DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

NATIONAL INSTITUTES OF HEALTH

NATIONAL CANCER INSTITUTE

NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
December 3-4, 1990

Building 31, Conference Room 10
National Institutes of Health
Bethesda, Maryland

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

Summary of Meeting
December 3-4, 1990

The National Cancer Advisory Board (NCAB) reconvened for its 76th regular meeting at 8:00 a.m., December 3, 1990, in Building 31, 6th floor, Conference Room 10, National Institutes of Health (NIH). Dr. David Korn, Chairman, presided.

NCAB Members

Dr. Erwin P. Bettinghaus
Dr. Roswell K. Boutwell
Dr. David G. Bragg
Mrs. Nancy G. Brinker
Mrs. Helene G. Brown
Dr. John R. Durant
Dr. Gertrude B. Elion (Absent)
Dr. Bernard Fisher
Dr. Phillip Frost (Absent)
Dr. David Korn
Dr. Walter Lawrence, Jr. (Absent)
Dr. Enrico Mihich
Mrs. Irene S. Pollin
Dr. Louise C. Strong
Dr. Howard M. Temin (Absent)
Dr. Samuel A. Wells, Jr.

President's Cancer Panel

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

***Ex Officio* Members**

Dr. Miriam Davis, NIEHS
Dr. Marvin E. Frazier, DOE
Captain Bimal Ghosh, DOD
Dr. John R. Johnson, FDA (Absent)
Ms. Rachel Levinson, OSTP (Absent)
Dr. Theodore Lorei, DVA
Dr. Hugh McKinnon, EPA (Absent)
Dr. Lakshmi C. Mishra, CPSC
Dr. William F. Raub, NIH
Dr. Louis W. Sullivan, DHHS (Absent)
Mr. John J. Whalen, NIOSH
Dr. Ralph E. Yodaiken, DOL

Members, Executive Committee, National Cancer Institute, NIH

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

Liaison Representatives

Dr. Eve Ida Barak, Associate Program Director for Cell Biology, Division of Cellular Biosciences, National Science Foundation, Washington, D.C., representing the National Science Foundation for Dr. Maryanna Henkart.

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

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

Dr. Edward P. Gelmann, Chief and Professor of Medicine and Anatomy and Cell Biology, Vincent T. Lombordi Cancer Research Center, Division of Medical Oncology, Washington, D.C., representing the American Society of Clinical Oncology.

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

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

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

Dr. John F. Potter, Professor of Surgery, Vincent T. Lombardi Cancer Research Center, Georgetown University Medical School, Washington, D.C., representing the Society of Surgical Oncology.

Ms. Yvonne Soghomonian, Associate Director, Candlelighters Childhood Cancer Foundation, Washington, D.C., representing the Candlelighters Childhood Cancer Foundation.

Chairpersons, Boards of Scientific Counselors, National Cancer Institute

Division of Cancer Prevention and Control--Dr. Edward Bresnick, James C. Chilcott, Professor and Chairman, Department of Pharmacology and Toxicology, Dartmouth Medical School, Hanover, New Hampshire.

In addition to NCI staff members, meeting participants, and guests, a total of 45 registered members of the public attended.

I. CALL TO ORDER, OPENING REMARKS, AND CONSIDERATION OF OCTOBER 1-2, 1990, NCAB MEETING MINUTES--DR. DAVID KORN

Dr. Korn, Chairman, called the 76th meeting of the National Cancer Advisory Board (NCAB or Board) to order and welcomed Board members, the President's Cancer Panel, liaison representatives, chairpersons of the divisional Boards of Scientific Counselors (BSC), guests, staff of the National Cancer Institute (NCI), and members of the public. He invited members of the public who wished to express their views on any part of the meeting to do so by writing to Mrs. Barbara Bynum, Director, Division of Extramural Activities (DEA), within 10 days of the meeting.

Approval of the October minutes was postponed until the following day's session.

II. FUTURE MEETING DATES

Dr. Korn called Board members' attention to the following confirmed meeting dates: February 4-6, 1991; May 6-8, 1991; September 23-25, 1991; and November 25-27, 1991. To be confirmed are the following dates: January 27-29, 1992; May 4-6, 1992; September 21-23, 1992; and November 30-December 2, 1992. (Note: Although 3-day meetings continue to be listed, the 2-day format will be used whenever possible).

Dr. Korn noted that the November-December 1992 dates will be changed due to conflicts expressed at the October meeting. He asked Board members to convey to Mrs. Bynum any problems with the tentative dates December 14-15, 1992.

III. REPORT OF THE PRESIDENT'S CANCER PANEL--DR JOHN A. MONTGOMERY FOR DR. ARMAND HAMMER

In Dr. Hammer's absence, Dr. Montgomery read the report of the President's Cancer Panel, which had been prepared by Dr. Hammer. In it, Dr. Hammer expressed regret at being unable to attend the December meeting of the NCAB but noted his continuing interest in its proceedings as well as those of the Panel. He reported that the Panel had held two meetings since the October NCAB meeting. The first, which took place at Roger Williams General Hospital at Brown University in Providence, Rhode Island, explored the topic, "Cancer Communication and Information." Featured speakers were as follows: Senator Claiborne Pell, who, Dr. Hammer noted, was responsible for much of the legislation that enabled NCI to build its cancer communication program; Ms. Susan Hubbard, who spoke on information dissemination by NCI's International Cancer Information Center; and Dr. Sandor Eckhardt of the National Institute of Oncology in Budapest, Hungary, who spoke on the need for increased communication with the cancer community in Eastern Europe and praised the efforts of NCI's communications programs and their value to the cancer community throughout Europe.

Dr. Hammer noted that the second meeting took place on the NIH campus and was devoted to hearing directly from NCI staff regarding the work of the Institute. The Panel heard reports from Dr. Steven Rosenberg on gene therapy involving tumor-infiltrating lymphocytes and from Dr. W. French Anderson of the National Heart, Lung, and Blood Institute, who spoke on the collaborative gene transfer project involving staff of the NCI. Dr. Hammer concluded his review of these meetings with the statement that the work at the NCI is unquestionably of the highest caliber and in the very forefront of cancer research and treatment. He reported that the final Panel meeting will be held at the Hooker Foundation, University of California, San Francisco, to consider the latest developments in oncogene research and to continue the discussion on cancer communication programs.

In conclusion, Dr. Hammer stated that the 9 years since his appointment as chairman had been a very rewarding experience. He spoke of his good relationships with the former Director of NCI, Dr. Vincent De Vita, and now with Dr. Samuel Broder and of the benefit derived from the wisdom and experience of all who

served on the Panel during his tenure as chairman. Dr. Hammer expressed appreciation on behalf of himself and the Panel members for the services and efforts of Dr. Elliott Stonehill as Executive Secretary of the Panel. He looked forward to a continued association with members of the NCAB in executing their responsibilities related to the National Cancer Program and noted the achievements to date and the prospects for dramatic advances in the future.

IV. REPORT OF THE DIRECTOR, NCI--DR. SAMUEL BRODER

Dr. Broder began his presentation by reporting the sad news that Dr. Joseph Cullen, former Deputy Director of DCPC and creator of the NCI Smoking, Tobacco, and Cancer Program, died on November 24, 1990. Dr. Cullen built a network of scientists and public health specialists to conduct intervention research and to develop programs throughout the country. He left NCI in September 1989 to head the AMC Cancer Research Center in Denver, Colorado.

Next, Dr. Broder announced awards as follows:

- Dr. Gertrude Elion was awarded the Medal of Honor of the American Cancer Society, and Dr. Walter Lawrence, Jr., was elected as vice president and president-elect of the American Cancer Society.

- Mrs. Irene Pollin received the International Psycho-Oncology Society and the European Psychosocial Oncology award from the Consortium for Consultation Liaison of Psychiatry.

- The Milken Family Medical Foundation gave basic science awards to two intramural scientists: Dr. Michael Gottesman, Chief of Molecular Cell Genetics, Division of Cancer Biology, Diagnosis and Centers, and Dr. Stuart Aaronson, Chief of the Laboratory of Cellular and Molecular Biology, Division of Cancer Etiology.

- Dr. Richard Adamson, Director of the Division of Cancer Etiology, who is also serving as Acting Deputy Director, NCI, received the Toxicology Forum Anderson Award for studies on chemical carcinogenesis and mechanisms of carcinogenesis.

- Dr. Carolyn Felix, Pediatric Branch, Division of Cancer Treatment, received a Young Investigator Award from the American Society of Pediatric Hematology-Oncology.

- Dr. Steven Rosenberg, Surgery Branch, Division of Cancer Treatment, was chosen by the American Society of Clinical Oncology (ASCO) to be the Karnofsky Awardee of 1991, and he will deliver the Karnofsky Lecture on May 20, 1991, at ASCO's annual meeting in Houston.

- Other awards from the Division of Cancer Etiology included:

  -- The NIH Merit Award given to: Dr. Joseph Bolen, Laboratory of Tumor Virus Biology; Dr. Steven Tronick, Laboratory of Cellular and Molecular Biology; Mrs. Ruth Kleinerman, Radiation Epidemiology Branch; Dr. Appasaheb Patel, Extramural Programs Branch; Mr. Dan Grauman, Biostatistics Branch; and Dr. Frank Gonzalez, Laboratory of Molecular Carcinogenesis.

  -- The PHS Commendation Medal given to: Dr. Carl Baker, Laboratory of Tumor Virus Biology; Dr. James Goedert, Environmental Epidemiology Branch; Dr. Iris Obrams, Extramural Programs Branch; Dr. Michael Alvanja, Epidemiology and Biostatistics Program; Mr. Glenn Hegameyer, Laboratory of Viral Carcinogenesis.

-- The PHS Unit Commendation award given to: Drs. John Boice and Charles Land and Ms. Rochelle Curtis and Ms. Michele Morin of the Radiation Epidemiology Branch.

Dr. Broder also reported that a President's Cancer Panel meeting was held in Bethesda on November 16, 1990. Drs. Rosenberg and Anderson addressed the Panel about gene therapy research. Another Panel meeting is planned on December 7, 1990, at the University of California at San Francisco (UCSF). Drs. Harold Varmus and Michael Bishop will host the meeting, which will include presentations on statistics and on cancer research focusing on the UCSF contributions.

To bring the Board up to date on gene therapy, Dr. Broder announced that the FDA approved the latest gene therapy protocol on November 13, 1990. This is the first trial to apply gene therapy per se to cancer. Patients in the study will receive transfusions of tumor-infiltrating lymphocytes (TILs) that have been altered by insertion of the human gene for tumor necrosis factor. Dr. Broder added this gene therapy research stands on the shoulders of years of study of the viral causes of cancer, of research into the biological response modifiers, and builds on the burgeoning area of recombinant DNA technology and other areas of biological engineering, and at least 6 years of preliminary research directed toward these specific studies.

Next, Dr. Broder stated that on November 14, 1990, Revlon and NBC hosted a luncheon to present a video film encouraging mammography entitled "Once a Year . . . for a Lifetime." Several celebrities and screen actors donated their services for the video, and Jane Pauley and Phylicia Rashad narrated the film. The NCI served as script consultants and provided information on mammography. The NCI Cancer Information Service also helped to answer telephone calls related to the video, which was released on November 16. The National Association of Broadcasters will help to make copies available as a public service to all television stations, and the NCI is answering requests from organizations that wish to use the film in their mammography screening programs. A copy was made available to members of the NCAB for their own use or to give to an organization of their choice.

Finally, Dr. Broder announced that NCI has established working groups involving the Department of Agriculture and the Department of Health and Human Services to collaborate in the development of taxol.

Turning to the budget, Dr. Broder explained that the NCI's budget in 1990 was $1.634 billion and that the 1991 budget will be approximately $1.714 billion (compared to an initial appropriation of $1.766 billion). A potential transfer of funds (i.e., ~17 million) may be implemented by the Director, NIH, to redirect funds to high-priority and emerging areas of science. This is a new authority provided in this year's Act.

Dr. Broder illustrated what the Congress specifically addressed in their deliberations:

- Over $60 million of directives were included in the House, Senate, and Conference reports. Since the increase over the President's Budget for 1991 was approximately $20 million, the NCI will do its best to follow the intent of the Congress in directing the increased funds into those areas identified.

- Very specific directives regarding Research Project Grants.

Dr. Broder provided a breakdown of the 1991 budget by mechanisms, as follows:

- Research Project Grants received among the greatest percentage increase (6.7 percent) over 1990, 17.1 percent in the competing line.

- For total Research Grants, an increase of over $57 million (6.2 percent) to a level of $987 million was provided.

- By percentage, because the base is comparatively low, construction received the highest percentage increase (35.8 percent).

- Cancer centers increased 4.6 percent.

- Other research, including research careers, cancer education, cooperative groups, and minority biomedical research, increased 3.8 percent.

For other areas, Dr. Broder reported a 4.1 percent increase for National Research Service Awards, a 1.9 percent decrease for R&D contracts, a 4 percent increase for intramural research, a 0.8 percent increase for research management and support, and a 13.6 percent increase for Cancer Prevention and Control. Thus, the total NCI budget received a 4.9 percent increase from 1990 to 1991.

In response to questions, Dr. Broder emphasized the Institute's high priorities to ensure an adequate number and resource allocation for new and competing grants. He noted that the figures shown in material provided to the Board do not show the potential 1 percent NIH-wide reduction that could be instituted.

Dr. Broder also delineated the total number of funded grants for 1990 and 1991 as 3,016 and 3,076, respectively (i.e., an increase of 2 percent); although he stated that the average length of award will drop from 4.1 to 4.0 years.

Dr. Broder then described the directives concerning grant funding included within House and Senate reports, as follows:

House and Senate:

- Average length of awards not to exceed 4 years.

- Average cost of a grant should not exceed the biomedical research inflation index.

- Total cost of grant should be considered in all phases of review.

- Study sections to decide if project merits funding based on "inherent value."

House:

- 6,000 competing grants annually.

- Arbitrary downward negotiations should be eliminated--RPGs and Centers.

- Limits number of centers to 640 across the NIH--distribution decided by NIH Director.

Dr. Durant expressed, and Dr. Broder confirmed, a concern about study sections considering indirect costs of grants, and Dr. Broder stated his feeling that the direct costs are the primary concern of study sections while the total cost of grants should be under NCI purview; NIH will publish recommendations in this regard in the near future. A draft of the recommendations was distributed to Board members.

Dr. Broder emphasized the importance of the centers program as a foundation stone of the NCI. In response to comments about the $5 million allocated for the Women's Health Trial and criticism about the amount of NCI funding for research on women's health, Dr. Broder stressed that the NCI has historically made, and will continue to make, women's health issues a high priority in Institute programs. The Women's Health Trial was discussed in detail later in the meeting (see below).

V. DIVISION OF CANCER ETIOLOGY (DCE) PROGRAM REVIEW--DR. RICHARD ADAMSON

Dr. Adamson presented a brief overview of the responsibilities, organization, and programs of the Division, referring the Board members to materials on his presentation distributed to them before the meeting. The organizational structure of the DCE, including the three major programs, and the two advisory committees to the Division (the Board of Scientific Counselors and the NCI Executive Committee) were detailed in these materials, and thus, Dr. Adamson focused his presentation on scientific highlights in each of the DCE program areas.

From the Biological Carcinogenesis Program, Dr. Adamson described the following three highlights:

- Identification of a "ZEBRA" gene-encoded protein, which acts as a switch between latency and replication of Epstein-Barr virus (EBV).

- Development of a vaccine for simian immunodeficiency virus (SIV).

- Intracellular targets of human papillomaviruses (discussed in detail by Dr. Howley; see below).

From the Chemical and Physical Carcinogenesis Program, Dr. Adamson highlighted:

- Investigations of genetic risk factors in human lung cancer that determined that rare H-*ras*-1 alleles were associated with an increased risk of lung cancer, that L-*myc* proto-oncogene polymorphisms were not associated with increased risk of metastasis or poor prognosis, and that extensive metabolizers of the anti-hypertensive drug, Debrisoquine, were at significantly greater risk for development of non-adenocarcinoma of the lung than poor metabolizers.

- The observation that antiestrogens can induce the secretion of tumor growth factor-beta (TGF-β), which may provide a mechanism independent of the estrogen receptor content of the primary tumor in the use of antiestrogens in breast cancer therapy.

- The identification of heterocyclic amines in cooked foods and their implication for human cancer (discussed in detail by Dr. Felton; see below).

From the Epidemiology and Biostatistics Program, Dr. Adamson listed:

- The nuclear facility study (discussed at the October 1-2, 1990, NCAB meeting).

- The finding that dietary factors contributed to a striking geographic variation in rates of stomach cancer in Italy.

- The study of germ line p53 mutation in a family cancer syndrome (discussed in detail by Dr. Li; see below).

Dr. Adamson also mentioned three managerial initiatives that occurred within the Division, including computer access of the central NIH financial database, centralization of DCE procurement operations, and EEO and personnel initiatives for recruitment of employees, such as targeted fellowship programs for the recruitment of women and minorities in biomedical science.

Next, Dr. Adamson outlined the DCE budgets for fiscal years 1989 and 1990. The budget increased $5.2 million (1.7 percent) from 1989 to 1990. This increase included a slight decrease in the intramural budget, a 4 percent increase in contracts and in the R01/P01 pool, and a decrease in RFAs and cooperative agreements. The only mechanism that increased in cancer dollars was the R01/P01 pool, and every

mechanism, except RFAs and cooperative agreements, increased in terms of AIDS dollars.

In reviewing the responsibilities of the DCE Board of Scientific Counselors (BSC), Dr. Adamson noted that five intramural laboratories had been site-visited by BSC during the previous fiscal year and that five others would be reviewed during the next fiscal year. Materials provided for these site visits were available for review by the NCAB members, and reports on the site visits and follow-up reviews conducted one year after each were also available for review by NCAB members.

In response to comments about the study of stomach cancer in Italy, Dr. Adamson stated that he would provide information on the incidence of stomach cancer in Seventh Day Adventists to Dr. Ralph Yodaiken of the Department of Labor.

MUTAGENS/CARCINOGENS IN COOKED FOOD: DOSIMETRY AND IMPLICATIONS FOR HUMANS--DR. JAMES FELTON

Dr. Felton, a member of the DCE BSC and a Section leader at Lawrence Livermore Laboratory in Livermore, California, reviewed studies conducted in his and other laboratories and by the Japanese of heterocyclic amines found in overcooked foods. These compounds have been found to be among the most mutagenic compounds that have ever been tested in bacteria.

The heterocyclic amines are present in parts per billion in the diet and are generated in a logarithmic fashion with cooking time and temperature. The production of the compounds appears to level off at cooking times of approximately 10 minutes per side of cooked meat. Dr. Felton noted that, because these compounds are produced from overcooking muscle products, they appear in chicken, fish, and other non-red meat products as well as red meats, but not in organ meats such as liver, kidney, or brain. One of the main reasons for this is that creatine is a major component of muscle and is one of the precursors for the production of heterocyclic amines.

Dr. Felton explained that in light of the fact that these compounds are present only in parts per billion, chemical isolation and identification have proved difficult. The Ames/*Salmonella* test was used for isolation and NMR for structural identification of these compounds, including the imidazofuropyridines.

Dr. Felton described the formation process of the heterocyclic amines, noting again the logarithmic increase in production with temperatures above 150°C (as in barbecuing, frying, and broiling, but not in boiling, most microwaving, and some baking). He stated that a precursor of these compounds, creatine or creatinine, a muscle component, is rate limiting, and that elimination of the precursors would be a major method for prevention of formation of the heterocyclic amines.

Dr. Felton stated that studies have shown that the presence of these compounds in cooked meat can be greatly reduced by microwaving the meat before using other cooking methods. For example, in one study 1.5 to 3 minutes of microwaving reduced the creatine content of meat by 40 percent, and a 30 percent loss of two of the heterocyclic amines (i.e., methyl IQx and dimethyl IQx).

In reviewing the testing of these compounds for tumorigenicity, Dr. Felton provided data from Dr. Sugimura's group showing that the compound IQ caused predominantly liver tumors, and some lung and forestomach tumors in mice, and primarily liver tumors, and some colon and clitoral tumors in rats. Another heterocyclic amine, PhIP, was not associated with liver tumors, but primarily lung tumors and lymphomas in mice, and colon and breast tumors in rats. Dr. Felton emphasized that studies to correlate the relative dosing in animals of 0.02-0.05 percent of the diet to real exposure in humans are ongoing; extrapolating the animal dosing data to the estimated human dose would result in approximately 2,000 cancer cases per million. A new instrument, an accelerator mass spectrometer, developed for biomedical applications at the Lawrence Livermore Laboratory, will be used to detect low doses of carbon 14-labeled heterocyclic amines

and their binding to DNA and tissues. Dr. Felton stated that preliminary data from such studies show a linear dose response in terms of DNA binding with levels in our diet with respect to the doses the animals received.

In addition, Dr. Felton illustrated some data from studies conducted *in vivo* as well as in culture showing that PhIP was very active in producing cytogenetic changes, such as SCEs, and chromosome aberrations. Studies are also ongoing to evaluate metabolism and tumor specificity of the heterocyclic amines in various tissues.

In conclusion, Dr. Felton stated that:

- Ten to 15 of these mutagenic compounds are present in overcooked meat products.
- Cooking moderately can reduce the mutagen yield substantially.
- Pre-microwaving for one to two minutes can reduce mutagen formation by approximately 90 percent.
- There is some effect, as yet unknown, of the consumption of well-done food in the Western diet and an increase in risk of cancer.

Dr. Felton noted, in closing, that a study of the epidemiology of how people eating a Western diet cook their foods has not been undertaken and is important in determining the level of risk of consuming foods containing these compounds.

The discussion following Dr. Felton's presentation focused on the implications of these studies for public guidance. The participants concurred that although these compounds are proven mutagens and consumption can be reduced by varying cooking methods, very little concrete public guidance can be given until the basic research is linked with epidemiologic studies.

TRANSFORMING FUNCTIONS OF HUMAN PAPILLOMAVIRUSES
--DR. PETER HOWLEY

Dr. Howley, Chief of the Laboratory of Tumor Virus Biology of DCE, discussed recent research that indicates that human papillomaviruses (HPVs) have a direct etiologic role in human cancer. He focused on the 20 of the 60 different HPVs that are associated with anogenital lesions, noting the association of these viruses with invasive carcinomas of the cervix.

Providing background to the research on HPVs, Dr. Howley stated that cervical carcinoma has long been recognized to be associated with a venereally transmitted agent. Epidemiologic studies have shown that women who have multiple sexual partners or whose partners have multiple sexual partners are at higher risk for developing cervical cancer than women who are monogamous. Dr. Howley stated that although molecular studies have failed to substantiate an association of cervical cancer prevalence with herpes simplex virus infections, a possible co-factor role for these viruses has not yet been ruled out.

Dr. Howley explained that research in the 1970s first linked the human papillomaviruses with preneoplastic cervical lesions. Subsequent studies showed that two HPVs (HPV-6 and HPV-11) that are associated with venereal warts were not associated with cervical cancer, but that DNA from two other HPV types--HPV-16 and HPV-18--as well as from a number of other HPVs could be isolated directly from carcinomas of the cervix. These "high-risk" HPVs were also found at high frequency in carcinoma *in situ* and severe cervical dysplasia.

Dr. Howley then focused on subsequent research in his and other laboratories to delineate the role of the viral gene products of the high-risk viruses, HPV-16 and HPV-18, in the carcinogenic progression. In summary, the E6 and E7 genes of these viruses are transforming genes and are expressed in cervical cancers. Studies further showed that the HPVs also contain regulatory genes, including E2, that regulate the expression of E6 and E7. Integration of the viral genomes is generally found in cervical cancer cells in a manner that disrupts the expression of the E2 genes, resulting in deregulated expression of the E6 and E7 transforming genes. In addition, the E6 and E7 oncoproteins encoded by the high-risk HPVs were shown to target important cellular regulatory proteins, including RB protein and p53, two tumor suppressor gene products, thus providing a molecular basis for the role of these viruses in human cancers with which they are associated. Complex formation between E7 and pRB is believed to knock out the normal function of this cellular regulatory protein. The association of E6 with p53 promotes its degradation.

In discussion, Dr. Howley clarified the role of these viral oncoproteins in the targeted degradation of the regulatory proteins, and noted that development of anticancer therapies could be aimed at inhibiting the E6 and E7 interactions with p53 and RB protein. He also clarified that the E7 proteins of the "low-risk" HPVs have a significantly lower affinity for complexing the pRB and that the targeted degradation of p53 appears to be a property of only the "high-risk" HPVs.

GERM LINE P53 MUTATION IN A FAMILY CANCER SYNDROME
--DR. FREDERICK LI

Dr. Li began his presentation by explaining the reasons underlying the study of cancer families: first, because inherited cancers are the most potent carcinogenic influences in humans and pose considerably higher risks than those associated with most environmental carcinogens. The second reason is that because the initial mutation in an individual in a cancer family occurs in a germinal cell and can be identified in body tissues, comparison of tumor with germ line tissue and identification of the second mutation can be done. (The second mutation is required to drive a normal cell into becoming a cancer cell, according to Knudson's two-mutation hypothesis.) Thus, studies of cancer families allow researchers to gain an understanding into mechanisms of carcinogenesis that also apply to sporadic cancers, in which the two mutations occur somatically.

Dr. Li explained that the finding of p53 mutation in a cancer family syndrome began with the observation of three members of a family who developed soft tissue sarcoma, a cancer that occurs in one per 100,000 of the general population per year. In addition, multiple family members were found to have breast and other cancers. These findings led to a study of some 700 records of children with soft tissue sarcoma which revealed many families with a striking prevalence of sarcomas and breast and other cancers. From a group of 24 families, six core components of a cancer syndrome were identified: soft tissue sarcomas, osteosarcomas, breast cancers, brain tumors, leukemia, and adrenocortical carcinoma. Other investigators, including Board member Dr. Louise Strong, reported findings of many other families with this cancer syndrome. Dr. Strong's study showed clear-cut dominant inheritance for cancers in these families, as did Dr. Li's.

Then, Dr. Li explained, a series of laboratory studies were conducted to attempt to identify the gene that was causing these cancers in these rare families, and p53 mutations were found. At that point, Dr. Li stated, these findings can be applied to the original objective of gaining understanding of sporadic cases of the cancers involved in the syndrome. Questions include: How many sporadic breast cancers, for example, might be explained by germ line p53 mutations? What is the frequency of these mutations in the general population? Might these mutations be involved in other common cancers? Collaborative studies have been initiated to pursue such questions in breast cancer, sarcoma, lung cancer, leukemia, brain tumors, colon cancer, and melanoma.

Dr. Li concluded by raising the issue of the implications of these study findings in relation to cancer control efforts. He listed some of the adverse effects and ethical considerations of screening for p53 mutations and emphasized that testing for carriers should be confined to the research setting. He urged cautious consideration of the application of these findings and that of other cancer susceptibility genes.

In discussion, it was noted that a portion of the human genome project budget is obligated to the examination of social, economic, and ethical issues, and committees have been formed to consider these issues. Mrs. Brown suggested that an update on these issues be presented at a future Board meeting.

VI. DIVISION OF CANCER PREVENTION AND CONTROL (DCPC) PROGRAM OVERVIEW--DR. PETER GREENWALD

Dr. Greenwald began with a statement in memory of Dr. Joseph Cullen, DCPC Deputy Director from 1982 to 1989. He praised Dr. Cullen's work in leading NCI's Smoking, Tobacco, and Cancer Program, which included building a program of intervention research aimed at smoking prevention or cessation, providing leadership in the development of the ASSIST concept, helping to develop the scientific basis for the prevention and control program that exists today, and influencing many scientists in choosing careers in prevention and control.

Dr. Greenwald reviewed the historical milestones in the development of the field of cancer prevention and control, concentrating on three periods: prior to 1970, the 1970s, and 1980 to the present. Milestones in the first period included 1964 Surgeon General's Report that established a consensus on the effects of smoking on health. He noted that the predecessor of DCPC, established in the 1970s, supported many community programs and saw the development of the hypothesis related to diet and cancer grow largely from the carcinogenesis and epidemiology fields. Milestones of the 1980s included (1) evolution of the old division into the current Division of Cancer Prevention and Control with Dr. Greenwald as Director; (2) establishment of the Board of Scientific Counselors; (3) the Doll and Peto study entitled "Estimates of Avoidable Risk for Cancers;" (4) development of a working definition for cancer control, which established the fact that the scientific method can be applied to cancer control and defined a set of phases to bridge basic cancer control research to application; (5) development of the Smoking, Tobacco, and Cancer Program, which sponsored about 60 large-scale trials involving millions of Americans; (6) development of the Diet, Nutrition, and Cancer Program, which featured intervention trials based on preclinical research into the biology of nutrition, surveillance of new food products that could have implications for cancer risk, and dissemination of dietary guidance consistent with the advice coming from other components of the Department of Health and Human Services (DHHS) and from the U.S. Department of Agriculture (USDA), (7) development of the Chemoprevention Program with its focuses on the tamoxifen breast cancer prevention trail, research grants, Cancer Prevention Research Units, and the Community Clinical Oncology Program (CCOP); and (8) an intramural program that emphasizes training for cancer control scientists of the future through the Cancer Prevention Fellows and Summer Science Enrichment Programs.

Dr. Greenwald noted that in 1986 NCI published goals for the year 2000 of 25 percent to 50 percent reduction in cancer incidence. He said the intent was to link the percentage of change to the level of effort related to smoking cessation or reduction, diet change, increased screening, and adoption of state-of-the-art technology in prevention and control. He added that the 1990 mortality data will be available late in 1992 and will be reviewed again in relation to the goals.

Dr. Greenwald listed other programs developed by DCPC or in collaboration with other NCI components or extramural agencies: (1) Comprehensive Minority Biomedical Program (DEA), (2) Cancer Prevention Awareness Program (OCC), (3) primary prevention and avoidable mortality projects, (4) cancer control networks for Black, Hispanic, and Native American populations, (5) an initiative to help build the cancer control capability of public health agencies through 34 awards to 28 states and the District of Columbia; and (6) the Surveillance and Annual Statistics Program.

Dr. Greenwald briefly reviewed the organization of the program, noted that the programs include both intramural (e.g., Laboratory of Nutrition and Molecular Regulation) and extramural (e.g., Early Detection Program, CCOP) components that are related to cancer and chemoprevention, prevention and control in special populations, biomarker and prevention research, public health and other control initiatives, smoking, and surveillance.

Dr. Greenwald reported that in 1990 about $75 million of the $150 million DCPC budget was in the cancer control project budget line and was distributed across the various programs, with the largest proportion in CCOP, smoking, and chemoprevention. He pointed out that approximately 7 percent of NCI's R01/P01 pool is the non-prevention and control half of the budget, and that the major expenditure in the contract line is for the SEER Program.

Noting that DCPC would receive new funding in the new fiscal year, Dr. Greenwald presented a list of DCPC priorities and estimates of the amounts to be allocated to each: (1) expand the chemoprevention effort--$1 million; (2) fund the tamoxifen breast cancer prevention trial through CCOP by adding $2.5 million to that program's budget; (3) expand smoking prevention through the ASSIST program--$2 to $3 million; (4) initiate the Women's Health Trial--$2.5 million; (5) initiate (in fiscal year 1992) a prostate, lung, colon, and ovarian cancer early detection trial; and (6) build up the intramural program in the area of biomarker research, which would be important for prevention as well as early detection. Dr. Greenwald emphasized that the figures are estimates and would vary according to the outcome of BSC concept reviews and technical reviews of the proposed projects. He also pointed out that three of the projects--the ASSIST program, Women's Health Trial, and early detection trial--could have very large outyear commitments for the prevention and control budget. He said information would be forthcoming from the early phases of the three projects that could be evaluated by the BSC and used as a basis for further prioritization of funds.

BOARD OF SCIENTIFIC COUNSELORS ACTIONS (FY90)--DR. EDWARD BRESNICK, CHAIRPERSON

Dr. Bresnick referred NCAB members to the material in the meeting book relating to the organization, functions, and actions of the DCPC BSC. He reviewed the composition of the current Board pointing out the broad scope of expertise and major areas of interest represented by the members. In reviewing the major functions of the BSC, Dr. Bresnick noted that the annual review of budgets and programs this year will include an attempt to develop a mechanism to assist the Division in establishing priorities for allocating funds in times of fiscal constraint. He highlighted the following: (1) many of the concepts approved by the Board in the past fiscal year involved other NCI divisions, other Institutes, and extramural institutions; (2) the Board, in approving some concepts, is attempting to stimulate research into the development of more precise methods for assessing adherence to dietary manipulations, and (3) NHLBI and DCPC are collaborating on a clinical trial to assess the effects of a fat-modified diet on hormones during adolescence.

Dr. Bresnick concluded with a brief review of three site visits of intramural programs and three workshops conducted by the BSC during the year. The workshops were convened on the following topics: (1) dietary intervention among women, (2) research designs for studying the health consequences of dietary modification among women, and (3) CCOP and chemoprevention trials to determine whether CCOP could be used as part of the mechanism for conducting chemoprevention trials.

PUBLIC HEALTH SMOKING PREVENTION--DRS. KATHERINE MARCONI AND JEFF McKENNA

Dr. Marconi announced that television commercials developed by the states of Minnesota, Michigan, and California, recipients of the first NCI public health initiative grants, would be aired for NCAB members to illustrate some of the potential and possibilities for public health initiatives in cancer prevention and control. She noted that the rationale for working through public health agencies includes their ability to

access populations at high risk for cancer, set regulations and policies, increase state and local resources, coalesce and convene state and local organizations, and improve the delivery of prevention and control services. Impediments to the effective use of this potential have been the lack of resources, expertise, and intervention models.

Dr. Marconi explained that while the NCI public health initiative grants did not pay for the videos or smoking prevention campaigns developed by Minnesota, Michigan, and California, they enabled those states to plan, acquire state resources, and train staff in cancer prevention and control. She pointed out that the states with cancer plans and funding to implement them are those with NCI technical capacity building or data-based intervention grants. Currently 28 states and the District of Columbia and Los Angeles County have NCI planning and intervention grants, and plans are underway to fund the ASSIST program in another 15 or 20 states, with the goal of building the cancer control capacity of every state and major local health agency. Dr. Marconi stressed the need to apply intervention strategies developed by NCI's intramural and extramural researchers in these public health settings if the objectives for the year 2000 are to be realized.

Dr. Marconi noted that the smoking campaigns in Minnesota, Michigan, and California were developed with state funds and are part of larger public health initiatives and that coalitions involving NCAB members have advised the states on how to plan, implement, and evaluate the initiatives. She introduced Dr. Jeff McKenna of the Office of Cancer Communications to describe strategies devised to market the commercials produced for the antismoking campaigns in Minnesota, Michigan, and California.

Dr. McKenna noted that because of increasing competition (from AIDS and drug abuse campaigns) for a diminishing amount of free time for public service announcements (PSAs), the three states bought media time, financing their projects as follows: Minnesota, one-fourth of a cent per pack tax on cigarettes; Michigan, tax on computer software; California, 25 cent per pack tax on cigarettes. Before showing the videos, Dr. McKenna provided additional information as follows: (1) Minnesota and Michigan spent about $1 million on their campaigns, whereas California will spend about $28 million to produce commercials and buy time on television, radio, and billboards; (2) the commercials target a number of different audiences with special focus on women, youth, and ethnic minorities; (3) the commercials focus on the social aspects of smoking and health issues such as passive smoking, smoking during pregnancy, and tobacco addiction; (4) advocacy spots--direct attacks on marketing practices of tobacco companies--are made possible by the paid-advertising approach. Dr. McKenna noted that NCI is exploring, with the Office on Smoking and Health, ways to make these commercials available nationwide.

In response to a request from Dr. Korn for a review of budget outlays for smoking control prevention, Dr. Greenwald reported that: (1) DCPC allocates about $19 million to smoking prevention and cessation and sponsors about 27 trials related to intervention; (2) a community intervention trial called COMIT is in progress and will be evaluated over the next few years; (3) the ASSIST program planned for the 1990s is expected to reach as many as 50 million people; and (4) the public health agency initiative is part of the total effort.

Before beginning the discussion of the Women's Health Trial, Dr. Greenwald introduced Dr. John Bailar, Science Advisor, Office of Disease Prevention and Health Promotion, to report on a workshop sponsored jointly by NCI and NHLBI on July 9-10. The objective of the workshop, chaired by Dr. Byron W. Brown of Stanford University, was to assist NCI and NHLBI in assessing the options for a study on the impact of dietary change on cancer and cardiovascular disease incidence and mortality rates.

WORKSHOP: RESEARCH DESIGNS FOR STUDYING HEALTH CONSEQUENCES OF DIETARY MODIFICATION--DR. JOHN BAILAR

By way of background, Dr. Bailar presented a summary of the 15-year trends in the rates of cancer incidence and mortality, which indicated that breast cancer incidence is increasing at a 1.7 percent rate per

year and breast cancer mortality has shown virtually no change. He suggested that the proposed Women's Health Trial be viewed against that background and stated that workshop participants discussed three issues in detail: (1) the strengths and weaknesses of the research designs that might be considered for examining the impact of dietary changes, (2) the feasibility of actually accomplishing changes, and (3) aspects of research designs that would ensure that research results could be extended to major population subgroups. Dr. Bailar listed the general recommendations included in the workshop consensus report: (1) that NCI and NHLBI support in some way a substantial program of research on the possible effects of diet on disease incidence and mortality, including basic, metabolic, clinical, and epidemiological research; and (2) that the two Institutes reconsider the need for a major long-term controlled field trial of effects of a reduced fat diet on human health, which trial might possibly serve as the central enterprise of this research program. The remaining recommendations dealt with the design of such a trial.

WOMEN'S HEALTH TRIAL--DR. GREENWALD

Dr. Greenwald presented a description of a new Women's Health Trial concept that was approved in October 1990 by the Division of Cancer Prevention and Control (DCPC) Board of Scientific Counselors (BSC). The proposed project is a randomized intervention trial of the impact of dietary modification on the incidence of cancer among women, particularly the combined incidence of breast and colorectal cancer. The main focus of the diet would include cutting the percent of fat in the diet roughly in half, to 20 percent of calories, and an increase in vegetables, fruits, and whole grains.

The proposed design of the study is a multi-institutional, randomized controlled trial with an intervention-to-control ratio of 2 to 3. The sample would be 24,000 women. There would be 12 clinical units, each of which would be expected to randomize at least 2,000 women. The duration of the study would be 15 years, with an average of 11.5 years of follow-up, which is a constraint based on the Executive Committee's standard of not having total dollars of more than 10 million in any one year. Derived from that are the calculations that indicate the sample size and the follow-up needed to achieve a statistical power, which would detect a 17 percent reduction of breast cancer alone with a probability of .81, and a 17 percent reduction of breast cancer and colorectal cancer combined with a probability of .94.

Eligibility criteria would include women ages 50 to 69 with a baseline percentage of dietary fat at 38 percent or more of total calories. Subjects would have to be able to comply with the protocol, which must be appropriate for the major population subgroups; there must also be minority representation.

Study endpoints would be histologically diagnosed breast cancer and colorectal cancer; the trial would also track other cancers. Based on planned collaboration with the National Heart, Lung, and Blood Institute (NHLBI), the study would also include heart disease endpoints and cause of death. Interventions would be developed and tested related to low educational level, low socioeconomic status, and minority populations. The Division has not given up on the idea of continuing to make an effort related to biomarker study options.

According to Dr. Greenwald, the most appropriate mechanism through which to fund the project would be a contract within the prevention and control budget. This is the most suitable mechanism for a collaborative effort with the NHLBI, and it gives the Institute a strong management capability in terms of cost control. Initial peer review would be managed by the Division of Extramural Activities, resulting in awards for a statistical and nutrition coordinating center, for nutrition coding, and for the clinical units.

In the first year, the NCI, working jointly with the NHLBI, would establish a Women's Health Trial Policy Board that would link to the DCPC Board of Scientific Counselors to provide oversight. This first phase of the project would include documentation of cost efficiency. Four requests for proposals (RFPs) would be issued in this initial phase. One would be for a coordinating center to develop, with the DCPC and the NHLBI, a protocol that would integrate cancer and heart endpoints.

An important question to be answered and brought back to the Board before moving ahead would be whether people were accruing to the study and were able to give full and accurate information. Other questions are whether Black, Hispanic, and other population groups were able to adopt the diet, and whether those groups could comply and maintain the diet.

The next step would be issuance of an RFP for clinical units. One would be located at the coordinating center, and one each in predominantly Black and predominantly Hispanic population groups that also have some low education or low income groups. Before going further with the study, Dr. Greenwald stated, the DCPC needs to know what populations are eligible for recruitment, and needs to know the sampling fractions. It is possible that the study would have to screen through larger numbers, at higher costs, to be effective for subset analysis of the study's target populations. This information is needed in order to determine if the study will be within budget restrictions.

Another issue Dr. Greenwald alluded to is the HHS/USDA Dietary Guidelines. The most recent revision of these guidelines, for the first time, contains a recommendation on dietary fat, advising the public to reduce fat to less than 30 percent of calories. An important ethical question is raised by this recommendation concerning the control group in a trial like the one proposed. Initial discussions have suggested that a reasonable and ethical approach to the controls would be to do a "one shot" meaningful effort, providing them with information on what is available in the community and offering information on the significance of lowered fat intake and the benefits of a balanced diet.

Dr. Greenwald invited comments and suggestions. In response to a question on whether the hypothesis for this study is the same as that of the Division's previous study, based on the assumption of a linear relationship, in the same age group, between reduced fat intake and cancer incidence, Dr. Greenwald stated that the hypothesis is basically the same, with a broadened intervention based on more fruits, vegetables, and whole grains, as well as cutting down on fat.

When asked whether the need to develop biomedical and biochemical markers, discussed at the DCPC Board of Scientific Counselors meeting in May, was still a concern, Dr. Greenwald replied that everyone agreed that the availability of biomarkers of exposure and of endpoints would collapse the time required for the trial. However, he noted that there are no assurances that such biomarkers will be available within the next few years. He argued that this is an important hypothesis that needs to be tested now, but that there is a need for aggressive research on biomarkers.

In response to a question for clarification about the tenure of the study, Dr. Greenwald explained that the proposed 15-year study included a fairly long period of accrual, a period when subjects are on the diet, and an analytic period, with an average duration of 11.5 years for follow-up observation.

In response to a question on the willingness of the NHLBI to support the project, Dr. Harlan replied that the NHLBI Advisory Council would act on the proposal in February, and that a budget has been put together for a parallel RFP for risk factor evaluation and endpoint evaluation. This budget covers about one quarter of this phase of the trial. The NHLBI would work with the NCI on all aspects of the monitoring of the trial and the diet. Dr. Greenwald added that, depending on the recommendation of their advisory council, the NHLBI might be expected to contribute $25 to 30 million over the 10-year course of the study to cover specific aspects relating to heart disease endpoints.

To a question on how the study would handle drift in the diet and control groups, Dr. Greenwald stated that there would be stop rules and that this would be specifically monitored. He added that current information on dietary fat intake among population subgroups is inadequate, but it is suspected that women with higher educational levels have had the largest reductions in fat intake. This could have an impact on this trial, and would be examined during the first phase of the project.

He speculated that if, in response to public education, women reduced their fat intake to 32 or 33 percent of calories, then the trial would not be interpretable. It would probably have to be converted to a cohort study at a much reduced cost. Over the first year, the project would have to work out what the stop rules would be; the first group in the initial phase is a vanguard group for looking at this.

Dr. Bettinghaus expressed concern about the ability of this group to keep adequate dietary records. Based on the length of the trial, he said that the issue was not the ability of 69-year-old-women to keep adequate records, but that of 83-year-old-women. He said that he knew of no work that has been done on older population groups in this regard, and that evidence is needed on what happens when individuals try to keep dietary records over time.

Mrs. Brown expressed concern over committing the estimated $106 million for the duration of the proposed trial, both given the competing needs for other types of studies and potential problems that might prevent the trial from producing reliable information. She asked for clarification of what was being proposed by the NCI for the first phase of the trial. Dr. Greenwald stated that $2.5 million per year was the NCI's estimated cost for a first phase of three years; he suggested that the DCPC Board of Scientific Counselors should look at the status of the project after two years, so that if the decision were made to implement the full trial, the efforts that were in place could continue without interruption. He explained that the Division expected to spend up to but no more than $10 million in any given year during the trial, and that the expenditure for this first phase was intended to be proportional, and could be scaled up if the groups involved in the initial phase demonstrated that the full study is do-able within budget constraints.

Dr. Strong asked whether this study would duplicate previous studies funded by the Institute. Dr. Greenwald replied that the previous studies were designed primarily for women with higher levels of education. Dr. Strong continued by expressing concern, in the absence of a biomarker, that significant shifts in diet, including shifts among minority populations, are likely to occur as a result of HHS directives and other kinds of public health initiatives. She observed that there is no reason to expect that in 15 years the population is still going to be at the level of 38 percent of calories from fat. She stated her concern, because of these factors, not only about the feasibility of the project but also about ethical considerations, since the success of the trial would depend on the control group not following dietary guidelines, and underlined the importance of an early review of the project.

In clarifying questions about activities planned for the first phase of the trial, Dr. Greenwald explained that randomization would begin during this phase in three of the anticipated 12 clinical units. This would be seen as a vanguard group to show that subjects could be accrued on schedule in adequate numbers to do an effective trial and that these individuals can get to 20 percent of calories from fat, while allowing for some downward drift in the control group to 35 percent. He clarified that the intent is not to maintain the control group at a high level of fat intake, but rather to provide them with guidance and to let them be exposed to what the general population is exposed to.

Dr. Korn noted that more information would be needed on the sensitivity of statistical analysis, given the likelihood of significant drift in the control population over the course of the trial, and given what will probably be an extraordinary amount of public pressure on the issue.

When asked to comment on the amount of time that was required to accrue women into the previous women's health trial, Dr. Greenwald acknowledged that some of the clinical centers were slow, and asked Dr. Clifford to comment. She reported that three centers recruited 303 women during a seven-month feasibility study and a total of 1,672 women after an additional 12-month period. There were variable rates among the centers.

Dr. Strong added a concern that the age distribution and competing other diseases could make it difficult for these women to comply with the diet.

When asked what he thought the Institute would know at the end of the feasibility study, Dr. Greenwald replied that the primary question that would be investigated is how to intervene effectively with minority populations, those with low educational levels, and perhaps also the elderly. Something that might also be linked to this information is lipid measurements in those population groups.

Dr. Greenwald deferred to Dr. Harlan on the question of endpoints of interest to the NHLBI. He stated that a trial of this size would not have the power to examine coronary heart disease as a primary endpoint, but would provide useful information on the effect of this diet on heart disease as a combined endpoint with, for example, breast cancer and mortality. The NHLBI would fund a separate coordinating center which would share information with the overall coordinating center for the study. The costs for the NHLBI activities would be in addition to those presented by Dr. Greenwald for the NCI.

In response to a question on types of monitoring that would be in place, Dr. Greenwald explained that monitoring within the trial would measure disease occurrence with histological endpoints, in conjunction with surveillance efforts independent of the trial. Information on population trends in diet, for example, are available from the National Center for Health Statistics, as well as some data from the Department of Agriculture. This is tracked and related to cancer incidence through the SEER Cancer Registry Program. It is anticipated that this will be done more explicitly in certain subgroups of the population.

Asked about evaluations of the people entering the study, Dr. Greenwald explained that in the previous study, subjects received a dietary questionnaire but no physical exam. There was a waiting period of two years in which diagnoses of cancer were not included in the study, based on the premise that the cancers were already present.

Dr. Bresnick offered some points on the discussion of this proposal by the Board of Scientific Counselors. He noted that the BSC had approved of the study as being conducted in phases with checks and balances. Although not specifically spelled out, it was perceived that after the second or third year, the Institute would know whether it could go on with subsequent phases of the study. He expressed confidence that available tools are sufficient, in the absence of a biomarker, to establish the nutritional status of individuals in the study; that the study design would not be compromised by drift in dietary fat intake; and that there would be sufficient statistical power to address the questions proposed in the study outline. Dr. Bresnick emphasized the importance of extending all trials of this type to include lower socioeconomic groups; he stressed the belief of the BSC that this was the best possible plan for a nutritional intervention life study involving fat and breast cancer, and argued that it should not be postponed.

Dr. Bettinghaus raised two issues: the status of women on estrogen therapy; and the design issue concerning whether Hispanic women, Black women, and low socioeconomic status women should be dealt with as a separate variable or thrown together into the larger design. In response to the latter issue, Dr. Greenwald said that it has to be analyzed as one group. Dr. Bettinghaus acknowledged that there could probably not be an independent analysis, but expressed concern that there are trade-offs in terms of power because of this, and noted that he had not seen any reworked analysis taking this into account. Dr. Greenwald replied that unless data are in hand, such an analysis would be hypothetical; one reason for the first phase, he continued, is to look at sampling fractions needed for the different groups in order to have an efficient design.

During a renewed discussion of the details of the proposed plan for the study, Dr. Greenwald clarified that the 3-year initial phase of the study would undergo a stringent review, but that it was envisioned as the first phase of a trial and not as a pilot study. The study would stay within the $2.5 million per year requested for the first three years; the project would be competitive, but the funds would come out of the cancer control budget, not the R01 pool, since it would be a contract.

Dr. Chabner returned to the issue of drift among the controls. He noted that in any clinical trial one compares a new with a standard treatment, and that in this case the study would have an obligation to attempt to reduce the control group's calories from fat to a level of 30 percent, which is the Government's recommendation for a healthy diet. Dr. Greenwald observed that if the study were required to maintain the control group at 30 percent it probably would not be feasible to conduct a trial with statistical significance.

Dr. Wells observed that there were many concerns and loose ends and that a number of Board members were still uncomfortable about the proposal. Based on a concern that after three years in which patients have already been entered into the trial the project would be difficult to stop, he asked whether Dr. Greenwald could bring the proposal back to the Board at the February 1991 meeting with a more detailed presentation on the study design. Dr. Mihich suggested that the Board discuss a motion on the limitations of what it would consider at this stage.

Dr. Bettinghaus argued that the plan presented by Dr. Greenwald was intended to provide what the Board was asking for while salvaging the people involved in the initial phase for the later trial. He expressed the opinion that at the end of three years the project probably would in fact be ended because of the difficulty of getting dietary compliance from the target group, but that the feasibility study is worthwhile to learn as much as possible.

Dr. Korn suggested that the Board request a detailed presentation in February on the implementation of the first three-year phase of the trial, with as much refinement of the issues as can be done in the interval, perhaps with further clarification from the NHLBI.

Mrs. Brown said that the items Dr. Greenwald had described as part of the first phase of the proposed trial would provide a great deal of information about working with minority populations. She moved that the NCAB express to the Board of Scientific Counselors its willingness to support the three-year phase of the study, not to exceed $7.5 million, and that the NCAB also take measures to assure itself that the full trial as approved by the BSC will not be undertaken until a report on the first phase comes back. Dr. Mihich seconded this motion.

Dr. Strong asked to clarify the motion by stating that the first phase be separated from the trial in the nomenclature, so that if the widespread trial is not conducted, the three-year study will have accomplished something on its own.

Dr. Durant said that he was still not resolved about the ethical issues. A discussion followed concerning the treatment of the control group, and the issue of whether the trial would be valid if the control reached a level of 30 percent of calories from fat. Dr. Greenwald explained that the design starts out with an 18 percent differential, 38 percent versus 20 percent. He said that the power design allows for a collapse of that differential to 9 points, so that if the controls reached a level of 30 percent and the subjects reached 20 percent, the effect of the intervention could still be detected.

Mrs. Brown repeated that a motion had been made and seconded to approve a feasibility study to establish a policy board with the NHLBI, issue an RFP to establish a coordinating center to develop a protocol, issue RFPs for three clinical units, continue studies on biomarkers, and document the cost of doing a complete trial; the feasibility study would be approved at a limit of $7.5 million. The motion passed with none opposed and one abstention.

CHEMOPREVENTION IN MEDICAL SETTINGS--DR. BARNETT S. KRAMER

Continuing with the DCPC program review, Dr. Kramer briefly reviewed the importance of prevention through vaccination and chemoprevention in the field of infectious diseases. While progress in chronic diseases has been slower, the science and practice of cancer prevention has been advancing. He introduced

Dr. Waun K. Hong from the University of Texas M.D. Anderson Hospital Cancer Center, whom he described as a major figure in the emerging science of preventive oncology, to present an overview of the field. He noted that Dr. Hong would review clinical studies of chemoprevention, the biology of malignant progression of epithelial cancers in the aerodigestive tract, the biology of the retinoid receptor, and future directions in the field.

PREVENTION OF SECOND PRIMARY TUMORS WITH ISOTRETINOIN IN SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK--DR. WAUN K. HONG

Dr. Hong stated that epithelial cancer in the aerodigestive tract is a significant public health problem, ranking as a major cause of death among cancers and exhibiting no decrease in incidence. He pointed out that there has been only minimum progress in treating lung, head and neck, and esophageal cancer and that second primary cancer is becoming increasingly common. The median survival, after the development of a second cancer, is less than a year. He stated that chemoprevention has the potential to reduce the morbidity and mortality of these diseases and noted that M.D. Anderson Cancer Center has studied the use of retinoids in oral premalignancy and the prevention of second tumors. Before reviewing these studies, Dr. Hong described the multistep process of tumor formation in the aerodigestive tract, pointing out the strong relationship between the premalignant foci and the second malignant tumor. He noted that although the primary tumor can be cured, the epithelium was condemned and can manifest second and third cancers as time goes on, which can occur in the aerodigestive tract and can be accelerated with further exposure to carcinogens.

Noting that retinoids are well known as effective agents in the control of differentiation and the growth of epithelial tissue, Dr. Hong stated that his study was designed to test the role of retinoids in suppressing and reversing the expression of oral premalignancy. Patients were randomized to treatment with 13-*cis*-retinoic acid (13-CRA) or placebo for 3 months and followed for 6 months after treatment; biopsies were performed and lesions measured at baseline and at 3 months. Dr. Hong summarized the results: 67 percent of the patients on the 13-CRA arm achieved either complete or partial response; dysplasia was reversed to hyperplasia or normal epithelium in 54 percent of those patients. He gave the example of one patient whose lesion disappeared during treatment but progressed afterwards, suggesting the need for long-term treatment. Dr. Hong concluded that data from this study, which was published in the December 1986 issue of the *New England Journal of Medicine*, demonstrated the efficacy of retinoids in treating premalignancies. He noted that the trial had been replicated worldwide (using either *trans*-retinoic acid or 13-CRA) with similar results.

Dr. Hong said the second trial was designed to take advantage of retinoids' demonstrated efficacy in suppressing premalignant lesions in the aerodigestive tract for the prevention of cancer. Patients, including about half in stages III and IV, were randomized after treatment of the primary tumor to either high-dose 13-CRA or placebo. Of 103 patients enrolled, 3 were ineligible, 100 were evaluable for survival and relapse, and 97 were evaluable for toxicity. Patterns of relapse were monitored. There were no significant differences between the two groups in the number of local, regional, or distant recurrences of primary cancers. However, patients on the 13-CRA arm developed fewer second primary tumors compared with the placebo group (P value, 0.005), and four patients in the control group developed multiple second primaries. Dr. Hong noted that doses were lowered after the initial high doses caused unacceptable toxicity. One-third of the patients in the 13-CRA group did not complete the 12-month course of treatment because of toxicity. Conclusions reached were that retinoic acid reduced the incidence of second primary cancers and increased the time to occurrence of the second cancer. The 100 mg/m^2 dose used for the study was found to be unsuitable for long-term assessment because of its toxicity. This study was published in the September 1990 issue of the *New England Journal of Medicine*. Dr. Hong expressed the opinion that this finding opens up new avenues for study and noted the need for a more definitive study before the results can be accepted into clinical practice.

Dr. Hong listed future investigations planned at M.D. Anderson as follows: (1) a definitive study of retinoic acid as preventive therapy, including only patients in Stages I and II and ascertaining the most tolerable and effective dose that will permit long-term treatment; (2) studies with other relatively nontoxic compounds, especially beta carotene and retinol; (3) basic science studies, especially testing the "field cancerization" hypotheses and molecular determinant of growth and differentiation of epithelial tissues; and (4) a study of the relationship between the expression of nuclear retinoic acid receptors and responses to retinoic acid.

THE COMMUNITY CLINICAL ONCOLOGY PROGRAM (CCOP) AND THE BREAST CANCER TAMOXIFEN TRIAL--DRS. LESLIE FORD AND ARNOLD KALUZNY

Dr. Kramer explained that CCOP provides a mechanism to apply cancer prevention and control measures at the community level, as well as to identify new interventions through clinical trials. He introduced Dr. Ford, Chief of the Community Oncology and Rehabilitation Branch, to present an overview of CCOP history and plans for the future, which include the tamoxifen trial.

Dr. Ford reviewed the purpose of the program, namely, to develop a mechanism to involve community physicians in clinical research and thereby increase accrual to clinical trials, diffuse state-of-the-art cancer management into the community where a majority of cancer patients are being seen, and establish a network for prevention and control research. CCOP links community-based physicians with clinical cooperative groups and Cancer Centers (as research bases) for participation in NCI-approved research. The first CCOP RFA was funded in 1983 with the express purpose of organizing oncologists to participate in treatment clinical trials; the RFA issued in 1987 added prevention and control trials to the requirements, with the concomitant need for incorporating experts (e.g., Dr. Hong) in the design of prevention studies for multi-institutional settings. Organizational relationships in this complex program include NCI as providing overall direction, project management, and funding; the individual community programs accruing patients to protocols, managing data, ensuring quality control, and forwarding data to the research bases; and the research bases developing protocols for data management and quality assurance. Dr. Ford added that the CCOP budget also provides for university members and outreach affiliates of the cooperative groups and centers to accrue patients to prevention and control studies. Another highlight of the program was the funding of minority-based COOPs in June 1990, creating the potential to increase minority accrual to clinical trials. Currently, NCI funds 63 CCOPs (12 minority-based) representing 300 hospitals, 1,500 physicians accruing to trials, and 1,000 support physicians. The cancer control network, which includes members and affiliates of cooperative groups, covers the entire country. Successes include increases in the number of accruals to treatment clinical and Phase III trials coming from CCOP, protocol development for cancer control research, and significant contributions to continuing care and rehabilitation research.

Dr. Ford listed as other activities of CCOPs the four chemoprevention studies (folic acid for cervical cancer, 13-CRA for head and neck second primaries, DFMO for superficially invasive bladder cancer, and alpha tocopherol for oral leukoplakia) and a number of screening and early detection studies involving family members at high risk for cancer. She pointed out that the evolution of chemoprevention studies has created the need for re-education in issues of INDs, drug distribution, and different methods for monitoring toxicity as well as the need to recruit more primary care physicians and surgeons who see patients before they become cancer patients.

Dr. Ford reported that, at the time of its last request to the BSC for continuation of the program, DCPC proposed an expansion of the cancer control research effort to utilize the CCOP network for DCPC high-priority research, and it is under this rubric that the tamoxifen trial is being conducted. She noted that two proposals have been received and will be subjected to peer review. The study design includes accrual of 16,000 women defined as high risk by age, family history, and personal history; treatment with 20 mg/day of tamoxifen versus a placebo for a 5-year treatment period; endpoints include incidence of breast cancer, total mortality, and cancer and cardiovascular mortality. Ancillary studies will depend on the availability of

funding and the interest of other Institutes but will include monitoring for other cancers and measuring lipids and lipoproteins (in collaboration with NHLBI), at a minimum.

Dr. Ford then introduced Dr. Arnold Kaluzny, Professor of Health Policy Administration at the University of North Carolina, who discussed evaluation of the CCOP programs, the emerging role of CCOPs, some of the challenges CCOPs face in the communities, and implications of the data in relation to the communities.

Dr. Kaluzny listed the focuses of the evaluation as follows: level of implementation and extent to which the program is complying with the RFA, impact on practice patterns of physicians within the surrounding communities, and characteristics of this unique organizational form.
He noted that a complicated evaluation design has been developed to accommodate a variety of data sources (e.g., annual reports of all components, a physicians survey, case studies on 20 CCOPs, data from SEER). Dr. Kaluzny highlighted the following observations made as the evaluation has progressed: (1) there is an interaction effect evolving between the CCOPs and research bases in terms of patient flow, information, money, and mutual recognition; (2) the various research bases have developed different strategies for integrating the CCOPs into their ongoing research base as well as different strategies for incorporating cancer control into their repertoire of activities; and (3) a sense of commitment is pervasive and has become a management tool. Values that can be measured will be changing practice patterns, recognition of the CCOPs physicians as *the* cancer doctors in the communities, changing patterns of referral among non-CCOP physicians, and the extent of collaboration that exists between CCOPs and the oncology departments of the local hospitals. Dr. Kaluzny concluded this part of his presentation by reading a statement from the evaluation group's chairperson attesting to the success of the technology transfer aspects of the program.

Dr. Kaluzny stated that the challenges facing the program and the emerging role of the CCOPs are the need to involve many new disciplines and community-based organizations in the cancer control and treatment activities and the need to design protocols that are relevant to the unique characteristics of patients and providers in these local communities, particularly by the minority CCOPs. He stated that an array of opportunities can be identified for building on the infrastructure that the CCOP program has made available, including the tamoxifen trial, DCPC's new rural health initiative, proposals to use the CCOP structure as an intermediary organization to increase utilization and awareness of PDQ, models for AIDS treatment testing and clinical trials.

In response to a question about the extent to which CCOPs can be implemented in this country, Dr. Kaluzny stated that one function of the evaluation will be to identify those environments in which CCOPs will be an optimal organizational structure. He estimated that the report on the evaluation would be ready early in the new year.

VII. SUBCOMMITTEE ON INFORMATION AND CANCER CONTROL FOR THE YEAR 2000--MRS. HELENE BROWN, CHAIRPERSON

Mrs. Brown introduced discussion of the draft NCI response to the Office of Technology Assessment (OTA) report, *Unconventional Cancer Treatments.* She noted that Dr. Michael Hawkins of CTEP, DCT, Ms. Dorothy Tisevich of the Legislative Office, Office of the Director, and Dr. Judy Karp had prepared the initial work for the document, and she expressed the Subcommittee's gratitude.

Responding to a question, Mrs. Brown reported that the NCI response would be sent directly to OTA. There will not be a press release. Dr. Broder noted that the report attempts to make clear that NCI is prepared to accept ideas from any source and review them for scientific validity, as it has done for many of the treatments now in use; however, unconventional treatments would be held to the same scientific standards and would compete for funds on equal terms with other NCI research proposals. He pointed out that while it sometimes may be difficult to develop technology for a new drug or therapy, it is usually easy to

document whether tumors will respond to it.

Mrs. Brown noted that specific editorial and technical comments would be solicited from Board members for the final document. A motion was made and seconded to endorse the draft NCI response to OTA's *Unconventional Cancer Treatments* report. The motion was passed unanimously.

VIII. STATUS OF RESEARCH SUPPORT AND TRAINING FOR INNOVATIVE CLINICAL INVESTIGATIONS--DRS. BRIAN KIMES AND MICHAEL FRIEDMAN

Dr. Kimes began his presentation on the current shortage of new M.D.'s pursuing careers in clinical oncology research by noting that, while fewer M.D.'s are pursuing research careers in general, there is a strong perception in the biomedical research community that careers in clinical oncology research, in particular, are not viable. Dr. Kimes urged the importance of erasing this perception and remedying the shortage as soon as possible. He pointed out that clinical oncology in this context includes all of its subdivisions, including surgical oncology, medical oncology, radiological oncology, and pediatric oncology.

Dr. Kimes gave information on four reports detailing the problems of training and sustaining physician-scientists.

- In 1989, Dr. James Wyngaarden appointed a number of task forces within NIH to review the biomedical research training programs. Two of the task forces that focused on training in clinical trial design and methodology, biostatistics, epidemiology, and demography concluded that NIH should focus on early recruitment of physician trainees at the predoctoral level, and develop better and more individualized training programs that integrate postdoctoral research training with clinical certification requirements.

- Dr. Jay Freireich conducted a survey of 20 training programs in medical oncology around the country, based mostly at comprehensive cancer centers and responsible for training 29 percent of all medical oncology trainees in the United States. Respondents included training directors, research program leaders, midlevel and junior faculty, and fellows in the training programs. The results of the survey indicated a pervasive perception of a decline both in the number and the quality of individuals being attracted to clinical oncology training programs, especially where patient care is an integral part of the research. Many respondents expressed the perception that clinical oncology research has little chance of getting funded through the NIH peer review system.

- In September 1990, the Institute of Medicine released a report on the funding of health sciences research. The report recommends assessment of the number of physician-investigators active and in training. If a real decline in number exists, the report recommends reallocating resources to create a more formal system and curriculum requirements for training. In addition, experimental federally funded training programs in clinical and public health research should be established.

- Also in September 1990, a joint DCBDC-DCT workshop was conducted to define clinical oncology research, review the reports and assess problems in clinical oncology research and the adequacy of training environments and funding mechanisms, and identify possible solutions. Participants included many of the cancer center directors and others involved in training issues. While the workshop definition of clinical oncology was not universally agreed upon, a majority of participants endorsed it. Workshop participants recommended that NCI reassess its current training programs both for adequacy and for flexibility to meet the needs of M.D.'s wishing to pursue clinical oncology research careers. Specifically, they recommended establishing a K-12 award for institutions to fund training for promising clinical oncology investigators, and awarding the T-32

institutional training grants for longer periods--both at the predoctoral and postdoctoral levels--to more effectively serve the career needs of young physicians in both basic and clinical sciences. The workshop also recommended using R01 grants to support innovative clinical oncology research and working to establish a fair but rigorous peer review system for clinical investigation grant applications. Dr. Kimes referred the Board to their copies of the workshop report for further information.

In response to the workshop recommendations, Dr. Korn noted that previous reports have recommended that clinical research trainees be given a thorough grounding in the foundational sciences in their field of research, and commented that the workshop recommendations appear to downplay the need for this. Dr. Kimes reported that workshop participants stressed the need for training clinical researchers in both basic and clinical research. Dr. Wells noted the lack of surgeons and radiologists participating in the workshop, and pointed out that there are problems unique to those fields that may not have been included in the workshop viewpoint. Dr. Kimes agreed, noting that the workshop was a beginning of a process, and that further dialogue is necessary and is being planned. Mrs. Bynum commented that the report does not reflect an awareness that there is a large community of minority clinicians that is underrepresented in clinical research and that is a potential source of researchers.

Dr. Friedman's presentation focused on problems of funding for clinical therapeutic investigation. He noted that while the R01 mechanism represents approximately 80 percent of the NIH grant pool and is a useful mechanism for funding small and midsized investigator-initiated clinical studies, relatively few awards are made for such studies in comparison with those made for basic research. Dr. Friedman presented data that showed the problem to be twofold: clinical researchers perceive a difficulty in getting R01 funding and are reluctant to apply, and the few applications that are received tend to be given low priority scores in peer review.

Dr. Mihich argued that the problem was not one of prejudice against clinical investigations among grant reviewers, noting that at one time, after criticism of the Experimental Therapeutics (ET) Study Section, an experimental duplicate study group composed mainly of clinical investigators was formed to review ET's grants and gave similar priority scores. Dr. Friedman conceded that some of the proposals given low priority scores are inferior, but maintained that the problem is one of attracting the many talented clinical researchers with innovative ideas for clinical studies to apply for R01 funding. To illustrate the potential for larger numbers of meritorious clinical grant applications, he pointed to the many high-quality proposals submitted in response to a recent R03 solicitation for small grants to stimulate pilot and Phase I and II therapeutic clinical trials to move new treatment strategies more rapidly from the laboratory to the clinic. The solicitation drew 162 proposals in a short time, the bulk of which were approved; however, only a few were awarded from the small pool of available funds.

Dr. Friedman recommended that (1) NCI should take steps to solicit more investigator interest, and (2) a clinical oncology study section with the same rigorous standards as other study sections should be formed to provide peer review. He noted that if 100 applications per year were submitted to such a study group and 20 percent were funded at an average of $200,000, the $4 million total would still represent a very small portion of the RPG pool, and would be double the current amount of clinical investigation currently being funded.

The following points were made in discussion:

- The ET2 Study Section currently reviews applications for research grants in all areas of clinical medicine, including surgical and radiological oncology, and includes reviewers representing those disciplines.

- The possibility must be considered that much of the clinical oncology research needed at this stage of knowledge about cancer cannot be conducted by individual clinical investigators but must be done by large groups.

- One can argue that any particular area does not have adequate access to grants or proportionate funding.

- The problem needs to be addressed of the debt level of the average medical school graduate, which compels many to seek the more lucrative branches of medicine.

- Funding for medical schools has shifted in favor of medical practice rather than medical research.

- There is a problem with the academic status of medical oncologists in university departments of medicine due to the lack of funding for clinical oncology research.

- Historically, in study sections where both basic and clinical applications were reviewed, the basic science proposals have received the higher (better) priority scores; this may be because the standards for review are different. A study group should be formed in which clinical proposals compete against each other.

The Board agreed to study in advance of a future meeting specific proposals on a new K-12 mechanism to support training as well as other possible solutions, and continue discussion at that time.

IX. NEW NIH POLICIES AFFECTING EXTRAMURAL AWARDS--MRS. BARBARA BYNUM

Mrs. Bynum distributed a series of documents to the Board dealing with new NIH policies that affect extramural awards. She first discussed NIH policy changes regarding the inclusion of women and minorities in study populations. The policy states that "applicants and offerors for NIH and ADAMHA clinical research grants, cooperative agreements, and contracts will be required to include minorities and women in study populations so that research findings can be of benefit to all persons at risk of disease, disorder, or condition under study and special emphasis is to be placed on inclusion of such groups when the disorders or diseases disproportionately affect them."

Mrs. Bynum reported that the entire NIH extramural staff attended a mandatory seminar on the implementation of this new policy, which will be accomplished in three phases. She informed the Board that the second phase is effective with applications that came in for the October 1/ November 1 receipt date, for review by study sections in February and March of 1991, and by boards and councils in May and June of that year.

Several things will take place as a result of this implementation schedule, she noted. First, the NIH application kit will contain a flier specifically addressed to this issue. Second, applications that are submitted from this time forward must be compliant with this policy. They may be returned or rejected from review, or the applicants may be asked to provide additional information to make their application compliant. Third, study sections will be taking into account the acceptability of proposed studies in light of this new requirement. Fourth, the boards and councils have a defined role in assuring as part of their review for funding that approved applications are consistent with this policy.

The summary statements that are prepared for such applications will be ranked and coded using a new series of numerical codes similar to those used for human subjects, animal use, and other issues that require oversight. The pink sheets also will include specific comments in the body of the critique, under a special section headed "Women and Minority Subjects." Mrs. Bynum told the Board that based on these critiques, it

will be asked to consider the degree to which the applicants have addressed this requirement as part of the evaluation by the Board. Noncompliant applications may be deferred and the applicant institutions will be notified that NIH funding components will not fund or award grants or contracts unless and until sufficient information is provided to assure compliance with this policy.

Mrs. Bynum pointed out that each application will be considered in the context of the overall portfolio of the funding institute, such as NCI. Under certain circumstances, the NIH may make a judgement that in its overall coverage of a specific disease, it has funded separate individual studies that, in the aggregate, include groups affected by the disease or disorder under study. Therefore, an IRG recommendation on a single application may have to be reconsidered in light of the institute's overall portfolio. Mrs. Bynum gave assurance that the Board will be apprised of NCI's portfolio by program staff when they report with regard to individual applications that may seem noncompliant.

Mrs. Bynum said this policy will be monitored at the central NIH level by the Office of Extramural Research in collaboration with the newly established Office of Research on Women's Health and the Office of Minority Programs, both of which are in the Office of the NIH Director. Mrs. Bynum added that the Boards of Scientific Counselors also play an important role in this approval process, as the approval of the concept for studies involving human populations must make reference to the question of inclusion of appropriate population groups. Mrs. Bynum will distribute a copy of the detailed implementation procedure for the new policy as soon as it is available.

Next, Mrs. Bynum addressed the issue of the changes in NIH policies and procedures made as a result of congressional action on cost containment practices. "The NIH Plan for Managing the Costs of Biomedical Research," which was distributed to the Board, is the NIH's position paper on this issue and will be the basis of a series of discussions involving NIH staff, NIH advisors, and the extramural community. These discussions will culminate in a meeting of the NIH Director's Advisory Committee (DAC) in Bethesda on December 18. A copy of the meeting agenda, which addresses specific issues of grant size, length, and other considerations needed to develop funding policies for extramural support instruments, also was distributed to the Board. Mrs. Bynum informed the group that Dr. Korn will attend the meeting as the NCAB representative. In addition, on December 17, a public hearing will be held in Bethesda regarding the document, which has been sent to approximately 50 major public health and biomedical organizations, associations, and societies for their comment in the form of testimony at the hearing. Mrs. Bynum said Board members who wish to comment on the document are invited to do so primarily through these organizations. However, members who may want to make a comment on their own behalf may submit these to the NIH Office of the Director by December 17. The results of the DAC meeting will be presented at the February NCAB meeting. Mrs. Bynum indicated that certain operational changes will have to be made as a result of the cost containment policy changes. She said the Board will be kept informed as these changes take place.

Dr. Korn expressed concern that the draft NIH document does not adequately address the reasons indigenous to the science that have led to the perceived increase in the average cost of grants. He said that if one looks at current areas of science, project for project, and compares them with the way the science was conducted 10 years ago, it is evident that with the technologies that are available today there is a huge increase in the "cost per scientific question." Dr. Korn said he believes the NIH document does not present this argument persuasively as a factor in the rise of the research grant costs.

Mrs. Bynum ended by briefly addressing three other issues. First, within the next few months, revisions to Application Form 398 will be in the final stages. After receiving OMB clearance, the new form should be in general use by the end of 1991. Second, with regard to the issue of early release of information on priority scores, she reported that ADAMHA has adopted a policy in which it releases such information to grantees immediately, including recommended budgets and numerical scores or percentiles. NIH has not yet fully adopted this policy; however, it has empaneled a working group to implement a transition to this kind of

early notification procedure within the NIH. Finally, Mrs. Bynum called attention to a booklet distributed to Board members on the NCI grants process, which is a new edition prepared by Mr. Leo Buscher and his staff in the Grants Administration Branch.

X. REIMBURSEMENT FOR ABMT FOR BREAST CANCER--DR. MICHAEL FRIEDMAN

Dr. Michael Friedman presented an update on recent activities in the field of autologous bone marrow transplantation (ABMT) that have led to the decision by a major insurance company to reimburse for this procedure. He began by acknowledging the important contributions made by Dr. Robert Wittes in initiating this effort many years ago and by Ms. Mary McKay in recent years.

Dr. Friedman said the interface between reimbursement and clinical investigation is an increasingly important issue and has been the subject of a number of public panels and discussions. ABMT is being integrated into standard therapies for certain breast cancers. He noted that the ways in which the ABMT issue is dealt with will provide information about how to deal with other new techniques that are being studied.

Dr. Friedman then gave the board a description of the ABMT treatment. ABMT is a toxic therapy that is very cost and effort intensive. The technique harvests bone marrow from pelvic bone. The patient from whom the marrow was harvested is then given high doses of chemotherapy, either single agents or combinations, either with radiation therapy or without radiation therapy, which ablates the patient's bone marrow. In order to keep the patient from dying of aplasia, the marrow is then reconstituted by reinfusing that patient's own bone marrow. The procedure requires hospitalization from days to a few weeks and the cost is between $75,000 and $150,000 per patient per treatment.

Dr. Friedman cited data published in the *Journal of Clinical Oncology* from studies with ABMT. Patients with stage IV metastatic breast cancer received chemotherapy as an induction at conventional doses. Those patients who were stable or who responded then received very high doses of combination of cyclosphosphamide, VP16, and platinum. Many other combinations have been given in other studies, either in one or two cycles, during this intensive chemotherapy phase. The number of patients with metastatic disease who responded to such therapy was exceedingly high. A complete objective disappearance of all disease was seen in more than half the patients in a small study. The vast majority of patients had a benefit, a shrinkage of tumor; it seemed as though the more intensive the therapy, the more often patients responded. Dr. Friedman noted that while all patients had disappearance of disease or even a benefit, 9 percent of patients died of toxicity. Therefore, he said the treatment is demanding, difficult, and expensive, but it also has considerable promise. Dr. Friedman said that while it cannot be definitely proved from these data that such patients are cured, it is highly suggestive that important antitumor effects are being achieved with the ABMT treatment.

Dr. Friedman continued by saying there has been a great controversy about AMBT from the reimbursement point of view. A number of insurers feel that, because of the expense and what they consider to be the investigational nature of this therapy, their contracts prohibit them from funding such clinical care. There has been a highly heterogenous pattern of reimbursement across the country: in some locales, insurance carriers are funding ABMT, while in other areas, they are not funding the treatment. Dr. Friedman informed the Board that some adversarial court proceedings have resulted where judges and juries have been asked to evaluate the merits of this complex medical issue.

Dr. Friedman said he believes there are two groups of breast cancer patients who should be carefully studied. These are those patients with resectable stage II disease with axillary lymph node involvement, but who carry a very poor prognosis. For those patients, Dr. Friedman recommended a randomization in which the best conventional surgery, chemotherapy, and radiation therapy would be used and would be compared to patient receiving the same surgery, radiation therapy, and chemotherapy, as well as an ABMT. A second

type of study would be of Stage IV metastatic patients. Patients first would be induced with conventional chemotherapy and then randomly allocated either to receive conventional chemotherapy or ABMT.

Dr. Friedman said a meeting was held recently with representatives from the major cancer centers and cooperative groups. It was agreed there that the cancer centers would look at an adjuvant study, in this case of high-risk women with resectable disease who have more than 10 axillary lymph nodes involved with breast cancer. This regimen will be compared to a more conventional dose chemotherapy. He reported that the Eastern Cooperative and Southwest Oncology Groups also will work together in a high-risk patient population, looking at a slightly different chemotherapy program. One other study that Dr. Friedman said seems likely to occur will involve approximately 400 patients with metastatic Stage IV disease. These patients will receive either standard therapy, intermediate dose chemotherapy, or ABMT. In addition to survival and disease-free interval, Dr. Friedman said these studies will look at the short-term economics, as well as the long-term economics, whether more patients are being cured and at what cost. Quality-of-life considerations will be taken into account as well.

Dr. Friedman reported that one major insurance company, Blue Cross-Blue Shield, has agreed to consider paying for the clinical care costs associated with these large multicenter intergroup studies as a demonstration project. The offer that has been made will be on a region-by-region basis; however, Dr. Friedman said, it appears that the majority of the local Blue Cross-Blue Shield associations will participate in this effort. He described this development as a positive precedent and a novel approach to finding support for clinical care costs of research, with good chances of obtaining successful results.

Dr. Friedman also expressed his appreciation for the study investigators, who have done an excellent job, temporarily submerging their individual preferences and research interests in order to answer the larger question, does bone marrow transplantation work?

In response to a question from Dr. Durant regarding how the insurance companies will define a successful outcome for the ABMT treatment, Dr. Friedman said that while he does not speak for Blue Cross-Blue Shield, he believes that published study results showing a survival benefit or a quality-of-life improvement would constitute a successful outcome.

XI. INVOLVING NBA PLAYERS' WIVES IN BREAST CANCER EDUCATION --MRS. IRENE POLLIN

Mrs. Pollin addressed the Board on the involvement of the wives of professional basketball players in educating women about the importance of early mammography. She said the idea surfaced at the Women's Symposium on Breast Cancer during a private discussion about the need to educate women, particularly Black and Hispanic women. Mrs. Pollin had suggested that the wives of well-known basketball players, who are articulate and have access to the local media, would be excellent spokespersons for this cause. With the encouragement and assistance of Dr. Broder, Ms. Connie Unseld, who is the wife of the coach of the Washington Bullets, David Stern, who is the commissioner of the National Basketball Association (NBA), and Sy Gordine, who is the president of the basketball players' association, a planning meeting was arranged. The meeting was held with the women who are interested in becoming involved. It was decided at the meeting that a model would be developed to be used nationally.

Mrs. Pollin estimated that the model will be ready by early 1991 and will involve 27 "teams" around the country, where at least four representatives will serve on each team. Each team will have community relations and public relations people available to be on local television shows, to speak to local groups, and to get the word out. Mrs. Pollin said that Mrs. Ginger Sullivan is doing some speaking on this subject and will be available to help the teams in the city she visits. Mrs. Pollin said she has appreciated the help of Paul Van Nevel's office, which has provided kits and training materials. Following Mrs. Pollin's presentation, Dr. Chabner and members of NCAB offered their services and those of their staffs to help this educational program.

XII. NEW BUSINESS--DR. KORN

Dr. Korn asked for and received a motion to approve the minutes of the October 1-2, 1990, NCAB meeting. The motion was seconded, and the minutes were approved.

Mrs. Bynum asked for suggestions for specific agenda items, noting that several items have evolved from the discussions during the current meeting that will be brought back for action in February. Dr. Mihich suggested that, on the basis of the excellent scientific presentations at this meeting, one highlight of current science that is supported by NCI be presented at each future meeting.

XIII. FREDERICK CANCER RESEARCH AND DEVELOPMENT CENTER (FCRDC) --DR. WERNER KIRSTEN

Dr. Kirsten reviewed the history of FCRDC since its beginning in 1972, noting its operation under a system of contracts which, initially, were designed to provide technical and operational support for intramural laboratories. In the early 1980s, a contractor-operated basic research program was added to the center's activity. Contract operations include the basic research laboratory, operations and support for FCRDC as a whole, a library, an animal production facility, and a computer laboratory. In addition, four operating divisions of NCI (DCPC, DCE, DCBDC, and DCT) and two other Institutes maintain laboratories there. Dr. Kirsten noted that FCRDC operates out of the Office of the Director, NCI, and has an advisory committee that performs the same functions as the divisional BSCs. He referred NCAB members to the Board book for a summary of the scientific highlights of the basic research program conducted at FCRDC, which include research on the c-*mos*, c-*kit*, and c-*ski* oncogenes, chemical carcinogenesis, molecular biology of HIV, and the structure of proteins specified by retroviruses.

Dr. Kirsten described the Advanced Scientific Computing Laboratory (ASCL) as the center of a national network of computing interests and noted that Congress had appropriated $33 million to upgrade NCI's supercomputer located in the ASCL. He predicted that the basic research program together with the Crystallography Laboratory and new supercomputer would put FCRDC in a position of leadership in structural biology in the nation.

Dr. Kirsten then called attention to the operations and technical support activities, which include the AIDS vaccine development program and a clinical immunology laboratory that supports research on biological response modifiers ongoing at Frederick Memorial Hospital. He emphasized two accomplishments of the collaboration between NCI/NIAID investigators and the contractors: (1) FCRDC now has the capability to produce large quantities of the HIV isolate MN that is seroprevalent in the United States and Europe; infectious stocks have been developed that are currently being tested in animal models. (2) FCRDC has produced a noninfectious but highly immunogenic mutant of HIV, which is going into vaccine trials sometime in the coming months.

Finally, Dr. Kirsten compared the FY89 and FY90 budgets, calling attention to the substantial increases for basic research, AIDS, and utilities (paid to the U.S. Army) and the declines in intramural OD and operations and technical support lines. He indicated that increases in the FY90 budget are unlikely to be repeated in FY91, but that amount paid for utilities would continue to increase. He noted that 25 percent of the total budget comes from AIDS money and the same percentage reflects the AIDS effort ongoing at FCRDC.

ski IN TRANSGENIC MICE--DR. STEPHEN H. HUGHES

Dr. Hughes reviewed recent research by investigators of the Advanced Bioscience Laboratories (ABL)-Basic Research Program at FCRDC on the effects of the oncogene *ski* on the growth of muscles in

transgenic animals. Specifically, he demonstrated that not only can oncogenes be made to play roles in uncontrolled growth as in human cancer, but also that they can, under appropriate circumstances, be directed to play roles in increasing growth without leading to any kind of pathological state. He reviewed the available information on *ski* since its discovery and the decision by ABL to investigate the apparent dichotomy of function exhibited by the oncogene. The decision was made to research the properties of the cellular homolog, the normal gene from which the viral gene derives, rather than those of the viral oncogene. Dr. Hughes described the experiments conducted to reach the conclusions that the apparently paradoxical property of *ski* is an inherent property of the cellular homolog from which the viral gene derives, that cellular homologs are also nuclear proteins, and that in the whole animal, the overexpression of the c-*ski* gene can lead to dramatic increases in muscle development (the animals often have more than twice the amount of muscle than is found in normal mice accompanied by an almost total absence of fat). In attempting to isolate the cellular homolog, three different types of cDNAs were found and these were completely sequenced. Dr. Hughes noted that from an examination of the sequence of the cDNAs and in a comparison with the genomic clones, it was deduced that the cellular homolog is one contiguous gene and not a fusion, that the RNAs that derive from c-*ski* are alternately spliced, that versions exist that lack both exon 2 and exon 6, and that the 3'-translated region contains a segment that is destabilizing. The next step was to produce *ski* protein in large enough quantities to examine the biochemical and biological properties that *ski* would have in the whole animal.

To that end, Dr. Hughes explained, ABL investigators inserted *ski* DNA into fertilized mice eggs. The resulting transgenic mice had twice (or more) the normal musculature and no fat, but were seemingly normal otherwise. These animals were tested to determine their biochemical and biological properties. Dr. Hughes described these experiments and then concluded that future research directions will include an attempt to produce domestic farm animals with the same sort of phenotype as the transgenic mice. He stated that a collaboration has begun with USDA to produce transgenic pigs and the preliminary indications are promising. Another potential use of the gene, according to Dr. Hughes, is to stimulate the growth of muscle tissue in humans in cases where genetic diseases or injuries have altered the ability to regenerate muscle. In response to a question, Dr. Hughes stated that NCI has applied for a patent on this work.

ROLE OF MICE IN IDENTIFYING NEUROFIBROMATOSIS (NF) GENE--
DR. NEAL COPELAND

Dr. Copeland began his discussion by noting that the high-tumor inbred mouse models developed by mouse geneticists have played instrumental roles in many fundamental discoveries in cancer research. He and his colleagues at the Mammalian Genetics Laboratory of the FCRDC, in collaboration with scientists at the University of Utah, have been conducting studies to identify novel cellular genes involved in the development of mouse cancer, so that the human homologs of these genes may be studied for their involvement in human cancer. Recent experiments culminated in the cloning of the gene for human neurofibromatosis (NF), one of the most commonly inherited genetic disorders in humans.

Dr. Copeland described the methods of generating common high-tumor mouse strains. Early strains were developed in the 1930s when mouse geneticists mated mice with a specific form of cancer, and then inbred the offspring for several generations. Newer strains, called recombinant inbred mouse strains, were derived by crossing preexisting inbred strains, and then inbreeding the offspring for 20 or more generations. Dr. Copeland noted that the BXH2 recombinant inbred strain, which was instrumental in the discovery of the NF gene, develops myeloid leukemia at an average age of 7 months. Scientists discovered that the BXH2 mice express high levels of an ecotropic murine leukemia virus, which leads to the development of myeloid leukemia in that strain. The retrovirus replicates itself and integrates into or near a normal cellular gene, converting it into an oncogene. The cell then grows into a monoclonal proliferation of tumor cells, with each cell containing the retrovirus. The retrovirus can cause the expression of a gene not normally expressed in that cell type, or may alter the expression of a tumor suppressor gene, both of which alterations may lead to cancer.

Dr. Copeland noted that a powerful new technique for identifying the gene causing the cancer involves cloning the virus and using it as a tag to locate the chromosomal domain where it is integrated and then the oncogene encoded by that domain. A new gene-mapping shortcut has been devised to determine whether a chromosomal domain tagged by a virus is likely to encode a new gene or a previously identified gene (e.g., *myc* or *ras*). This mapping process often aids scientists in predicting where the human homolog will be located. A few years ago, Dr. Art Buchberg of the FCRDC Mammalian Genetics Laboratory used this technique to map the oncogene involved in generating myeloid leukemia in BXH2 mice and thereby began the process by which the human gene responsible for NF was cloned. Human geneticists have speculated that because NF is an autosomal dominant disorder and appears to induce benign and neoplastic tumors, the NF gene may be a tumor suppressor gene. Dr. Copeland and his colleagues are currently working to determine if the NF gene is the same gene that predisposes mice, and possibly humans, to myeloid leukemia.

XIV. ADJOURNMENT--DR. KORN

There being no further business, the 76th meeting of the National Cancer Advisory Board was adjourned at 2:17 p.m., December 4, 1990.