations of NIH.

The Panel agreed that holding Panel meetings in various regions has been successful. He invited the Board members to the Panel's final meeting of 1983, to be held on December 1 at NCI; discussions at this meeting will form the basis of the Panel's annual report to the President.

V. Director's Report--Dr. Vincent T. DeVita, Jr.

Dr. DeVita summarized the origin, purpose, and format of the annual program review, and sketched the three major activities of the Boards of Scientific Counselors: giving detailed scientific advice to the Divisions, approving concepts of all contracts, and conducting site visits.

Budget

Dr. DeVita reported that the actual 1983 final budget was $986,811,000, and discussed the budget for FY 1984, pointing out the changes made by the Congress since the President's last budget.

Congress has appropriated $1,053,442,000 for FY 1984, excluding National Research Service Awards, which are funded separately under continuing resolution. With continuing resolution funds of $23.9 million added, the total budget for FY 1984 is $1,077,342,000. Both chambers of Congress added to the President's cancer budget; the largest amount was given to the research project pool, allowing restoration of indirect costs and payment near recommended levels for both competing and noncompeting grants.

The congressional increases restore funding to the actual FY 1983 level rather than adding extra funds, because in 1983 grants were funded at 15 percent below the recommended level, and noncompeting grants were funded at commitment level, adjusted for previous year reductions. This results in a 6 percent increase for noncompeting grants over FY 1983 applications.

The $20 million increase in the budget for cancer centers offers some flexibility and will enable cancer center grants to be funded at the beginning of the year at 85 percent of the recommended levels. Research and development was allocated a $7.5 million increase, restoring FY 1983 levels.

The total budget of $1.077 billion can be compared to the bypass budget of $1.076 billion, which was prepared when the budget base was $955 million, and the Board had agreed that the bypass budget estimate should be conservative. Similarly, the 1985 bypass budget of $1.189 billion will be compared to the base of $1.077 billion, but it was built on the base of $986 million.

Relative percent increases to various programs were presented, with intramural research programs receiving an aggregate increase of 4.1 percent and the research project pool receiving a 15 percent dollar increase. Research

and development contracts received $134.6 million, a decrease of .6 percent from FY 1983.

Survival Statistics

Dr. DeVita presented updated survival data from the Surveillance, Epidemiology, and End Results (SEER) program report on cancer patients diagnosed between 1973 and 1979. Relative survival rates for white male and female patients of 25 types of cancer were shown. The survival rate from the 1980 data for all sexes, cancer types, and races is 48 percent, up from the 46 percent survival rate in 1979 data. Dr. DeVita estimated that 1983 data will show a relative survival rate of more than 50 percent, a "landmark achievement" for the cancer program.

Tables showing relative survival rates for 19 cancer sites in white and black patients were presented. Because of the size of the populations involved, a difference of 1 percent is significant in most cases, and most sites showed significant improvement. Though the survival rate starts at a lower point for blacks than whites, black survival rates have also increased. Survival rates for eight cancer sites in children indicated improvements, especially in areas where treatment has recently improved, such as non-Hodgkin's lymphoma.

Significant improvement in the survival rates of white men with non-seminoma testicular cancer and of white children with acute lymphocytic leukemia has occurred within the time frame of the National Cancer Program and the operation of the SEER data base.

National mortality data were also presented for adult white males and females and for white children. The mortality rate for multiple myeloma has decreased from 1969-1980, and the survival rate has increased to 23 percent. In some cancers, data indicate a rising mortality, which is associated with a rising incidence and stable cure rate. Melanoma incidence increased for males, and lung incidence increased in both males and females. For females, the mortality rate for lung cancer will replace breast cancer as the leading cause of death from cancer in 1984.

VI. Cancer Control Objectives--Dr. Edward Sondik

Dr. Sondik discussed the Program's cancer control objectives, illustrated the process of networking through the Cancer Control Program, and described the SEER program as a way of monitoring progress.

The goal of the Cancer Control Program is to reduce cancer incidence, morbidity, and mortality. Specific objectives based on SEER data analysis results will be used to set long-term program directions, guide program planning, help set priorities in resource allocation, and provide measures of accountability for program evaluation. Charts depicted cancer survival rates if state-of-the-art treatment were uniformly applied, e.g., the survival rate for Hodgkin's disease among white patients would be 85 percent compared to the current 70 percent.

Two strategies for setting objectives are: broad national statements based on national incidence and mortality data and statements about specific cancer sites in defined geographic areas. Current objectives are preliminary national objectives; specific targets are being developed based on comparing incidence and mortality data in counties to the national average.

Objectives in the areas of mortality, incidence, knowledge, and behavior were presented.

Program objectives are:

- Develop by early 1985 a 15-year strategy for cancer control research and intervention, with subobjectives to quantify prevention and management objectives for specific cancer sites.
- Integrate chemoprevention, diet and nutrition, and smoking with occupational cancer, diagnosis, and detection, and Centers in Community Oncology.
- Develop a plan for cancer control surveillance to provide measures of progress in geographic areas and specific cancer sites.
- Develop a strategy for identifying specific geographic regions that suffer from excessive cancer risks, excessive mortality, and low survival.
- Develop methods of working with local areas to formulate and implement cancer control objectives.
- Conduct comprehensive evaluations to measure progress toward objectives and provide program feedback.

VII. Information Dissemination

Overview--Mr. J. Paul Van Nevel

Mr. Van Nevel and members of his staff reviewed the information dissemination programs of the Institute as mandated in the National Cancer Act. The mandate is fulfilled through the International Cancer Research Data Bank (ICRDB) and the Office of Cancer Communications (OCC) programs. The Director is authorized to keep open communication channels between NCI and other organizations involved in cancer.

The largest information dissemination effort at NCI is getting information to other scientists. Other efforts work to get information to health professionals, patients, people at risk to cancer, and other special audiences and the general public.

The Office of the Director, Office of International Affairs (OIA) houses most information dissemination programs to scientists. The OCC disseminates public information. The Division of Resources, Centers, and Community Activities

(DRCCA) is involved in all categories of information dissemination, and other Divisions disseminate information on a smaller scale.

The OCC is divided into response systems and outreach activities. Response activities include answering telephone and written inquiries from the public. Publications are developed to respond to questions about specific aspects of cancer. A Cancer Information Clearinghouse identifies existing public education programs. The OCC assists the Cancer Information Service (CIS) by providing publications.

Since 1975, media inquiries to OCC have increased from 800 to 3,000 per year; telephone inquiries have risen from 9,300 to 90,000 calls per year; written inquiries have risen from 21,400 to 115,000. Publications distribution has risen from 2 million in 1975 to 14 million in 1982.

Outreach activities include assessing audience information needs and developing patient and professional education programs and materials, e.g., the smoking cessation program and kit and the breast cancer education program. The Special Audiences Program is aimed primarily at blacks and Hispanics, with a small component for the Oriental population. A prevention awareness program is currently being developed.

For FY 1983, the program budget was $19.7 million, and in FY 1984 it is estimated at $25.5 million. The largest difference occurs in the area of contracts, with an increase from $1.7 million to $4.6 million. When annualized, the figure is relatively stable, since it reflects funding of contracts awarded during FY 1983 and 1984.

Communications to Scientists--Ms. Susan M. Hubbard

The Scientific Information Branch's mission is to speed information dissemination to shorten the time lag between research advances and improvement in national mortality rates. The Branch, located in the OIA, consists of four sections:

- The Journal of the National Cancer Institute (JNCI), which originally served to publish the research findings of NCI scientists. Over 90 percent of manuscripts now published in the journal are contributed by extramural scientists. The JNCI is also responsible for publication of the National Cancer Institute Monograph series.

- Cancer Treatment Reports, NCI's primary information source on cancer treatment and related research. Cancer Treatment Reports also publishes conference proceedings.

- The International Cancer Research Data Bank, which consists of on-line data bases (including the PDQ system) that are disseminated through the National Library of Medicine.

- The Literature Research Section, which provides literature review services to NCI staff on request, including selected bibliographies, abstracts, and computer printouts.

Cancer Information Service--Ms. Judith A. Stein

The Cancer Communications Network (CCN) is part of the Health Promotions Sciences Branch of DRCCA and includes 21 regional offices that serve approximately 65 percent of the United States' population. Each CCN office is located at a comprehensive or community cancer center; responsibilities include compiling resource directories and conducting special projects to meet cancer information needs in a particular region. The CIS, the most visible component of the CCN, provides telephone information to cancer patients and families, health professionals, and the general public.

The CIS has answered more than 1 million inquiries since 1976; 293,000 were answered in 1983, more than double the number of the previous year. The CIS is promoted through public service announcements and the 1-800-4-CANCER telephone number. An evaluation program consists of quality control, developing a common data set, conducting user surveys and special studies, and identifying comparative data sources.

Patient Education--Ms. Barbara D. Blumberg

Ms. Blumberg presented the "Coping with Cancer" project as an example of OCC patient education programs. The goal of the program is to give cancer patients and their families and friends information on cancer, its treatment, and its psychosocial aspects to help them gain a sense of control over their lives. To help convey information, the program enlists intermediaries such as professional and volunteer organizations.

The patient and family are the primary audiences for patient education materials. The secondary audience consists of those persons whom patients and family look to for care, information, and support, such as health professionals and educators. Materials are designed for each audience. Patient and family materials are further divided into those for young children, adolescents, and adults. All materials undergo extensive review and pretesting.

VIII. DEA Program Review--Mrs. Barbara Bynum

The Division of Extramural Activities (DEA) administers, directs, and coordinates peer review activities for NCI grants, cooperative agreements, and research, resource, and intramural support contracts. These activities are carried out through the Contracts Review Branch and the Grants Review Branch.

In the past year, program project guidelines have been revised, as directed by the Board in May 1983. The ad hoc Subcommittee on Program Project Grants will have its last meeting in mid-January. The final report for implementation of the Outstanding Investigator Grant Award will be given at the January 1984 Board meeting. Schedules for site visits concerning the Organ Systems Headquarters applications are being developed.

Cooperative Minority Biomedical Program

Mrs. Bynum introduced the new Director of the Cooperative Minority Biomedical Program, Dr. Lemuel Evans, and described how the Division works with the Minority Advisory Group to develop additional ways of initiating grants to minority institutions, and to support training of minority scientists. The Division proposes to use faculty fellowships or visiting scientists awards to increase minority interaction with NCI. The honors undergraduate training grant also provides an opportunity for minority funding with the cancer center as the resource. An NIH-wide forum is now considering a supplement mechanism covering costs to the center by making awards to minority institutions. The Advisory Committee has developed a draft describing such a mechanism.

Other models for developing minority scientists and institutions include:

- Work order contracts to develop prototype instruments for disseminating cancer information to minority audiences.

- Orienting honors undergraduates of the Minority Access to Research Careers (MARC) program to institutions that have NCI training grants for graduate and postdoctoral training.

- Offer staff training, residence periods, curriculum development, or other linkages to recognize and enhance health professional programs provided in schools that primarily train minority students.

Current Cancer Research at Drew Medical School: Training Efforts and Future Directions--Dr. Lawrence J. Alfred

Dr. Alfred described the minority training and research activities at Drew Medical School. Drew is working with the UCLA Cancer Center to develop training activities for a Minority Biomedical Research Support consortium and a MARC program of students at area colleges. Behavioral scientists are developing programs in alcoholism and cancer, diet and nutrition, and patient and community education. To accommodate the patient load of approximately 50 percent Hispanics, programs are conducted in English and Spanish.

Dr. Alfred described current research in immunotoxicity and cytotoxicity of chemical oncogenes, supported by NCI and the Environmental Protection Agency. Initial and continuous impact of chemical oncogenes on the immune system are being investigated.

Drew is also conducting clinical research. Plans for future research include developing stem cell cloning approaches and building an epidemiologic base.

IX. Division of Cancer Cause and Prevention Program Review*-- Dr. Richard H. Adamson

The mission of the Division of Cancer Cause and Prevention (DCCP) is to plan and conduct a coordinated program research on cancer causation and basic research on cancer prevention. This research is conducted by intramural laboratories and extramural research programs. The DCCP scientists study the mechanisms of cancer induction at each step of the cellular process, from initiation to transformation of normal cells to the malignant state. The purpose of these studies is to provide information to prevent, reverse, or interrupt the cancer process before the development of clinical disease.

The Division has five major components: the Administrative Management Branch, the Office of the Scientific Coordinator for Environmental Cancer, the Carcinogenesis Intramural Program (which includes 12 laboratories), the Epidemiology and Biometry Program, and the Carcinogenesis Extramural Program. The DCCP Board of Scientific Counselors (BSC) works closely with the Office of the Director in administering and overseeing Division activities. The function of each of these programs was described.

Division Reorganization

Since the November 1982 program review, the Division has undergone several changes. Its new title will be the Division of Cancer Etiology. Activities will continue to include basic research on carcinogenesis, cancer induction, prevention, and chemoprevention. The Field Studies and Statistics Program is to be renamed the Epidemiology and Biostatistics Program. Biological carcinogenesis, and chemical and physical carcinogenesis programs will be established, and associate directors appointed. Intramural and extramural laboratories and activities will coexist under the associate directors.

Staff from the Laboratory of Tumor Virus Genetics, which was not reconstituted, have been reassigned to existing intramural laboratories. Two new laboratories are planned and should be established in 1984, one in cellular genetics and one in DNA viruses. An additional DNA replication and repair laboratory may be also established. The Laboratory of Molecular Oncology has moved to the Frederick Cancer Research Facility.

In the Field Studies and Statistics Program, the SEER project has been transferred to DRCCA. The Biostatistics Branch will retain responsibility for developing statistical methodology for various laboratory experiments and for developing mathematical models to explain basic processes of carcinogenesis, as well as conducting trend analyses and analytical studies correlating suspected environmental factors with the risk of developing cancer.

The Board of Scientific Counselors

The DCCP BSC consists of 20 members, one of whom is newly appointed this year. In 1983, the BSC conducted two intramural site visits, namely the

* Recently renamed Division of Cancer Etiology

Environmental Epidemiology Branch and the Viral Pathology Section in the Laboratory of Viral Carcinogenesis (a followup visit requested by the Board).

Major Initiatives in 1983

Major achievements in biological carcinogenesis include finding evidence that links an oncogene and a known biological function, gene mapping that can relate retroviral oncogenes to specific human chromosomes, and studying genetic elements called "enhancer sequences" indicating that specific segments of DNA control the rate at which particular genes are transcribed.

Significant achievements in chemical carcinogenesis include development of monoclonal antibodies for different classes of cytochromes P450's, studies of transforming growth factors, studies suggesting three rather than two stages involved in tumor formation, and an emphasis on biochemical epidemiology research combining human population studies and laboratory experiments.

Scientific highlights of the epidemiology and biometry area activities include publication of SEER data for patients diagnosed from 1973 to 1979 and followed through 1980, publication of a special incidence survey for nonmelanoma skin cancer, analysis of National Bladder Cancer Survey results, epidemiologic studies of the relationship between the retrovirus HTLV and T-cell leukemias and lymphomas, and international collaborative studies of Acquired Immunodeficiency Syndrome (AIDS).

Managerial initiatives undertaken in 1983 include increased accountability for intramural laboratory budgeting; development of a computerized system to provide information on laboratory expenditures at the section, project, or investigator level; continued consolidation of intramural laboratory facilities to on-campus sites; continued personnel reviews; implementation of a payback system incorporating a user fee for the chemical repository; issuance of two new RFA's; development of an AIDS cooperative agreement cosponsored by National Institute of Allergy and Infectious Diseases (NIAID); initiatives in the area of equal employment opportunity; and providing support to the NCAB ad hoc Subcommittee on Cancer and Minorities.

Budget

The budget for FY 1984, using the President's budget as allocated to NCI, is summarized by research program for the division. The nutrition research program receives the largest increase, mainly in grants; biological carcinogenesis increases by 3 percent. Chemical carcinogenesis funds decrease slightly, primarily because of reduction in contracts. The epidemiology and biometry area increases 5.4 percent. Extramural programs increase by 4.9 percent. Changes in program mechanisms include a 3.3 percent decrease for contracts, a 50 percent increase for cooperative agreement, and a 5.5 percent increase in R01 grants, with a smaller P01 increase.

In FY 1984, one RFA will be issued in the Chemical and Physical Carcinogenesis Program, for $1 million. An RFA will also be issued in the Biological Carcinogenesis Program, for $1 million. A cooperative agreement will be implemented with NIAID for research on the infectious etiology of AIDS, for $1 million. In 1983, 58 project concepts totaling $14.8 million were approved by the Divisional BSC.

Board of Scientific Counselors Report--Dr. Peter Magee

Dr. Magee reported on BSC activities for the year, because the new chairman, Dr. G. Barry Pierce, was unable to attend.

Board members have backgrounds in biological and chemical carcinogenesis, genetics, biometry, and epidemiology. Three meetings are held each year to consider the Division budget and perform concept and program reviews.

In 1983, the Board heard reports on the strategy of using human cells and tissues for carcinogenesis research, a review of radiation epidemiology research ongoing in DCCP and the Radiation Research Program of the Division of Cancer Treatment (DCT), and recommendations for potential new laboratories. Other presentations addressed the housing of USSR nonhuman primates in the United States and recent studies of the colony and transformation genes of retroviruses and cancer cells. Two RFA concepts were approved at $1 million each: one to study new natural and synthetic inhibitors of carcinogenesis and one on hepatitis B virus and primary hepatocellular carcinoma. A cooperative agreement cosponsored by NCI and NIAID on the infectious etiology of AIDS was approved. Together with projects from the previous year, these projects have added more than $9 million to the grants program. In addition, DCCP reprogrammed approximately $3.5 million in FY 1982 and 1983 to be added directly to the R01-P01 grants pool.

Carcinogenesis Studies Using Human Tissues and Cells--Dr. Curtis Harris

Dr. Harris, Chief of the Laboratory of Human Carcinogenesis, discussed the rationale and strategies in the use of human tissues and cells to study various facets of carcinogenesis. He described three areas: individual differences in carcinogenesis, biochemical and molecular epidemiology, and *in vitro* carcinogenesis.

Human epithelial cells from a variety of sites can be maintained *in vitro* for use in side-by-side comparative studies comparing results from human tissues with results from animal models. Carcinogen metabolism, formation of carcinogen DNA adducts, and DNA repair all show person-to-person variations. Generally, carcinogen DNA adducts in human tissue carcinogen metabolism pathways are qualitatively similar to those found in experimental animals, a finding that strengthens confidence in extrapolation of animal model carcinogenesis data to the human situation. Wide quantitative differences, however, exist in carcinogen metabolism and carcinogen-DNA adducts among individuals, different tissues, and outbred animal species, including humans.

Goals of biochemical and molecular epidemiology include the identification of individuals at high risk to cancer because of environmental and host factors. Markers to help identify cancer initiation include metabolism of carcinogens, such as drug probes or enzyme activities, and measurement of different types of DNA damage, such as carcinogen DNA adducts.

In vitro carcinogenesis studies of human cells demonstrate that cancer development is a multistage process, and tumorigenicity is a late and rare event. These studies also show the particular sensitivity of human mesothelial cells to asbestos. The role of oncogenes in human cell carcinogenesis is also under study.

X. Division of Cancer Treatment Program Review--Dr. Bruce A. Chabner

The research mission of the Division of Cancer Treatment is to discover, develop, and evaluate new methods of cancer treatment. Emphasis is on chemotherapy research, the development of new techniques of radiotherapy, investigation of the usefulness of biological compounds that alter host defenses or influence tumor growth environment, and exploration of new alternatives in surgery. In addition, the Radiation Research Program is responsible for research in diagnostic imaging and evaluation of the effects of low level radiation.

The five programs of DCT are: the Cancer Therapy Evaluation Program, the Developmental Therapeutics Program, the Biological Response Modifiers Program, the Clinical Oncology Program, and the Radiation Research Program. Several new branch chiefs were hired during the past year.

The Board of Scientific Counselors has 18 members, representing the fields of radiotherapy, virology, cell biology, diagnostic radiology, medical and pediatric oncology, immunology, pharmacology, radiobiology, medicinal chemistry, pediatrics, biochemistry, and surgery. Dr. Samuel Hellman serves as chairman.

During the past year, there were several major developments in DCT. The Office of the Director expanded cooperation with industry in the process of drug development. Uniform procedures for contract and grant review were established.

The Developmental Therapeutics Program consolidated its animal research facilities. A symposium on drug resistance was conducted. The tumor panel for testing anticancer drug activity has been reduced from eight to four different types of tumors, resulting in a savings of $1.5 million. A working group to investigate the correlation of blood levels of anticancer drugs to toxicity has been established. Investigational New Drug Applications have been filed for eight new agents. A review of older drugs has been completed and four are being reevaluated. Rapid progress was made in designating a role for human T-cell leukemia virus as a possible cause of AIDS.

The Radiation Research Program established grants for research in diagnostic imaging and for low level radiation effects. Neutron generator projects are approaching completion of construction, and clinical trials are

scheduled. An ad hoc working group was established to evaluate the effects of iodine 131 on the thyroid, specifically as a causative agent for thyroid cancer. Research on the bioeffects of ultrasound has begun. Four new radiosensitizers were identified, one of which has entered clinical trials.

In the Biological Response Modifiers Program, the major organizational change was the establishment of the Laboratory of Molecular Immunoregulation. A grant announcement was published regarding cytokine and anticytokine monoclonal antibodies. Phase I and Phase II trials of two types of interferon were completed. Clinical trials of certain monoclonal antibodies were initiated. The natural killer cell continues to receive a great deal of attention in the intramural program.

The Cancer Therapy Evaluation Program established a protocol review office to evaluate clinical protocols for completeness and compliance with FDA regulations. Site visit monitoring has been expanded to include cancer centers, organ systems, and group affiliates. A computerized protocol and clinical drug file system has been completed. To strengthen the extramural statistical support for the program, a Biometrics Research Branch was established. Major scientific developments were the introduction of new agents into clinical trials and the initiation of intergroup surgical studies in breast cancer, melanoma, testicular cancer, and soft tissue sarcoma.

In the Clinical Oncology Program, the ambulatory care contract program was renegotiated with a substantial dollar savings. The Surgery and Radiation Oncology Branches have relocated to new facilities in the Clinical Center. The most important scientific achievement was the completion of clinical trials of PROMACE-MOPP in diffuse histocytic lymphoma; 75 to 80 percent of patients enter complete remission, and the long-term disease-free survival rate is about 65 percent for a disease that was uniformly fatal 15 years ago. One research effort has shown that gene amplification is a unique mechanism of drug resistance in human tumors. Extensive efforts are under way to characterize the human leukemia associated with the HTLV virus. A major advance is the completion of a trial of limb-sparing surgery in soft tissue sarcoma that shows that radiation therapy and adjuvant chemotherapy is as effective as amputation. Expanded clinical trials are ongoing at the Clinical Center in the AIDS syndrome.

Budget

The estimated budget for DCT in FY 1984 is $290,134,000, a 2 percent increase over FY 1983. Major expenditures in the Division are for preclinical drug development, biological development, and clinical trials which together account for almost 80 percent of the budget. About half of the Division's expenditures is for grants.

Board of Scientific Counselors Report--Dr. Samuel Hellman

Scientific and administrative advisory functions of the Board of Scientific Counselors include intramural site visits; initiation, termination, and

alteration of DCT scientific activities; evaluation of new scientific leads proposed by the scientific community and intramural scientists; and approval of new funding initiatives including RFA's. Site visits were conducted to the Surgery Branch and the Navy Medical Oncology Branch. Drug Discovery Groups are being established; the human tumor colony forming assay is being used to screen new chemotherapeutic agents. Workshops were conducted on monoclonal antibodies, lymphokines, acquisition and distribution of biologics and possible identification of immunomodulators, and the use of screens for biologic compounds. The Board was very active in supporting surgical research.

Diagnostic and Therapeutic Research on Monoclonal Antibodies--
Dr. Ronald B. Herberman, Dr. Steven M. Larson, Dr. Kenneth Foon, and Dr. Thomas A. Waldmann

Dr. Herberman defined and described monoclonal antibodies and reviewed methods of monoclonal antibody production. Advantages of hybridoma-produced monoclonal antibodies are their specificity and unlimited supply. Techniques used to evaluate monoclonal antibodies are immunofluorescence and analysis of patterns of reactivity in target tissues.

Dr. Larson discussed diagnostic applications of monoclonal antibodies. By tagging the antibodies with radioactive isotopes, they can be used either for diagnosis or treatment of cancers. Phase I trials of radiolabeled monoclonal antibodies were described. Radiolabeled monoclonal antibodies appear to be useful tools for the diagnosis of occult tumor in the liver and other organs. Possibilities for therapy are being explored; higher doses of radiation are necessary if monoclonal antibodies are to be effective for treatment. Dr. Larson stressed that much research remains to be done before radiolabeled monoclonal antibodies will be available for wide clinical application.

Dr. Foon described Phase I clinical investigations with monoclonal antibodies. In patients with T-cell lymphoma, positive skin responses were observed in more than half of the patients, but no response was observed in 14 melanoma patients. Although the antibodies bind to tumor cells, they do not inhibit their growth. A new, promising approach is to tag the antibodies with a toxin or an anticancer drug such as adriamycin. The antibody carries the antitumor agent to the tumor cells where it is incorporated into the tumor and kills the tumor cells. This concept has been proven effective in an animal tumor system. It is hoped that the FDA will approve clinical trials of adriamycin-conjugated monoclonal antibodies within the next 6 months. In addition, anti-idiotype antibodies have been prepared. Clinical trials in lymphoma patients are scheduled to begin early next year.

Dr. Waldmann described specific therapeutic applications of monoclonal antibodies. His laboratory has prepared a monoclonal antibody, called anti-TAC, that prevents the interaction of T-cell growth factor with its cell surface receptor. This anti-TAC monoclonal antibody can be used to identify leukemias associated with the human T-cell leukemia lymphoma viruses. Anti-TAC monoclonal antibodies, either unmodified or bound to toxins or radioisotopes, are now being evaluated for the therapy of patients with TAC antigen positive adult T-cell leukemia.

XI. Division of Cancer Biology and Diagnosis Program Review-- Dr. Alan S. Rabson and Dr. Peter C. Nowell

The Division of Cancer Biology and Diagnosis (DCBD) supports research on cancer cell biology and immunology. The Division's diagnosis program is concerned with applying principles of cell biology, immunology, and pathology to diagnosis of cancer.

Extramural Division activities are carried out through the two branches of the Extramural Research Program, the Cancer Biology Branch and the Diagnosis Branch. The Intramural Research Program is carried out in 13 laboratories. The total intramural research budget for FY 1984 is $42 million. Dr. Rabson described the research being performed in each of these laboratories.

The Laboratory of Molecular Biology is investigating drug resistance and how immunotoxins enter cells. The Laboratory of Biochemistry is studying gene regulation. Angiogenesis, the ability of tumor cells to generate new blood vessels as they advance, is the subject of research in the Laboratory of Pathophysiology. The Laboratory of Mathematical Biology is developing mathematical models of the immune system. The Laboratory of Genetics is investigating chromosome changes that seem to activate oncogenes. The Metabolism Branch is working on diagnostic and therapeutic applications of the anti-TAC antibody. The Dermatology Branch has demonstrated that the skin is an immunologic organ and that exposure to sunlight or ultraviolet light damages this immune system. The Immunology Branch is studying transplantation biology and transplantation immunology. The emphasis of research in the Laboratory of Cellular Oncology is on the role of viruses in cancer biology. The Laboratory of Pathology studies the pathology of tumor tissue. The Laboratory of Immunobiology is concerned with understanding how cytotoxic antibodies actually kill cells. The Laboratory of Tumor Immunology and Biology (LTIB) is working on the clinical applications of monoclonal antibodies and on understanding oncogenes. The Laboratory of Cell Biology is investigating tumor antigens in chemically induced tumors.

The Board of Scientific Counselors has 12 members and is chaired by Dr. Matthew D. Scharff. The Board is composed of experts in the fields of cell biology, pathology, immunology, biochemistry, immunodeficiency diseases, dermatology, physiology, microbiology and molecular genetics. During the past year site visits were conducted to the Laboratory of Cell Biology, the Laboratory of Molecular Biology, and the Dermatology Branch. Visits to the Laboratory of Immunobiology, Laboratory of Pathophysiology, and the Immunology Branch are scheduled for 1984.

Managerial initiatives accomplished in 1983 included the creation of the Laboratory of Cellular Oncology; the relocation of the Laboratory of Immunobiology, the Membrane Biology Section, and the Pathologic Technology Section to the Frederick Cancer Research Facility; relocation of Dr. Jeffrey Schlom's laboratory (LTIB) to the NIH campus; relocation of most Division operations from Building 8 to Buildings 36 and 37; relocation of the Diagnosis Branch to the Westwood Building; and implementation of a computerized budget system for intramural senior investigators.

Budget

The estimated budget for FY 1984 is $175,532,000. Most extramural research is supported through R01 and P01 grants; the Contracts Program accounts for only $5 million. Extramural research will account for an estimated $133.6 million in FY 1984; the budget for intramural research is estimated at $41.8 million. The one large RFA for the year is "Application of Recombinant DNA Technology to the Diagnosis of Cancer." Six concept reviews were presented to the BSC in 1983; four were approved, representing $3,450,000. Of the approved concepts, two were in diagnosis, one in tumor biology, and one in intramural resources support.

Board of Scientific Counselors Report--Dr. Peter C. Nowell

Dr. Nowell presented a brief review of the activities of the BSC. After the site visits that Dr. Rabson described, specific suggestions and recommendations were made, all of which have been implemented. Plans are under way to reorganize and strengthen the Diagnosis Program.

Human Chromosomes and Cancer--Dr. Nowell

Chromosome studies provide a useful bridge between clinical cancer and fundamental studies at the level of individual genes. These investigations are now possible because of the development of newer techniques of molecular genetics. Most tumors have chromosome abnormalities and, within a given tumor, all cells show the same or related chromosome changes. These changes occur in a nonrandom fashion, which suggests that specific genes are important in neoplasia. Chromosome abnormalities observed in tumor cells include extra chromosomes, commonly found in many leukemias; long unbanded or abnormally banded chromosomes, seen in neuroblastomas; loss of a piece of an arm of a chromosome; and rearrangement of chromosome material as seen in chronic myelogenous leukemia. Translocation of genetic material is observed in most Burkitt tumor cells, which may activate an oncogene. It is now possible to focus on specific genes that play a role in the development of early stages of human cancer. Implications of these findings in vivo are not yet clear.

Chromosome changes are also implicated in the phenomenon of tumor progression. In general, the degree of chromosome abnormality in tumors correlates with tumor progression. As the disease becomes more aggressive, additional chromosome changes are observed in the neoplastic cells. This observation has been helpful in understanding drug resistance and increased aggressiveness in later stages of tumor development.

Chromosome studies have also provided a means of diagnostic and prognostic applications, especially in the leukemias. Specific chromosome changes help to diagnose subtypes of leukemia which, in turn, indicates the probability of response to therapy.

Pathology of Acquired Immunodeficiency Syndrome--Dr. Cheryl M. Reichert

Dr. Reichert reviewed the functions of a pathologist and the methods used to prepare specimens of human tissue for microscopic examination.

Pathology of Acquired Immunodeficiency Syndrome may be divided into four parts: definition or diagnosis of the syndrome, opportunistic infections, neoplasms to which AIDS patients are susceptible, and the pathology of profound lymphoid depletion.

The criteria for AIDS are that the patient has no known cause of immunosuppression and has a disease that is indicative of a defect in cell-mediated immunity. Under the microscope, lymph nodes from AIDS patients may show many germinal centers; at higher power, lymphoid elements, plasma cells, and immunoblasts are detectable.

Opportunistic infections to which AIDS patients are susceptible include pneumocystis, cytomegalovirus, mycobacterium avium, candida, cryptosporidiosis, herpes, toxoplasmosis, and cryptococcus. Appropriate pathology methods make it possible to visualize the causative organisms as well as their histologic effects. Pneumocystis pneumonia must be diagnosed quickly so that the patient can be put on appropriate therapy. Using frozen sections of the diseased lung tissue, diagnosis can be made within an hour.

The AIDS patients develop peculiar kinds of cancers, particularly Kaposi's sarcoma, and unusual lymphomas. The gross and microscopic appearances of Kaposi's sarcoma were exhibited.

The pathology of lymphoid depletion was described using slides of various tissues from AIDS patients. Although many lymphocytes are normally present in the appendix, lymph nodes, and spleen, decreased numbers were observed in the tissues from AIDS patients.

Dr. Reichert stressed that there is no extraordinary risk in handling tissues from AIDS patients.

Immunological Approach to the AIDS Problem--Dr. Gene M. Shearer

Helper T-cells, components of the immune system, function to raise the level of the immune response. Their counterparts, suppressor T-cells, depress the immune response to particular infections. The populations of these two types of cells are delicately balanced to regulate the immune system. In OIDS patients the balance of helpers and suppressors has been shifted in favor of the suppressor T-cells so that the immune system of AIDS patients fails to function, and these individuals become susceptible to numerous infections.

Dr. Shearer suggested that the cause of AIDS may be a new infectious agent, perhaps a new virus, a combination of infectious agents that act synergistically to suppress immune function, or a combination of insults, both infectious and noninfectious, to the immune system. Evidence for each of these hypotheses was presented.

The noninfectious cofactors include exposure to sperm and semen, exposure to foreign transplantation antigens, lack of natural resistance, and exposure to drugs of abuse, all of which induce immunosuppression. Experimental support for these factors was gained by injecting sperm into the bloodstream

of mice, repeated intrarectal injection of small amounts of semen into mice, and intravenous introduction of foreign lymphocytes into the bloodstream of mice. In each case a dramatic reduction in the immune response was observed.

To solve the AIDS problem, more time is needed to identify and isolate an AIDS infectious agent, to develop an effective therapy, to identify AIDS high-risk groups by defining cofactors, and to take preventive measures to reduce risks. Identification of noninfectious cofactors that contribute to AIDS should reduce the panic of the general population toward this disease.

XII. Division of Resources, Centers, and Community Activities Program Review*--Dr. Peter Greenwald

Mission, Organization, and Programs

The Division of Resources, Centers, and Community Activities supports programs in cancer control research and application, applied prevention, and a national system of cancer centers and community oncology programs.

The Division is organized into three major program areas: Cancer Control Science, Centers and Community Oncology, and Prevention. The Division also includes a Biometrics and Operations Research Branch, and an Administrative Office.

The Cancer Control Science Program has three branches: Cancer Control Applications, Health Promotional Sciences, and Cancer Training Branch. These branches support programs in technical, research, and outreach competence and in behavioral medicine, education, cancer training, and career development.

The Centers and Community Oncology Program supports cancer centers, community oncology and rehabilitation programs, the Organ Systems Program, and the Research Facilities Program. Sixty-three Comprehensive Clinical and Basic Science Centers have focused efforts of more than 40 medical schools on the cancer problem. This year, core grant guidelines have been modified to give center directors the opportunity to select program leaders, subject to peer review.

The Prevention Program supports studies in chemoprevention, diet and cancer, occupational and worker education, and cancer detection, including programs in lung and breast cancer screening. The Division is developing plans for prioritizing areas for cancer control intervention trials and cancer detection technique research.

*Recently renamed Division of Cancer Prevention and Control.

Budget

Approximately one-third of the Division budget is a line-item allocation for cancer control activities. After congressional modifications, the cancer control total for FY 1984 is $63 million, divided fairly equally among programs.

Contract research has decreased, in an attempt to channel funds into RFA's, which increased. In the Prevention Program, support for diet and cancer and chemoprevention programs increased, as did funding for occupational and worker programs. As screening and detection studies were completed, support decreased. In Cancer Control Science, health promotion remains level, as future plans are under development. In Community Oncology Programs, Clinical Cooperative Groups also remain level. Funding for cancer centers increased to $79 million. Training funds include $22.8 million for the National Research Service Awards.

Major Initiatives

To track research progress, a system of cancer control phases from basic research to programs of broad public benefit has been instituted. The Division has begun programs of excellence in cancer control research, called Cancer Control Research Units. The Cancer Control Applications Branch is stimulating the development of defined population studies, which tell the potential impact of various interventions.

The NCI's first cancer prevention intervention trials have begun, with major emphasis on chemoprevention and dietary prevention; 20 trials are under way or in late stages of planning. Smoking intervention trials have been developed beyond etiologic research.

In other initiatives, cooperative efforts with centers and other key institutions are being developed. The Organ Systems Program has been modified. In the Career Development Program, the Physician Investigator Award has been renamed the Clinical Investigator Award and should help develop more physician scientists, including surgical oncologists. Other cancer training initiatives focus on nutrition, epidemiology, surgical, and radiation oncology. Data bases, such as SEER, will be integrated with other available data bases for a National Cancer Control Surveillance System.

Board of Scientific Counselors Report--Dr. Lester Breslow

The BSC has 20 members; the Chairman is Dr. Lester Breslow, UCLA Cancer Center and UCLA School of Public Health. The BSC includes individuals with backgrounds in medical and surgical oncology, communications, pathology, epidemiology, nutrition, sociology, pediatrics, cancer control, and behavioral science.

The BSC is to be organized into four subcommittees. The Cancer Control Science Subcommittee identifies and prioritizes new opportunities for cancer control research. A subcommittee on cancer centers and community oncology monitors and sets priorities for research in cancer centers, Community Oncology

Programs, and the Organ Systems Program; it also reviews and promotes linkages among cancer centers, community facilities, and physicians. The Prevention Subcommittee identifies and sets priorities for new research opportunities in cancer prevention, especially in defined populations. The Budget and Evaluation Subcommittee reviews evaluation activities and the tracking of cancer control.

Dr. Breslow described bases for proceeding in cancer control. Research efforts over the past decade have begun to yield substantial results. An infrastructure is developing among communities at the State and local levels. Substantial public support exists. Favorable trends in cancer provide another base. These trends include reduced mortality in cancers (excluding respiratory cancer). In some groups, lung cancer mortality has peaked and is declining. Cigarette smoking among young people is beginning to decline. Finally, recent statistics indicate that deaths from cancer could be reduced by 50 percent by the year 2000 if current knowledge were perfectly applied.

Cancer Control Research Units will test whether prevention and other control studies demonstrated to be effective in limited situations will also be effective when applied to defined population groups. The Division has reviewed one round of Cancer Control Research Unit grant applications and made one award, to the University of Washington.

Recent results from the SEER Program show progress in diagnosis and treatment in the past decade. The SEER Program also provides an opportunity to observe segments of defined populations where cancer occurs to a greater extent. Registration of cancer cases provides an opportunity to establish case control studies for further exploration.

Randomized Trial of Carotene and Cancer in U.S. Physicians--Dr. Charles Hennekens

Dr. Hennekens described a nationwide randomized placebo control trial among 21,400 U.S. male physicians to investigate the possible preventive roles of beta-carotene (the vegetable form of vitamin A) on cancer and of aspirin on cardiovascular mortality. The study, projected to last 5 years, is the first large clinical trial in the United States aimed at cancer prevention rather than cancer treatment. Physicians are sent calendar packs of beta-carotene or placebo capsules and aspirin tablets or placebos, and periodically answer health status followup questionnaires.

Dietary factors may account for 30-35 percent of all cancer deaths, making diet a priority in new cancer prevention research. The possibility of adding an effective protective agent to the diet enhances interest in this area, particularly considering the potential for late-stage carcinogenesis inhibition by micronutrients.

Both laboratory and epidemiologic findings indicate that vitamin A and its analogs provide an opportunity to test hypotheses concerning preventive and protective dietary influences in cancer development. However, a randomized trial of beta-carotene and placebo more directly assesses whether health benefits can be attributed to regular consumption of beta-carotene.

The choice of using U.S. male physicians for a study population offers several advantages. Physicians can give truly informed consent, based on their knowledge about beta-carotene and its potential benefits or adverse side effects. They can promptly recognize side effects. They are more aware of their medical history and health status and report it more accurately than other groups.

Other advantages include the tendency of physicians to be less mobile and easier to trace than members of the general population. These factors made it possible to conduct the entire study by mail, thus greatly reducing costs.

Results from the initial 6-month followup indicate that 98.5 percent of randomized subjects are still taking at least one of the two types of pills. Followup questionnaires yielded 93.8 percent response. Morbidity and mortality followup is 99.4 percent and 100 percent, respectively. Seventy-five percent of the participants have sent in blood samples for analysis. By using a group of highly cooperative subjects and devising a low-cost methodology, investigators have enhanced the likelihood of obtaining either a definite positive result on which to base public health policy, or an informative negative result with which to guide future channels of research.

XIII. Adjournment--Dr. Carter

The 48th meeting of the NCAB was adjourned at 11:30 a.m., on Wednesday, November 30, 1983.

JAN 20 1984

Date

Tim Lee Carter, M.D.
Chairman
National Cancer Advisory Board