Department of Health and Human Services

Public Health Service

National Institutes of Health

National Cancer Institute

National Cancer Advisory Board

Summary of Meeting
November 26-28, 1984
Building 31
National Institutes of Health
Bethesda, Maryland

Department of Health and Human Services
Public Health Service
National Institutes of Health
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Minutes of Meeting
November 26-28, 1984

The National Cancer Advisory Board (NCAB) convened for its 52nd regular meeting at 8:30 a.m., November 26, 1984, in Building 31, National Institutes of Health (NIH), Bethesda, Maryland. Dr. David Korn, Chairman, presided.

Board Members Present

Mr. Richard A. Bloch
Mrs. Angel Bradley
Dr. Victor Braren
Mrs. Helene G. Brown
Dr. Tim Lee Carter
Dr. Gertrude B. Elion
Dr. Robert C. Hickey
Dr. Geza J. Jako
Dr. J. Gale Katterhagen
Dr. David Korn
Mrs. Rose Kushner
Ann Landers
Dr. LaSalle D. Leffall
Dr. Enrico Mihich
Dr. William E. Powers
Dr. Louise C. Strong

President's Cancer Panel

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

Ex Officio Members

Dr. Hollis Boren, VA
Dr. Allen Heim, FDA
Dr. Ralph E. Yodaiken, LABOR

Chairmen, Boards of Scientific Counselors
National Cancer Institute

Dr. Barbara Hulka, DCPC
Dr. G. Barry Pierce, DCE
Dr. Matthew Scharff, DCBD
Dr. Samuel Wells, DCT

Absent

Dr. Roswell K. Boutwell
Dr. Ed L. Calhoon

Liaison Representatives

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

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

Mr. John Madigan, Coordinator for Governmental Relations, American Cancer Society, New York, New York, representing the American Cancer Society, attending for Mr. Alan C. Davis.

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

Dr. David F. Paulson, Director and Chairman, Division of Urology at Duke University Medical Center, Durham, North Carolina, representing the Society of Urologic Oncology.

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

Dr. James Robertson, Director, Human Health and Assessment Division, U.S. Department of Energy, Washington, D.C., representing the U.S. Department of Energy.

Dr. Antonio Romano, Program Director for Cell Biology of the National Science Foundation, Washington, D.C., representing the National Science Foundation.

Members, Executive Committee, National Cancer Institute

Dr. Vincent T. DeVita, Jr., Director, National Cancer Institute
Dr. Richard H. Adamson, Director, Division of Cancer Etiology
Mr. Philip D. Amoruso, Associate Director for Administrative Management, 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 Cancer Prevention and Control
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, National Cancer Institute

In addition to NCI staff members, meeting participants, and guests, a total of 12 registered members of the public attended the meeting.

I. Call to Order--Dr. David Korn

Dr. Korn, Chairman, called the meeting to order and welcomed members of the Board, the President's Cancer Panel, liaison representatives, guests, staff of the National Cancer Institute (NCI), and members of the public.

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. Dr. Korn emphasized the importance of having a quorum of 12 members present for each occasion when a vote is taken.

II. Future Board Meeting Dates

Future Board meeting dates were confirmed as follows: February 4-6, May 13-15, October 7-9, and December 2-4, 1985. The following dates were proposed for 1986: February 3-5, May 19-21, October 6-8, and December 1-3.

III. Consideration of NCAB Minutes of September 1984

The minutes of the September 1984 meeting of the National Cancer Advisory Board were approved without objection.

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

Dr. Hammer reported on two meetings held by the Panel since the Board last met. In October, the Panel met in Seattle at the Fred Hutchinson Cancer Research Center, completing the West Coast portion of the Panel's study of the role of cancer centers in the National Cancer Program. The meeting was attended by Dr. Korn and by representatives from Olympia, Portland, and Anchorage. Oregon, which does not have its own cancer center, was suggested as an appropriate area for a consortium grant. The Panel's meeting at the Honolulu Cancer Research Center was attended by Dr. Longmire, Dr. Montgomery, and Dr. DeVita.

Dr. Hammer briefly reviewed the accomplishments of the Panel since 1981 and stated that its study of cancer centers will be completed in 2 years. Also under consideration is the establishment of a consortium of minority medical schools.

Dr. Hammer announced that one-half of the $100,000 Hammer Cancer Prize for 1984 will go to Dr. Robert Gallo of NCI for his discovery of the first human leukemic viruses, HTLV-1 and -2. The other half of the prize will go to three Japanese scientists working in the same area. The award ceremony will take place in Los Angeles in February; all members of the NCAB are invited to attend.

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

Dr. DeVita discussed the origin, purpose, and format of the annual program review, pointing out that the review is organized along the lines of NCI's organizational structure. The four Boards of Scientific Counselors are responsible for concept review of both intramural and extramural programs, for providing scientific advice in major areas, and for conducting site visits. The role of the President's Cancer Panel is to help the Institute solve problems that are blocking the implementation of the National Cancer Program. In response to the Board's providing suggested topics for discussion, the current program review will include eight rather than four scientific presentations.

Budget

Dr. DeVita reported that NCI obligated 99.99 percent of its funds in FY 1984. The FY 1985 budget of $1,183,000,000 represents a 9.5 percent increase over FY 1984 of $102.3 million, with $71 million committed to the research project pool. Of that $71 million, however, $57.8 million is for noncompeting grants, leaving only $13.2 million for competing grant applications.

The FY 1985 budget contains approximately $175 million in the competing pool, or 15.4 percent of the total budget. The tap for Small Business Innovation Research (SBIR) awards amounts to $9.1 million. No funds have been allocated to restore prior year cuts for cancer centers, the increase for clinical trials is minimal, and funding for the cancer control program is essentially flat, with an increase of 0.9 percent.

In FY 1984, the Institute funded 969 competing grants, almost 39 percent of approved applications, which was higher than the estimated number of 923. The Institute expects to fund its share of the NIH target of 6,500 grants for FY 1985, even though the target of paying 1,030 competing grant applications will probably not be reached, because such funding mechanisms as the Outstanding Investigator Grants and the SBIR grants and contracts could diminish the number of grants awarded but not the number of investigators funded.

NCI received no additional funds for research in AIDS, and the Board will be asked to discuss the redistribution of NCI funds and advise the Institute on this issue.

The bypass budget has been submitted to OMB and requests an increase of $276 million, or 23.3 percent, over the FY 1985 budget. This budget is predicated on funding 40 percent of approved applications at recommended levels, and providing additional money for equipment and restoration of funds. It restores the cooperative groups, provides for more resources for cancer control, and provides for an increase in contracts to further drug and biological development as well as epidemiological studies.

Survival Statistics

Dr. DeVita discussed the Surveillance, Epidemiology, and End Results (SEER) Program, indicating that the program has attained sufficient maturity for comparing the first half of SEER (1973-75) with the second half (1976-81).

For the 1976-81 period, the overall relative survival rate for white patients is 50 percent; for blacks it is 38 percent. The data indicate an improved relative survival rate and a decreased mortality rate for colon cancer, a failure of improvement in breast cancer, and a decreasing mortality rate as well as a rising relative survival rate for testicular cancer.

SEER Update--Dr. Edward Sondik

Dr. Sondik discussed the SEER statistics and the trends derived from the SEER Program, explaining that the program includes approximately 10 percent of the U.S. population, following persons from the onset of cancer, when possible, or identifying them at the time of death. Thus, the program has yielded a population-based estimate of cancer incidence and survival for 10 percent of the country. With the recent addition of the State of New Jersey to the SEER Program, the population base has increased to approximately 12 percent.

The SEER data are grouped according to survival trends; mortality trends; survival by stage; and incidence, mortality, and survival. Relative survival (the estimate of the probability of surviving cancer for a particular number of years) has, for whites for the 5-year period 1976-81, increased to 50 percent compared with 49 percent for the 1973-75 period; for the same periods, survival among blacks increased from 37 to 38 percent. Survival for all races increased from 48 to 49 percent, and for children from 53 to 60 percent.

Relative survival data for various cancer sites show that survival for colon cancer is up from 49 percent in the 1973-75 period to 52 percent for the 1976-81 period and relative survival for testicular cancer is up from 76 percent to 87 percent for the same periods, respectively.

Trends in the age-adjusted mortality rates indicate a slight increase for males between the ages of 65 and 74, and a decrease for males in the 0 to 14 and 15 to 44 age groups. In females, there is also a decrease in mortality trends in the 0 to 14 and 15 to 44 age groups, with flat rates for other age groups. An exception to these trends appears in the mortality rates for white females for lung cancer, which show a significant rise, even in the 35 to 44 age group. The overall increase in mortality rates for lung cancer in white females has been increasing at an average rate of 6.2 percent per year, which equates to an increase of almost 100 percent over a period of 10 years.

The following points were brought out during the discussion period:

- Relative survival rates exclude or at least neutralize deaths from other causes.
- For cancer of the bladder and prostate, 5-year statistics hold some validity, but 10- and 15-year survival rates should also be examined.
- The issue of racial differences and the lethal character of certain tumors was raised.
- SEER uses essentially the same classification system as the American College of Surgeons.

- The mortality and incidence of breast cancer is up sharply in Scotland, an increase that is attributed to use of the pill.

VI. Frederick Cancer Research Facility Program Review--Dr. Peter Fischinger

Dr. Fischinger reviewed the activities and future directions of the Frederick Cancer Research Facility (FCRF). FCRF has displayed the ability to react rapidly and on a significant scale, exemplified by its work on the AIDS problem and in new developments in genetics and transforming genes. The facility consists of 60 buildings on 70 acres and employs 1,100 people. There are five major contracts at the facility. A series of intramural programs represents all the NCI Divisions. Two extramural programs are involved in the Biological Response Modifiers Program and the Animal Genetics Program.

The Program Resources, Inc. (PRI) contract is responsible for supporting the infrastructure necessary to run the facility, and includes the fermentation plant, animal holding, carcinogen testing, and other functions that go into the basic research program that is carried out through the Litton Bionetics contract. The other contracts are for animal production, computer services, and the library. Dr. Fischinger reported the budgets for the five contracts, by contract, for the current year and estimates for the next year.

Two new laboratories in the research program are the Laboratory of Eucaryotic Gene Expression headed by Dr. Jeffry Strathern and the Mammalian Genetics Laboratory headed by Dr. Neal Copeland. The genetics research emphasis has shifted from procaryotic mechanisms to eucaryotes, yeast genetics, mammalian genetics, and gene expression.

The FCRF's immediate goals in the area of AIDS are to develop further diagnostic tests to prevent any further transfusion-associated AIDS, and to develop a vaccine within the next 2 to 3 years. Currently, 250 liters per week of virus-infected cells are being produced at FCRF. Plans to develop various aspects of vaccine research as well as intervention strategies through subcontracts are in progress.

In the next year two new shared services will be formulated--recombinant DNA technology and fermentation technology--and a supercomputer will be installed.

VII. Division of Extramural Activities--Mrs. Barbara Bynum

Mrs. Bynum described the organization and functions of the Division of Extramural Activities (DEA). In addition to the review activities of its Contracts Review Branch and Grants Review Branch, the Division is involved in numerous trans-NCI program coordination functions, under Associate Director Dr. Vincent Oliverio. Among these is the cofunding, with other Institutes of NIH, of minority-based programs; another is related to NCI initiatives to identify and implement opportunities in the minority community for research, training, education, awareness, prevention, and patient access and care.

The broadening efforts of the four programmatic Divisions toward control and prevention have led to the approval of a large number of concepts, which, in turn, has increased the workload of DEA in assessing the technical merit of the resulting award instruments. In response, the Grants Review Branch is being reorganized, and new section chiefs are being selected. This expansion will also account for an increase in the review and approval expenditures for FY 1985.

Six applications for the January Board have been received for the minority investigator's supplement. DEA anticipates funding a total of ten awards in FY 1985 at $25,000 each.

Outstanding investigator grant applications (currently 99) are being mailed to reviewers and will be presented to the Board for approval either in February or in May.

VIII. Comprehensive Minority Biomedical Program--Dr. Lemuel Evans

Dr. Evans discussed the present status and future plans of the Comprehensive Minority Biomedical Program (CMBP), formerly called the Cooperative Minority Biomedical Program. The CMBP promotes broadened participation by minorities in cancer-related research and training activities. It seeks to enhance the effectiveness of programs in cancer medicine and cancer control in reaching the minority community and other medically underserved segments of the population.

The funding level for CMBP has gradually increased during the past 10 years, and in FY 1984 60 awards were made to more than 30 institutions for a total of nearly $3.2 million.

To broaden its focus, the CMBP has developed some new approaches for involving minority communities in NCI-supported research, including developing manpower to serve in relevant areas that lack minority participation, involving the affected minority populations in the implementation of intervention programs such as cancer prevention, and providing specialized research training for minorities at cancer centers.

The Cancer Minority Program Advisory Committee (CMPAC), which has Institute-wide representation, advises the Director of CMBP on cancer-related research and training activities involving minority institutions and investigators. CMPAC also plays a major role in developing NCI recommendations for funding for cancer-related applications in other NIH minority programs. The committee sets goals for CMBP, develops plans for their implementation, serves as counselors and catalysts to minority investigators already funded by NCI, and interacts with faculty, administrators, and students of minority institutions. CMPAC has recently initiated the Minority Investigator Supplement, a grant mechanism that provides supplemental funding to current NCI grantees who submit applications for supporting minority scientists interested in cancer research. A variation of this award, the Minority Satellite Initiative (MSI), contributes to the support of NCI and Clinical Cooperative Research Groups to enable NCI's research to reach minority populations that are par-

ticularly susceptible to cancer. The rationale for the MSI stems from data indicating that cancer survival rates of blacks lag far behind that of whites. This interdivisional program seeks to increase the number of minority patients participating in NCI-supported clinical trials.

IX. Division of Cancer Prevention and Control Program Review--Dr. Peter Greenwald

The Division of Cancer Prevention and Control (DCPC) defines cancer control as the reduction of cancer incidence, morbidity, and mortality through an orderly sequence from research on interventions and their impact in defined populations to the broad, systematic application of the research results. A new emphasis has been evolving during the past 3 years that provides a framework for addressing problems in cancer prevention and control.

The framework provides a means whereby new research initiatives in cancer control will fall into one of five clearly defined phases from basic research through wide diffusion and adoption of state-of-the-science technology. These phases form a continuum for testing ideas in human populations and consist of: 1) hypothesis development--determining, from basic science and clinical trials data, what intervention might benefit a population; 2) methods development--research into development of interventions; 3) controlled intervention trials--testing the interventions with randomized study designs; 4) defined population studies--e.g., determining if an intervention will reduce cancer mortality in special populations and determining barriers to wide application; and 5) demonstration and implementation. The Clinical Cooperative Group Outreach Program, the Community Hospital Oncology Program, and the Community Clinical Oncology Program are now being evaluated to determine how well they foster adoption of state-of-the-science cancer treatment.

The Division is organized into three major program areas: prevention, centers and community oncology, and cancer control sciences. The Division also includes the Biometry Branch, responsible for design of research methods and analysis of trials, and the SEER Program; Smoking, Tobacco, and Cancer Program; Operations Research Branch; and an Administrative Office.

The Prevention Program has one intramural research branch for cancer prevention studies. Other branches in the Prevention Program support extramural research in chemoprevention, diet and cancer, occupational cancer, and cancer detection.

The Centers and Community Oncology Program supports cancer centers, community oncology and rehabilitation, and research facilities. The Organ Systems Program was recently included under the Cancer Centers Branch.

The Cancer Control Science Program has three branches. The Cancer Control Applications Branch transfers research results into programs of broad impact. A new initiative in the Cancer Control Applications Branch provides assistance to state and local health groups to develop strong local programs in cancer prevention. The Health Promotion Sciences Branch focuses on strategies for cancer prevention for individuals and groups and includes the Cancer Communi-

cations Network. The Cancer Training Branch, important to all NCI Divisions, supports predoctoral and postdoctoral training for more than 1,500 scientists. Training efforts are also focused on minority groups, curriculum development in professional schools, and continuing education.

The Division's estimated budget for FY 1985 is $253 million, of which $63.8 million is allocated to cancer control activities. Much of the cancer control program has been undergoing transition to greater emphasis on applied research. Between now and 1990 the largest increases are expected to occur in grants through the RFA mechanism. Increases in cancer control are allocated for the smoking program, CCOP evaluation, diet and nutrition, chemoprevention, cooperative group outreach, and field programs aimed at reducing mortality for those cancer sites where effective treatments exist. In areas other than cancer control, increases are allocated for traditional grants, cancer centers, construction, and cancer training programs.

The Board of Scientific Counselors approved 51 research concepts. The Board placed a strong emphasis on cancer control, prevention trials, and application of trial results. Highlights of the Board's concepts relating to cancer control include: smoking prevention and cessation among blacks, Hispanics, and women; evaluation of the role and effectiveness of tumor boards; reduction of avoidable mortality from cancers; Small Grants Program funding for postdoctoral studies; low fat and breast cancer trials; and cancer communications.

Board of Scientific Counselors, DCPC--Dr. Barbara Hulka

The main function of the Board of Scientific Counselors (BSC) is to review the research concepts developed by DCPC. The Board consists of 19 members. To facilitate its work, the Board has four subcommittees: Prevention, Centers and Community Oncology, Cancer Control Science, and Budget and Evaluation. Each subcommittee may invite ad hoc experts. The concepts developed by each program area are studied in detail by the subcommittee before they are presented to the full Board.

Dr. Hulka reviewed the concepts in prevention, the most active area in the Division. The Information Management Systems for Chemopreventive Agents acquires comprehensive and specific data from the published literature on the efficacy, toxicology, and epidemiology of chemopreventive agents. The most promising agents can then be prioritized for further experimental studies and clinical trial intervention.

The In Vitro Study and Evaluation of Chemopreventive Agents screens and evaluates the activity of chemopreventive agents in inhibiting cell transformation in vitro. Those chemopreventive agents which are effective at this stage are then screened in vivo in selected animal models. This process enables the most likely candidates for effective cancer inhibition or prevention to be tested in animals and ultimately enter clinical intervention trials in humans. In the Diet and Cancer Prevention Program, a series of studies is under way to identify the constituents of dietary fiber, carotenoids, and retinoids which may have the greatest inhibitory effect on cancer and to study the physiologic effects and metabolism of the various components.

Clinical chemoprevention trials include two nutritional intervention studies testing the effectiveness of multiple vitamins and minerals in reducing cancer in high risk areas in China.

Approximately 26 Cancer Prevention Trials in lung cancer and skin cancer are already in progress; for example, Chemoprevention of Skin Cancer in Albinos, which will document factors affecting the occurrence of skin cancer in a high risk Tanzanian population and will determine the efficacy of beta-carotene in inhibiting or reversing the development of skin cancer. Further chemoprevention trials are being requested for cancer of other organ sites such as breast, colon, rectum, and bladder.

The Breast Cancer Detection Demonstration Project is near completion. In 1980 a sample of 65,000 women were selected for followup from the original population of more than 280,000 women in 28 centers in the United States. This cohort continues to be an important resource for further clinical intervention trials and for learning about the natural history of breast cancer. Current activities aim to increase the study's efficiency and continue follow-up by consolidating the study in one central location. Major phase III intervention trials are investigating the effect of a low fat diet on survival of women with breast cancer and on the incidence of breast cancer in high risk women.

The Radiation Dose Reduction Studies project supports activities for reducing unnecessary radiation exposure to patients and improving image quality. The Radiologic Physics Centers and Coordinating Program supports six regional centers and provides for physics reviews at more than 260 facilities supported by DCPC.

The Clinical Nutrition Research Units seek to strengthen biomedical research about nutrients, provide for nutrition education of patient care personnel, and provide nutrition information to the public.

X. SEER Data--Dr. Earl Pollack

The Surveillance, Epidemiology, and End Results (SEER) Program reports detailed information on cancer incidence and cancer patient survival in the United States. The program also detects changes in cancer incidence and mortality over time.

The SEER sample consists of 12.8 percent of the United States population and includes six entire states, Puerto Rico, and four large metropolitan areas. The sample is population based in that the program attempts to identify every case of cancer among the residents of the 11 areas. Ethnic groups such as Hispanics, Japanese, and American Indians are deliberately oversampled to allow detection of differences among various population subgroups. The sample method allows the program to relate the numbers of cases of cancer that occur in these populations and to measure the cancer patients' survival rate within an entire area.

The population based method has several advantages. It allows testing of specific hypotheses in case-control studies where control subjects can be drawn from a population having similar characteristics to the patients. By examining data by geographical area or by ethnic subgroup, effects can be quantified and related to information derived from other sources and the factors which might account for the differences can be investigated. For example, in Utah the incidence rate for lung cancer is half that for other areas probably because the Utah population smokes less than other populations. The SEER data not only quantify the difference but provide a target for cancer control efforts in other areas. SEER data also reflect increases in survival rates following introduction of new treatments, as in testicular cancer.

More accurate and earlier diagnoses of cancer may be reflected in increased survival rates for some cancers such as prostate cancer and melanoma, but for most other cancers, e.g., colon cancer, the increased survival rate represents a better general level of medical care.

Discussion brought out the following:

- Only a crude estimate can be made, based on age differences, of the pre- or post- menopausal state, when diagnosed, of patients who have died from breast cancer.
- In collecting data, the SEER program attempts to identify all organized facilities for diagnosing and treating cancer, and to abstract information from medical records.
- Melanoma is increasing faster among white males for most age groups.

XI. Division of Cancer Etiology Program Review--Dr. Richard Adamson

The Division of Cancer Etiology (DCE) is responsible for planning and conducting NCI's coordinated research program on cancer causation and basic research on prevention. The Division supports both intramural laboratories and extramural programs which seek to elucidate the mechanisms of cancer induction from initiation to the transformation of normal cells into malignant ones. Investigators pursue the disciplines of cellular and molecular biology, biochemistry, immunology, microbiology, pharmacology, and chemistry. Epidemiologic studies are also carried out to identify risk factors predisposing human beings to various cancers.

The Division's major components are the Administrative Management Branch and three program areas: biological carcinogenesis, chemical and physical carcinogenesis, and epidemiology and biostatistics. The Biological Carcinogenesis Program includes five intramural laboratories and the Biological Carcinogenesis Branch, and is responsible for managing contracts and supporting grants studying the etiologic role of viruses and other biological factors in cancer. The Laboratory of Tumor Virus Biology was added to the Division in the past year.

The Chemical and Physical Carcinogenesis Program includes eight intramural laboratories and two extramural research branches.

The Low Level Radiation Effects Branch was transferred to DCE since last year. This extramural branch administers grants and contracts studying the biological effects of low level radiation and the molecular mechanisms involved in radiation-induced DNA lesions.

The Epidemiology and Biostatistics Program includes four intramural branches and the Extramural Programs Branch. The Radiation Epidemiology Branch was upgraded from a section since last year.

Dr. Adamson discussed the scientific highlights of each of the three major program areas of the Division. Both intramural and extramural accomplishments were presented.

Major achievements in biological carcinogenesis include establishing a strong association between human papilloma viruses and cervical cancer, demonstrating that ras oncogenes are present in a wide variety of hematopoietic malignancies, isolating a new oncogene, isolating a retrovirus from monkeys which causes a disease in these animals similar to human AIDS, and studying the prevalence of retroviruses in AIDS patients.

Significant achievements of the chemical and physical carcinogenesis program include: developing sensitive assays to detect carcinogen-DNA adducts in individuals exposed to environmental carcinogens, demonstrating a type of transforming growth factor that inhibits tumor cell growth in vitro, studies on metabolic activation of certain carcinogens, and demonstrating that tobacco-specific nitrosamines are present in persons using smokeless tobacco.

Scientific highlights in epidemiology and biostatistics were: demonstrating an elevated rate of oral cancers among women using snuff in southern rural areas, showing a lower risk for squamous cell lung cancer associated with higher consumption of fruits and vegetables, field studies in Jamaica indicating that over half of all adult lymphomas may be linked to HTLV-I, identifying risk factors for ovarian and endometrial cancer, and quantitating the association between thyroid cancer and head and neck irradiation during childhood.

Managerial initiatives undertaken in 1984 include the reorganization of DCE into three main program areas, establishing a new laboratory and a new branch, and moving a branch into DCE; formalizing the intramural site-visit and followup procedure; completing renovations for the Laboratory of Chemoprevention; issuing new cooperative agreements on AIDS, an interagency agreement with NOAA, and several new RFA's; and several equal opportunity initiatives to recruit handicapped and minority employees.

Budget

The estimated DCE budget for FY 1985 is $237 million, an increase of $22 million or 9.6 percent over FY 1984. Every program area has increased since FY 1984; nutrition, which is listed separately at congressional request, has increased by 28 percent. Grants, including RFA's and cooperative agree-

ments, have increased by 11.4 percent since 1984. Contracts are going up 9.2 percent and inhouse research is going up 4 percent.

There are eight noncompeting RFA's for $5.3 million in the research programs. Six new RFA's will be issued including dietary mutagens, obesity and cancer risk, validation of markers of dietary exposure, carcinogenic potential of involuntary inhalation of cigarette smoke, biochemical epidemiology, and development of chemopreventive agents. In 1984, 59 project concepts, including cooperative agreements, were approved by the Divisional Board of Scientific Counselors.

Board of Scientific Counselors, DCE--Dr. G. Barry Pierce

Dr. Pierce reviewed the functions of the DCE Board of Scientific Counselors. The BSC consists of 17 members with expertise in biological carcinogenesis, including viral oncology, chemical carcinogenesis, radiation carcinogenesis, genetics, biostatistics, and epidemiology.

The Board meets three times a year and is responsible for budgetary advice and concept reviews of contracts, RFA's, cooperative agreements, and interagency agreements. The Board also conducts site visits to the intramural laboratories. The site visits provide evaluative information on scientific performance of staff, available resources in the labs, such as space and personnel, and quality of research. Site visits since the last program review were: the Laboratory of Molecular Virology, the Laboratory of Biology, the Clinical Epidemiology Branch, the Laboratory of Cellular and Molecular Biology, and the Laboratory of Molecular Carcinogenesis. Followup actions resulting from site visits are presented to the Board approximately 1 year after the visit.

The Board has also established ad hoc committees to address special areas of importance. For example, an ad hoc committee discussed the scientific issues related to legislation to compensate individuals for cancer that may have been caused by radioactive fallout from weapons testing in the 1950's and 1960's. The committee's recommendations to the Senate Committee on Labor and Human Resources are included in its report, Development of Radiation Tables. The ad hoc Committee on Epidemiology will examine the relationship and potential collaboration between the intramural and extramural epidemiology programs. Board members also participate in workshops sponsored by the Division.

During the discussion, the following points were raised:

- Techniques of molecular biology and viral cross hybridization have permitted the demonstration of an association between two strains of papilloma virus and cervical cancer. A role for papilloma virus in the development of laryngeal cancer is suggested by the observation that some patients treated with radiation for papilloma virus infection of the larynx subsequently develop cancer.

- Studies have been initiated to determine whether oncogene activation is related to antitumor activity of current anticancer agents. The relationship between adduct formation and antitumor response is being examined in a collaborative study. A Board presentation has been scheduled on this work.

- The Board and the Institute should take a strong position concerning television advertisements promoting the use of smokeless tobacco. A member expressed the need for tracing the history of how the ban on advertising smoking tobacco went into effect; another need is to obtain more convincing data on the linkage between using smokeless tobacco and cancer so that more than mere association can be indicated. The staff was charged with putting together some materials on this issue and its background that would form the basis for the Board's deciding on some action.

- Multiple studies are currently attempting to quantify the relationship between radiation exposure and various types of cancer.

- The basic studies on chemoprevention--on the mechanisms of chemoprevention and on the discovery of new agents--come to DCE; the studies concerned with preclinical toxicity and the clinical intervention studies to DCPC.

XII. Epidemiology--Dr. Joseph Fraumeni

DCE's Epidemiology and Biostatistics Program is responsible for intramural, cooperative, and grant-supported investigations into the causes of cancer and means of preventing it. Dr. Fraumeni described the research areas of each branch within the program.

The Biostatistics Branch, headed by Dr. William Blot, is developing statistical methods for use in epidemiology and laboratory research, and quantitative risk assessment, including models to help describe carcinogenic mechanisms. The Clinical Epidemiology Branch, headed by Dr. Robert Miller, studies cancer-prone families and other high risk groups, operates a clinic studying genetics of human cancer, and investigates the origins and late effects of childhood cancer. The Environmental Epidemiology Branch, headed by Dr. Robert Hoover, studies a wide variety of environmental and host factors involved in cancer etiology including nutrition and occupational exposures. The Radiation Epidemiology Branch, created in 1984 and headed by Dr. John Boice, studies populations exposed to various kinds of radiation to clarify the effects of low dose exposure and evaluates the potential risks from treatment by radiation and chemotherapy. The Extramural Programs Branch, headed by Dr. John Cooper, stimulates and administers extramural research in epidemiology and biostatistics, and has recently been emphasizing the areas of biochemical epidemiology, diet, and AIDS research.

Dr. Fraumeni described the principles of epidemiology and their application to detecting risk factors in human cancer, clarifying the carcinogenic potential of specific agents, and understanding the mechanisms of human carcinogenesis.

Using the cancer maps that illustrate the geographic distribution of site-specific cancer mortality in the United States and other countries, Dr. Fraumeni discussed the epidemiologic evidence for identifying various exposures as carcinogenic in man. A chief area of NCI program interest lies with tobacco use, in-

cluding smoking, smokeless tobacco, and passive smoking. Dr. Fraumeni pointed out the excess rates of mouth cancer resulting from the use of snuff among women in rural counties in the south. This finding is of particular concern because the increased use of smokeless tobacco among young people incurs not only risk of oral cancer but a high probability of youth adopting the smoking habit.

Other areas of intramural and extramural investigation include cancer risks associated with environmental factors such as alcohol use, ultraviolet and ionizing radiation, hormones and other medicinal agents, occupational exposures, air and water pollution, viruses, and dietary patterns. The role of genetic determinants was also discussed. Studies that integrate epidemiologic and laboratory methods (biochemical epidemiology) were emphasized as a major program thrust.

XIII. The American Cancer Society's Prospective Epidemiologic Study: Cancer Prevention Study II--Mr. Lawrence Garfinkel

Mr. Lawrence Garfinkel, Vice President for Epidemiology and Statistics for the American Cancer Society (ACS), described the Society's prospective epidemiology study on cancer and risk factors.

The first cancer prevention study (CPS I), initiated in 1959, surveyed 1,078,000 persons recruited by ACS volunteers and followed them for 12 years. CPS I produced valuable information on risk factors not only for cancer, but also for other causes of death such as cardiovascular disease and stroke.

CPS II, initiated in 1982, was motivated by new questions on potential risk factors. The study has recruited more than 1,200,000 subjects through ACS volunteer organizations throughout the United States and Puerto Rico. The questionnaire contains questions on a variety of possible risk factors for cancer such as family history of cancer and other diseases, smoking habits, diet, drinking habits, and occupational exposures. Substantive information correlating mortality data for various sites of cancer with questionnaire items will be available after the first followup and analysis is completed. Followup is planned for 2-year intervals until 1988; death certificates will be obtained for deceased subjects to determine cause of death.

Mr. Garfinkel made several demographic comparisons between the study populations of CPS I and II including the older age range of subjects, socioeconomic and educational levels, and the underrepresentation of blacks (4.3 percent).

XIV. Division of Cancer Biology and Diagnosis Program Review--Dr. Alan S. Rabson

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

The Division's extramural activities are carried out through the two branches of the Extramural Research Program: the Cancer Biology Branch, which is subdivided into tumor biology and immunology, and the Diagnosis Branch. The Intramural Research Program is carried out in 13 laboratories and branches.

The Board of Scientific Counselors has 15 members and is chaired by Dr. Matthew Scharff. The Board is composed of experts in the fields of cell biology, pathology, immunology, biochemistry, oncology, physiology, microbiology, and molecular biology.

Intramural site vists carried out in FY 1984 included the Laboratory of Immunobiology, the Laboratory of Pathophysiology, and the Immunology Branch. In FY 1985, a site visit has been made to the Metabolism Branch and two more are scheduled for the Laboratory of Biochemistry and the Laboratory of Tumor Immunology and Biology.

Managerial initiatives for FY 1984 included key personnel appointments and developing and implementing plans to establish a supercomputer facility, redistributing the workload of the administrative staff, and abolishing the Pathologic Technology Section of the Division's Laboratory of Pathology.

Budget

The estimated budget for FY 1985 is $213 million, an increase of 9.61 percent over the FY 1984 figure of $192 million, with approximately $163 million estimated for grants ($127 million for the traditional R01 grants).

Project concepts presented to the BSC in FY 1984 included four in diagnosis, three of which were approved, and one in intramural research.

Board of Scientific Counselors, DCBD--Dr. Matthew Scharff

Dr. Scharff presented a brief review of BSC activities. The Board met twice during the year. A new subcommittee of the BSC was formed to provide advice to the Diagnosis Branch on new opportunities. Some administrative modifications were also made in this branch.

Site visits to the Laboratory of Immunobiology and the Laboratory of Pathophysiology illustrate the Board's process of identifying problems and formulating solutions. After the site visits, specific suggestions and recommendations were made, all of which have been implemented.

The Board reviewed the intramural program and concluded that it is very effectively carrying out its important work of doing research in cancer biology and tumor biology.

XV. Cancer Metastases--Dr. Lance Liotta

Cancer invasion and metastasis are major causes of treatment failure for the majority of tumors. Many patients have already developed microscopic,

clinically silent metastases at the time of primary tumor diagnosis. Research in cancer metastases is aimed at developing new methods to predict whether a tumor will develop metastases, to detect microscopic metastases, to identify and treat micrometastases, and to prevent metastatic spread of primary tumors.

The Laboratory of Pathology, DCBD, is conducting investigations into the basic biochemical and molecular genetic mechanisms involved in tumor invasion and metastases formation. Investigations in the laboratory have demonstrated how certain invasive tumor cells can degrade laminin, a protein in the basement membrane of organs. The unique molecular structure of laminin has also been determined by electron microscopy. Investigators identified a protein that interacts with laminin on the tumor cell surface called the laminin receptor. Actively invading tumor cells have increased amounts of laminin receptor on their surface, while benign tumors have fewer receptors. Studies are under way to measure the laminin receptor content of human tumors, which may provide a means to predict the aggressiveness of a patient's tumor.

Preliminary studies have been carried out in animals to block the laminin receptors and thereby inhibit or abolish the ability of a tumor cell to migrate out of an organ and form metastases. Investigators have also identified enzymes in metastatic tumor cells that facilitate breakdown of the basement membrane once the tumor cell has attached to the membrane. Studies are under way on antibodies to the enzyme that may inhibit metastases and thus serve as potential treatment.

During the past year, a new research program was initiated to study the molecular genetics of metastases. The program provides a new approach to studying the invasion process.

XVI. The Role of the Supercomputer in Cancer Research--Dr. Jacob Maizel

The Laboratory of Mathematical Biology conducts research in molecular biology, the study of membrane structure and function, mathematical modeling of the genetic phenomena in cells, and the application of computers to analyzing the structure and function of proteins.

The supercomputer planned for NCI will be the first of its kind to be totally dedicated to biological sciences. It will be able to perform most calculations and procedures 50 to 100 times faster than alternative computing methods. Research topics that can be addressed by a powerful computer include sequence analysis of proteins and nucleic acids, e.g., determining the sequence of nucleic acid subunits that make up genetic structure, predicting the properties and structures of proteins from their amino acid sequence, and predicting protein folding patterns; studying homologous relationships between regions of different nucleic acids and comparing them with existing data bases of genetic material sequences; graphically representing the structures of molecules; simulating molecular dynamics; and X-ray crystallography studies.

The computer network is expected to grow, linking with different laboratories within NIH as well as with extramural collaborators.

XVII. Immunotoxins in Cancer Therapy--Dr. Ira Pastan

During the past 7 years, researchers in the Laboratory of Molecular Biology have identified the biochemical pathways by which large molecules enter cells and are directed to their site of action. The cell has an elaborate "sorting mechanism" to bring molecules into the cell. Once this process was elucidated, research focused on developing methods of delivering specialized molecules such as drugs or immunotoxins for treating cancer and understanding the process by which these molecules destroy cancer cells.

Researchers have identified cancer cells that are susceptible to attack by immunotoxin molecules created by coupling a specific monoclonal antibody with a specific toxin. Screening is under way to determine the cell-killing capacity of various other monoclonal antibodies coupled with toxins.

Dr. Pastan discussed cell biology approaches and problems involved in enhancing immunotoxin action and applying immunotoxins to effective cancer therapy. Active immunotoxins demonstrate selective cell killing in culture by a pathway that is still under study.

Further clinical experiments in appropriate animal models are needed to determine whether immunotoxins are a potentially useful method of cancer treatment.

XVIII. Diagnostic Imaging--Dr. Fred Ruzicka and Dr. David Bragg

The Diagnostic Imaging Research Branch was transferred to the Radiation Research Program of NCI in 1981 from the Institute of General Medical Sciences. Since then the program has grown considerably from a budget of $4 million in 1981 to more than $14 million in FY 1984. As part of the extramural program of NCI, its objectives are to develop and support research in diagnostic imaging and nuclear medicine primarily in NCI, to provide expertise and consultation for other Institutes in the area of diagnostic imaging, and to identify qualified diagnostic radiologists for appointment to study sections and advisory councils.

A conjoint committee whose members are experts in diagnostic radiology and nuclear medicine provides advice and recommendations for research in diagnostic imaging and maintains liaison with the research centers throughout the United States. A major accomplishment of the conjoint committee was publication of its task force committees' plan for diagnostic imaging research.

Program announcements for 1985 include developing new and improved contrast agents for conventional radiography, nuclear magnetic resonance, and nuclear medicine; developing radioactive-labeled pharmaceuticals and the associated tomographic imaging systems; and characterizing tissue by ultrasound and by X-ray computed tomography. Future interests in nuclear medicine imaging are to quantitate blood flow to organs noninvasively, plan and monitor response to chemotherapy, and to develop radiologic techniques for diagnosing and staging tumors and planning treatment of tumors.

Dr. Chabner pointed out that NCI provides approximately 30 percent of the research support for diagnostic imaging at NIH. Dr. Ruzicka will continue to coordinate the NIH support for diagnostic imaging and determine future needs in the field among the various Institutes that participate in the program.

Dr. Bragg, a member of the DCT Board of Scientific Counselors, reviewed research opportunities in oncologic imaging. He stressed future roles for diagnostic imaging in screening and detection, especially for breast cancer, characterizing the tumor burden to allow surgical, medical, and radiation oncologists to target their treatments more precisely. In the area of diagnosis, further research is needed using longer electromagnetic wavelengths that can yield better diagnostic information about tumors than shorter wavelengths. More precise computer techniques are needed to view tumors in three dimensions and methods need to be refined for viewing low contrast tumor margins, e.g., more clearly identifying early lung cancer. Applications of techniques to convert analog radiographic signals to digital signals will help in developing more sensitive diagnostic tools. Another major horizon is educating the radiologic community to use current technology in a more cost-effective and appropriate manner in detecting tumors in their primary and metastatic sites.

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

The research mission of the Division of Cancer Treatment (DCT) is to discover, develop, and clinically evaluate new methods of cancer treament. This includes all modes of cancer treatment--chemotherapy, radiation therapy, biologics, and surgery. An additional objective of the Division is to conduct a research program in all aspects of diagnostic imaging. A common flow for development of all therapeutic modalities was described.

DCT's five programs are the Cancer Therapy Evaluation Program, the Developmental Therapeutics Program, the Biological Response Modifiers Program, the Clinical Oncology Program, and the Radiation Research Program. A large cooperative agreements program supports clinical trials in the cooperative groups around the country. The National Cancer Drug Discovery Groups are another of the Division's cooperative agreements. This recent initiative is an effort to encourage development of drugs for cancer treatment in academic centers and industry.

Significant activities in the office of the Division Director included extensive efforts to expand cooperation with industry in drug development resulting in an unprecedented amount of cooperation for clinical trials and development of industry initiatives in preclinical drug development. The office directed the competition for the AIDS diagnostic blood test. It was involved with an examination of immunoaugmentative therapy, an unproven treatment method. Samples of the material used in this therapy were found to be contaminated with hepatitis virus and bacteria and showed no evidence of being useful in treating cancer. These findings, which were published, led to the closing of offices in this country offering information about the therapy.

Extensive efforts were made to increase the coordination of bilateral agreements with France, Italy, and Japan. A program was initiated to support clinical trials in minority hospitals through the cooperative group program.

In the Clinical Oncology Program some major scientific discoveries are being made. Through this program adoptive immunotherapy models were developed using lymphokine activated killer cells to inhibit growth of pulmonary metastases in an experimental murine sarcoma system. Researchers demonstrated that adjuvant chemotherapy can improve disease-free survival and overall survival in patients with soft tissue sarcomas. They also developed a small pilot study to test the feasibility of intravenous administration of suramin to patients with early AIDS/KS.

The Radiation Research Program received concept approval to conduct all neutron therapy clinical trials under the contract mechanism, awarded comparative clinical NMR contracts, and transferred the Low Level Radiation Effects Branch to the Division of Cancer Etiology. Progress in the Clinical Neutron Therapy Program was reviewed.

In the Cancer Therapy Evaluation Program several new efforts to increase grant support for surgical oncology were undertaken in response to recommendations of the Surgical Oncology Research Development Working Group of the BSC. These were: reissuing an RFA for planning surgical oncology research and awarding a number of grants in this area, initiating the Physician Investigator Development Award, reissuing a program announcement in surgical oncology, and including surgery in the group specialties to which the Professional Oncology Education Program has been targeted. Other significant accomplishments in the Cancer Therapy Evaluation Program include expansion of the analog development program, and establishment of liaison with the European Organization for Cancer Treatment Research to test drugs developed in our system. Several high priority clinical trials have been initiated in the past year.

Within the Biological Response Modifiers Program the following intramural activities are taking place in response to recommendations of the Board of Scientific Counselors: consolidation of certain intramural programs in cellular immunology, expanded efforts in molecular biology, and maintaining the current level of effort in clinical research. Two major clinical studies of the Biological Therapeutics Branch involved interferon and monoclonal antibodies. Extramural research accomplishments were reviewed.

The Developmental Therapeutics Program is the largest program in terms of the extent of its activities. Its main concern is the development of new drugs. Other major activities are a large intramural pharmacology effort and work on the HTLV-III virus in the Laboratory of Tumor Cell Biology. Significant accomplishments in FY 1984 were: discovery of the HTLV-III virus as the cause of AIDS, the review and competition of the National Cooperative Drug Discovery Groups to try to move drug development into industry and academia, review of the effort to use the human tumor stem cell colony forming assay as a screening tool for drug development, and the establishment of a Lung Cancer Drug Discovery Program.

Budget

The estimated budget for DCT in FY 1985 is $339,000,000--an 11 percent increase over FY 1984. Most of the increase is for grants. Major expenditures in the Division are in the therapeutic programs--radiation research, developmental therapeutics, and the clinical extramural programs. Grants constitute slightly more than half of the budget.

Board of Scientific Counselors, DCT--Dr. Samuel A. Wells, Jr.

Scientific and administrative advisory functions of the Board of Scientific Counselors include intramural site visits; initiation, termination, and alteration of DCT scientific activities; and advice on funding plans for RFA's. DCT staff arrange scientific presentations for the Board to keep the members informed of intramural activities and advances in basic and clinical research in the broad field of oncology.

The BSC consists of 18 members representing relevant specialties and is chaired by Dr. Wells. During the past year the Board conducted site visits to the Biological Response Modifiers Program, the Clinical Pharmacology Branch, the Clinical Oncology Program, and combined visits to the Laboratory of Medicinal Chemistry and Biology and the Laboratory of Chemical Pharmacology, both in the Developmental Therapeutics Program. The DCT Board established an NCI Task Force on AIDS to solicit advice from DCT and DCE. Under the auspices of the BSC, DCT established the Surgical Oncology Research Development Working Group. An ad hoc committee of the BSC reviewed the Developmental Therapeutics Program drug information system. The Board formed a Neutron Therapy Working Group to consider the appropriate mechanism for supporting clinical trials in this area. Another ad hoc committee was formed to assess progress in using the human tumor colony forming assay for drug sensitivity.

Discussion brought out the view that greater industry participation in the development of chemotherapeutic drugs is desirable.

Attracting young surgeons into the field of surgical oncology is encouraged as a goal for NCI.

XX. Chairman's Remarks and New Business--Dr. David Korn

Dr. Korn proposed that the Board establish a subcommittee on cancer information, chaired by Mr. Bloch, with Mrs. Kushner, Mrs. Brown, Ms. Landers, and Dr. Calhoon serving as members. An update of the proposed subcommittee's structure and a statement of its mission were distributed. The Board voted unanimously that this subcommittee should meet before the February meeting to review and refine its mission statement.

There is an anticipated significant reduction in mortality from cancer if the PDQ information can be widely disseminated. Problems associated with the latter were explored in detail.

Board members discussed the challenge of maintaining the accuracy of the information in PDQ with regard the 10,000 physicians listed in the data base.

Mr. Bloch discussed the issue of the availability of PDQ and read a letter that he had mailed to the Board members in October 1984, asking them to consider the following three items for discussion at the November Board meeting:

- Separating the list of physicians from PDQ into an individual program.
- Directing PDQ publicity to the entire population as well as to physicians.
- Making PDQ available to any vendors with no or relatively few strings.

These issues will be discussed by the Subcommittee on Cancer Information and presented to the Board at the February meeting.

Because of time constraints, the presentation of the chemotherapy program was deferred until the February meeting.

XXI. Adjournment--Dr. David Korn

The 52nd meeting of the NCAB was adjourned at 1:20 p.m., on Wednesday, November 28, 1984.

MAY 10 1985

Date

David Korn, M.D.
Chairman
National Cancer Advisory Board