DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE
NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
January 27-28, 1992

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[1]
January 27-28, 1992

The National Cancer Advisory Board (NCAB) convened for its 81st regular meeting at 8:00 a.m. January 27, 1992, in Building 31, C Wing, 6th Floor, Conference Room 10, National Institutes of Health (NIH).

NCAB Members

Dr. Paul Calabresi (Chairman)
Dr. Frederick F. Becker
Dr. Erwin P. Bettinghaus
Dr. David G. Bragg
Mrs. Zora Brown
Dr. Kenneth Chan
Dr. John R. Durant
Dr. Bernard Fisher
Dr. Phillip Frost (Absent)
Mrs. Brenda Johnson
Dr. Walter Lawrence, Jr.
Mrs. Marlene A. Malek
Ms. Deborah Mayer (Absent)
Mrs. Irene S. Pollin
Dr. Sidney Salmon
Dr. Howard M. Temin
Dr. Samuel A. Wells, Jr.

President's Cancer Panel

Dr. Harold P. Freeman (Chairman)
Mrs. Nancy G. Brinker
Dr. Geza J. Jako

Alternate Ex-Officio NCAB Members

Dr. Miriam Davis, NIEHS
Dr. Roy Fleming, NIOSH
Dr. David Galas, DOE
Captain Bimal Ghosh, DOD
Dr. John Johnson, FDA
Dr. Hugh McKinnon, EPA
Dr. Lakshmi C. Mishra, CPSC
Dr. Raymond Sphar, DVA
Dr. Ralph Yodaiken, DOL

Members, Executive Committee, National Cancer Institute, NIH

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

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[1] For the record, it is noted that members absented themselves from the meeting when discussing applications (a) from their respective institutions or (b) in which conflict of interest might occur. The procedure does not apply to en bloc actions.

Liaison Representatives

Ms. Eleanor McGowan, Program Officer of Cell Biology of the National Science Foundation, Washington, D.C., representing the National Science Foundation.

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

Dr. Robert W. Frelick, Past President, Delaware State Tumor Registry, Wilmington, Delaware, representing the Association of Community Cancer Centers.

Dr. Edward P. Gelman, Chief of the Division of Medical Oncology at the Vincent T. Lombardi Cancer Center, representing the American Society of Clinical Oncology, Inc.

Dr. Lee W. Wattenberg, President-elect, American Association for Cancer Research, representing the American Association for Cancer Research.

Dr. Marston W. Linehan, Head, Urologic Section, Surgery Branch, DCT, Society of Urological Oncology, representing the Society of Urological Oncology for Dr. Jerome Richie.

Marilyn Ayoob, Clinical Research Coordinator for Radiation Oncology at Georgetown University, Oncology Nursing Society, representing the Oncology Nursing Society.

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

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

Dr. James Bell, Acting Executive Vice President, American Cancer Society, representing the American Cancer Society.

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

In addition to NCI staff members, meeting participants, and guests, a total of 40 registered members of the public attended the meeting.

I. CALL TO ORDER AND OPENING REMARKS—DR. PAUL CALABRESI

Dr. Calabresi called the meeting to order and welcomed members of the National Cancer Advisory Board (NCAB), members of the President's Cancer Panel, and representatives of the divisional boards of scientific counselors. He introduced several guests representing medical, research, and professional organizations.

Dr. Calabresi welcomed the members of the public in attendance and informed them that they could express their views on issues discussed during the meeting by writing to the NCAB Executive Secretary, Mrs. Barbara Bynum, within 10 days of the meeting. He also announced that copies of the November minutes had been distributed into the Board members' notebooks. He requested that members review the minutes before the end of meeting so that a vote of acceptance could be taken.

Dr. Calabresi stated that the 20th Anniversary Symposium that was held in conjunction with the November meeting was videotaped and transcribed. Videotapes may be made available to Board or Panel members by contacting Ms. Nancy Brun at the Office of Cancer Communications at (301) 496-4394. The transcription will be available after final editing is completed. Dr. Calabresi expressed satisfaction with the turnout of the Symposium and thanked the staff whose efforts made it possible.

Dr. Calabresi informed members that the closed session of the day's meeting would begin at exactly 1:00 p.m. and requested that all Board members or staff with closed session business arrive promptly to ensure that a quorum was obtained. He stated that grant applications would be reviewed during the closed session and that any Board member who wished to submit one for discussion should alert Mrs. Bynum before the end of the coffee break.

Dr. Calabresi announced meeting times and locations for the Subcommittee on Information and Cancer Control, the Subcommittee on Planning and Budget, and the Subcommittee on Women's Health and Cancer and stressed to the Board the importance of attending the meetings. He reminded the Board that without a quorum of 12 members, no votes could be considered official.

II. FUTURE MEETING DATES—DR. PAUL CALABRESI

Dr. Calabresi reminded members that the dates for 1992 and 1993 Board meetings were approved by the Board at the last meeting. He reiterated that although meetings were listed as requiring 3 days, whenever possible only 2 days would be used. He requested that members check the bulletin board for messages and that guests avoid taking seats marked "Reserved."

III. REPORT OF THE PRESIDENT'S CANCER PANEL—DR. HAROLD FREEMAN

Dr. Freeman announced that the next President's Cancer Panel will be hosted by Dr. Joseph Martin at the University of California in San Francisco. The topic will be "Cancer Research and Technology Transfer in the 1990s: Preparing for the Future." It will address many key issues, including: preparedness for future cancer research needs; methods of training better scientists; and the role of cancer centers in cancer research for the 1990s.

Dr. Freeman informed members that a meeting would be held in New York City to discuss the relationship of lifestyle to cancer. He also updated members on the progress of the President's Cancer Panel breast cancer subcommittee that was requested by Vice President

Quayle. The names of the members will be announced as soon as final approval is received. Sixteen members were chosen from more than 165 nominations. The subpanel will examine all aspects of breast cancer, including research and clinical applications, and is expected to take at least one year to complete its assignment.

Dr. Freeman stated that an annual report is being prepared for the President. Upon completion within the next few months, Panel members hope to meet directly with President Bush to discuss their concerns.

IV. REPORT OF THE DIRECTOR, NATIONAL CANCER INSTITUTE (NCI)—DR. SAMUEL BRODER

Dr. Broder announced that Dr. David Kessler, Commissioner of the Food and Drug Administration (FDA), would be present at this NCAB meeting to discuss issues related to off-label use. Dr. Broder also informed members that the NCI had participated in an experiment that was conducted in space, in which crystals of human immunodeficiency virus reverse transcriptase were orbited about the earth to study the crystallization process of complex proteins at zero gravity. Dr. Stephen Hughes of the ABL Basic Research Program at the NCI Frederick Cancer Research Center prepared the crystals in his laboratory, and Dr. Ed Arnold conducted the crystallographic studies at Rutgers University.

Honors, Awards, and Staff Changes within the NCI

Dr. Broder announced that Dr. Philip Pizzo, head of the Pediatric Branch, received the Scientific Excellence Award of the American Italian Foundation for Cancer Research in recognition of his excellence in developing innovative ideas in the area of pediatric AIDS. Dr. Thomas Waldmann received the Bristol-Myers Award for his many accomplishments in broadening the understanding of immunodeficiency diseases and cancer, as well as developing a number of applications for new technologies. Drs. Michael Grever, Saul Schepartz, Matthew Suffness, Gordon Cragg, and Kenneth Snader were given the Departmental Special Acts of Service Award for numerous accomplishments, including the expedited development of taxol. Dr. Michael Gottesmann, who works in the Division of Cancer Biology, Diagnosis, and Centers, received the NIH Lectureship and the Richard and Hinda Rosenthal Award. His topic was molecular analysis of resistance to anticancer drugs. Dr. Marston Linehan was honored with the Charles J. Robertson Lectureship.

Dr. Broder thanked Dr. Michele Evans for her work as a special assistant to the Director from June 1989 to December 1991. Her efforts addressed the entire spectrum of minority health and training in the biomedical area. In addition, Dr. Evans has been invaluable to the Adopt-A-School Program, and she will continue to assist the NCI in such areas as minority recruitment. Dr. Evans will be returning to the Division of Cancer Treatment (DCT) as a clinical oncologist and senior investigator in the Laboratory of Molecular Pharmacology.

Dr. Broder then announced some staff changes. Dr. John Gohagen was appointed Chief of the Detection Branch in the Early Detection and Community Oncology Program. Ms. Adele Leff, Deputy Chief, Grants Management Officer at the Grants Administration Branch, has retired and will be replaced by Ms. Roslyn Bacon. Dr. Samuel Wilson, Section Chief in the Laboratory of Biochemistry, has also retired.

New Developments within the NCI

Dr. Broder stated that two conferences related to the 20th anniversary of the National Cancer Act were held by the NCI. One meeting, held on November 26, was sponsored by the NCAB and attended by many members who attended the last NCAB meeting. The other, a

meeting on the Virus Cancer Program, took place on December 16. Dr. Temin spoke about the program and discussed the three components of what he referred to as the "universe of science, society, and scientific knowledge." Dr. Broder praised the event and emphasized the importance of the reunion as a chance to review work and inspire everyone.

Dr. Broder announced that Dr. Eli Glatstein is leaving the NCI to become Director of Radiation Oncology at the Southwestern Medical School at the University of Texas at Dallas. On January 8, a symposium was held in honor of Dr. Glatstein, who has made remarkable contributions to research in radiation oncology and radiation biology and has seen seven people who trained with him become chairpersons of academic departments of radiotherapy.

Community Service and Outreach Activities

A significant study on the treatment of breast cancer has been reported in the *Lancet*. The study, led by Mr. Richard Peto, was based on a meta-analysis of data from 154 studies around the world on nearly 80,000 women. A significant increase in 10-year survival rates in women with early stage breast cancer (from 71 percent to 75 percent) and with axillary node positive breast cancer (from 42% to 50%) was induced by tamoxifen. In addition, for women with more advanced breast cancer, tamoxifen used in conjunction with other therapies improved survival rates and, used alone, reduced the risk of developing a new primary tumor by 40 percent. The study showed that if one million women were treated with tamoxifen, some 100,000 would benefit. This research confirms two NIH consensus conferences which concluded that tamoxifen and combination chemotherapy could each produce a moderate improvement in outcome among women with early breast cancers. This study stands as an important independent validation of the work of the NCI but is not sufficient to induce satisfaction with the level of progress in breast cancer. Dr. Broder stated that this work should serve only as a baseline for future research.

Other efforts in the area of breast cancer are progressing. The NCI will soon begin a randomized prevention clinical trial with tamoxifen in 16,000 women who are at a high risk of developing breast cancer. This study will be carried out by the National Surgical Adjuvant Breast Program. If the study has positive results, tamoxifen may come into common use as a form of chemoprevention.

Dr. Broder announced that the National Basketball Association wives, in conjunction with the NCI, have begun work to develop programs in their communities to encourage the use of mammography. The work of Ms. Irene Pollin on the Bullets Wives Save Lives initiative inspired this project. On January 9, the women attended a meeting at NIH to listen to experts, visit the NIH Clinical Center, and learn about mammography and breast cancer. Relying heavily on the Cancer Information Service and the toll-free number for cancer, these women intend to build strong community coalitions.

Finally, a number of grants will be provided to NCI-designated cancer centers to hold a series of regional breast cancer summits. The program, Dr. Broder said, will be introduced at a press conference after the NCAB meeting, at which time the grants, chosen centers, and names of principal investigators will be announced. Mrs. Marlene Malek is representing the NCAB in this effort and Mrs. Nancy Brinker is the liaison with the President's Cancer Panel. Mrs. Marilyn Quayle will also assume an active role in this effort.

Ovarian cancer is also receiving a great deal of attention lately. A workshop entitled "Perspectives on Ovarian Cancer in Older Age Women: Current Knowledge and Recommendations for Research" was sponsored by the NCI, the National Institute on Aging, and the American Cancer Society. The demographics of the disease validate the importance of such meetings. Some 20,000 new cases of ovarian cancer and 12,500 related deaths are

anticipated this year. Despite declines in the death rate due to ovarian cancer in women under age 65, a 16 percent increase in mortality rates has occurred for women over 65. In addition, the more advanced forms of the cancer have extremely low 5-year survival rates (20 percent), and tend to manifest in older women.

Update on Taxol

Dr. Broder also discussed progress with taxol. Despite its scarcity and side effects, taxol seems quite promising, especially for treatment of breast and ovarian cancer. The NCI has conducted a number of taxol-related clinical trials, and the drug has been made widely available to women who need it through numerous cancer centers. Dr. Broder stated that he is quite pleased with the rapid progress made by the NCI with this drug.

FDA Update

Dr. Broder announced that the FDA Advisory Panel voted to recommend oncocint for full approval. Although this does not ensure FDA approval, the panel was unanimous in its vote. Oncocint is the radiolabeled form of a monoclonal antibody, B72.3, which was developed in the NCI's Division of Cancer Biology, Diagnosis and Centers. If approved, it will be one of the first monoclonal antibodies the FDA has allowed to be used in cancer patients. The panel did approve the use of oncocint for the detection and localization of tumor lesions in patients suspected of having ovarian or colorectal cancer. Phase II therapeutic trials of this and other related antibodies have begun.

The FDA Advisory Panel also voted to recommend approval of interleukin-2 (IL-2) for renal cell cancer. In addition to making IL-2 available to kidney cancer patients, this development will ensure that there will be an ample supply of IL-2 for biological treatment studies, clinical trials, and proper access for patients. NCI's Cancer Treatment Evaluation Program, the Clinical Oncology Program, and the Biological Response Modifier Program should all be recognized for their efforts in studying this agent.

Congressional Update

Congress has been devoting a great deal of attention to a number of cancers. Prostate cancer's demographics provide the rationale for its recognition by Congress and NCI. Approximately 120,000 cases of prostate cancer are anticipated in the United States this year, and there will be over 30,000 deaths from this disease. One out of every eleven men in America develops prostate cancer, and mortality rates are twofold higher for Black Americans than for White Americans. This unexplained disparity is expected to continue to widen. Early detection provides an 85 percent chance of 5-year survival. Special research units will be established by the Specialized Programs of Research Excellence (SPORE) grants that were mentioned earlier. These units will provide a more targeted approach to fighting prostate cancer. A new endeavor by the Division of Cancer Prevention and Control, the PLCO study, will involve screening an estimated 37,000 men for prostate, lung, and colorectal cancer. The intent of this study is to determine whether specific screening technologies for the early detection of these cancers produce a benefit. A comparable number of women will be screened for lung, colorectal, and ovarian cancers.

Dr. Broder stated that diagnosis and treatment of prostate cancer is improving. NCI-supported scientists have found that prostate-specific antigen (PSA) provides a marker for prostate cancer and can aid in the diagnosis and evaluation of treatment responses. A number of innovative treatments have been implemented, including the use of suramin for hormone-resistant prostate cancer.

Despite advances in diagnosis and treatment, prevention is still the highest priority. Two potential agents for treating prostate cancer, 4HPR—a vitamin A-related compound—and Proscar, may have success in preventing the formation of tumors. Diet-based prevention is receiving increased support. An estimated 35 percent of all cancer deaths may be related to diet. Previous efforts have been made to offer dietary guidelines for reducing cancer risk, and a new initiative, the Five-A-Day for Better Health Program, has been created based on scientific studies. The goal of this program is to increase the average American's two and one-half servings per day of fruits and vegetables to five servings per day, due to proven health benefits and decreased risk of heart disease and certain cancers provided by such a diet. A 1988 NCI grant to the California Department of Health Services began this program. The support of industry and health organizations has helped to expand its success. The NCI signed a Memorandum of Understanding with the Produce for Better Health Foundation that provided for the creation of a national program and a license agreement.

The Government Accounting Office (GAO) has issued a report on off-label use of drugs by oncologists at the request of Senator Edward Kennedy (D-MA). A survey of nearly 1,500 oncologists who are members of the American Society of Clinical Oncology received 681 responses, with information on over 2,000 patients. Findings of this survey indicate that when third-party payers refuse to reimburse cancer patients for the use of off-label drugs it has an influence on the treatment given to the patient. Off-label use is more common in treating the most severe cases. Two-thirds of the surveyed doctors admit patients to hospitals for treatment to obtain reimbursement for therapy that would not be covered on an outpatient basis. The GAO also recommended that the Secretary of Health and Human Services issue a policy for Medicare reimbursement for off-label drug use.

Specialized Programs of Research Excellence (SPOREs)

Dr. Broder announced that a number of applications for P50 grants have been received in response to the Request for Applications (RFA) for SPOREs in the areas of prostate, lung, and breast cancer. SPOREs are a new effort by the NCI to create targeted, integrated, disease-oriented research in addition to research funded through R01s and P01s. The P50s are more flexible and will encourage the translation of knowledge into better clinical applications. It is not necessary to be a cancer center to receive a P50 grant and new ideas that will have an impact on reducing the incidence and mortality due to the three major cancers are being actively sought.

NIH Strategic Plan

Dr. Broder detailed the continuing efforts to develop a framework for a strategic plan for biomedical research at the NIH-wide level, and said that Dr. Healy is focusing on this endeavor. The NCI is the lead ICD for the plan for progress in molecular medicine, one component of this strategic plan. The times and dates of four regional meetings on the strategic plan were provided. Dr. Broder stated that NCI grantees have been invited to attend these meetings and urged all relevant professional societies to send representatives.

Discussion of the NCI Budget

Dr. Broder discussed the impact of new travel budget restrictions on operations. The reduction will cause a 40 percent cutback in program and scientific travel. Patient travel to NIH to participate in an experimental protocol is protected from such reductions. As part of the effort to reduce travel costs, the Division of Extramural Activities (DEA) will, insofar as is possible, implement the following procedural changes:

- For the May 1992 NCAB meeting, all project site visits in connection with the peer review of cancer centers (P30s), program projects (P01s), and the clinical cooperative groups (U10s) will proceed as scheduled.
- For the September 1992 NCAB meeting, site visits for centers and cooperative groups will continue; however, automatic site visits for the review of program project grant applications will be discontinued.
- Those P01s not site-visited will be initially reviewed by an ad hoc committee located in Bethesda. The review will be augmented by an applicant interview process (reverse site visit) or by teleconferencing. Traditional site visits might still occur, but will not be automatic.

Dr. Broder also stated that during the transition period, all applicant P01 principal investigators should ask the appropriate DEA Scientific Review Administrator to determine whether their application provides adequate detail for peer review. He reminded Board and Panel members that their travel to any but the scheduled meetings will also be affected by the new budget reductions.

Dr. Salmon stated that he felt it would be more prudent to cut all Board and Panel travel, rather than cut the onsite review for program projects. He asserted that the onsite visits help to elucidate the interrelatedness of the different projects in a P01. Dr. Broder replied that certain scientific and program travel is required for peer review, but that they are willing to hear other alternatives. Dr. Salmon suggested that it is easier to review a core (P30) grant by reverse site visit than a program project. He stated that the program projects involve a detailed understanding of the science, while the core grants are more administrative in nature.

Dr. Broder added that the fight was lost to have patient travel considered as a separate category from scientific and program travel. An appeal was made, but that was also denied. Dr. Broder then introduced Mrs. Barbara Bynum, who provided more detailed information on the changes. Mrs. Bynum emphasized that the intent of these changes was to eliminate the automatic site visit and to cut back on unnecessary site visits. Discretion in individual cases is still possible. Some institutes depend entirely on the written applications for review; while, in the past, NCI has been flexible in allowing correction of omissions, or modifications of the written application at the time of a site visit; this may no longer be possible. Mrs. Bynum reiterated the necessity for applicants to submit as complete a presentation of their project as possible in the written application. Dr. Salmon restated his assertion that it is easier to review core grants via written application and telephone than P01 grants. Mrs. Bynum expressed her doubt that this contention would be supported by the Cancer Centers Program, but indicated that his point of view would be considered in individual cases.

Dr. Broder encouraged expanded dialogue on this topic. He stated that, in addition to their effect on peer review, these travel policies will make it difficult for intramural scientists to attend scientific meetings where important information on rapidly changing fields is exchanged. Dr. Freeman expressed a concern that was transmitted to him through a letter from the outgoing Chief of the Radiation Oncology Branch, who felt it would be difficult to attract young scientists to the NCI who need to travel to present their work and attend scientific meetings if these restrictions were enacted. He suggested that the President's Cancer Panel should consider this dilemma. Dr. Broder agreed with Dr. Freeman and then continued to express his own reservations. He stated that his biggest concern was for the young scientists who have not yet had a chance to prove themselves and for whom the flow of information at these meetings is essential to their continued growth. Dr. Broder asserted that more experienced scientists may attend a superfluous number of meetings, but are often resourceful enough to find other means of travel support. Chairman Calabresi suggested that he appoint a small committee of Drs. Durant, Salmon, Freeman, and Temin to address this issue during the lunch break. Dr. Broder

stated in response to a question that this restriction was imposed by Congress for all of PHS and therefore is NIH-wide, and that the NCI was getting a fair proportion of an unfair budget restriction. Dr. Fisher asked the magnitude of that reduction; Mr. Hartinger replied that for NCI it was $1.3 million.

Dr. Broder then began his summary of the 1992 budget. The final appropriation was approximately $1.989 billion. This figure, however, does not include surcharges. The travel reduction was $1.3 million. Salary and expense reductions were about $22 million. The NIH Director asserted the authority given to her by Congress to transfer $15 million out of the NCI budget to other ICDs for cancer research, and the NCI received an instruction to hold another $16 million in reserve. Consequently, the actual available funds total $1.95 billion. This number does not take into account that the Director of NIH can transfer 1 percent from any account to another, if an emergency arises. Dr. Durant asked to whom the Director is accountable for these expenditures. The reply was that the Director is accountable to Congress for these transfers. Dr. Broder added that the transfer authority came from the two appropriations committees, so they would also need to be satisfied. Dr. Salmon asked why the potential $31 million transfer was not part of the 1 percent. Dr. Broder responded that this transfer is for emergency situations only and, therefore, not considered as part of the surcharges.

Dr. Broder then returned to a discussion of budget figures. The actual obligations in 1991 were $1.7 billion, and the adjusted FY 1992 appropriation was $1.95 billion. Some $210 million of the budget will only be available on the last day of the year. Responding to a question, Dr. Broder stated that no overexpenditures may occur.

Dr. Freeman expressed his concern over the small amount of money that is paid to scientists that work at the NCI. He stated that this is a significant problem for attracting young people into the scientific field. He asserted that at the present level of pay it is not possible for the NCI to be competitive in attracting and keeping staff.

Dr. Broder recognized the problem and agreed to discuss it further at another time. He then moved back to a budget discussion. Approximately $980 million is committed to the research project grant pool. This figure is a 13 percent increase from fiscal year 1991. The Cancer Centers Core Grant line has also increased by 13 percent, from $110 million to $125 million. Although the SPORE program will be accounted for separately, it will still remain in the Centers budget line. The $17.5 million of new money being put into SPOREs, combined with other increases, totals about a $32 million raise from $110 million to $143 million (a 30 percent increase) in the total Centers Program budget. Dr. Broder added that it was expected that a majority of SPORE applications will come from existing cancer centers and that many of them will be successful in their efforts. The Research Career Program is increasing by $3 million to $13.5 million. The Cancer Education Program is being raised from about $3 million to $6.5 million, for a 114 percent increase. A 28 percent increase in the budget for cooperative groups will raise the figure from $61 million to $78 million. Minority Biomedical Support grants will receive a 12 percent increase in funding, from $2.7 million to a little over $3 million. In sum, over $1 billion is allotted for the total grants-in-aid. This figure represents a 15 percent increase, some $151 million above last year's total.

Dr. Becker asked Dr. Broder where the money for the 1 percent transfer allowed in emergency situations would come from. Dr. Broder replied that at this time no plan has yet been worked out in case the $20 million transfer becomes necessary. Dr. Broder added that if the special authority were exercised, inevitably some of the funds would be moved from the research project grant line, as it is the largest component of the Institute's budget.

Chairman Calabresi then asked Dr. Broder for an approximate comparison between the number of dollars requested for SPORE applications and the total amount appropriated. Dr.

Kimes responded that about 50 applications have been received,all of which are requesting approximately $1.5 million. Dr. Broder added that the deadline for applications is past; therefore, no more requests will be accepted.

Dr. Broder continued his budget discussions addressing training (National Research Service Act) funds. Due to a lack of reauthorization, the funding level for NRSAs has not been increased. Dr. Wells suggested that the void caused by the lack of increased funding may be filled through other lines; for example, the Career Development Awards. Dr. Broder added that SPORE mechanisms are highly flexible and, therefore, may also help fill the gap.

Research and Development contracts show a 12 percent increase, from $180 million to over $200 million. The Intramural Program was raised from about $326 million to approximately $355 million, a $29 million increase. Research Management and Support, which includes the Office of Cancer Communication and Office of International Activities as well as other activities, received a 14 percent increase (from $84 million to $96 million). The Cancer Prevention and Control budget increased from $85 million to about $106 million, for a 24 percent increase. A $5 million dollar increase in construction funding was appropriated.

Dr. Broder then stated it is his intention that this year, the NCI fund the largest number of new and competing grants in the history of the Institute. Dr. Broder said that investigator-initiated mechanisms are the most appropriate method for addressing the problems of cancer. Therefore, new awards and competing supplements are being encouraged through the RPG pool. He added that he would like to see more new ideas receive funding and the investigators begin work to validate the support the Congress and the Administration has provided the NCI. Figures for the noncompeting grant budget line show a slight increase from $595 million to $621 million, and, for the competing grants, a $70 million increase brought their total to $270 million. An additional 50 noncompeting and about 200 competing grants will be awarded this year. Dr. Broder expressed confidence in the level of basic and applied research currently underway and said that he felt it was worthy of receiving the largest number of new and competing grants in NCI's history. Overall, the increase in the number of funded projects would bring the total to over 3,200 from 3,000. Dr. Broder encouraged anyone with a new idea to submit a grant application.

Dr. Becker expressed his concern that many people are misinterpreting the goals of NCI's funding. He stated that people are viewing the massive amounts of money being put into breast cancer research and SPORE programs as a return to organ site research and are worried that this will translate into a decrease in the innovative investigator-initiated research. Dr. Becker added that Dr. Broder did make it quite clear that this was not the case, but stressed the importance of clarifying and disseminating this information, thus making it clear to research investigators that they are actually in a better position to obtain support for innovative approaches under this new mechanism. Dr. Broder responded by informing the members that the current budget includes the largest dollar increase in the history of the NCI, and that with the level of quality science the NCI is currently being asked to fund, the amount is more than justified. Dr. Broder said that, therefore, innovative and advanced ideas such as gene therapy would now receive the funding they had been denied in the past. He then stressed that SPOREs were not diverting money from the research project grant pool and that their use was intended to inspire better applications of the kind of research that are likely to have a noticeable effect on national cancer statistics. Each SPORE grant awarded will carry with it an obligation for some national impact; for example, an institution having certain tissues must attempt to collaborate and make the tissues available for inspection after the necessary work has been done with them. The SPORE program is not a commitment to epithelial tumor research, it is a commitment to address the most frequent cancers of men and women. Dr. Broder described the SPORE initiative as an administrative experiment, one which will be altered based upon evaluations of its results. He further explained that SPOREs would concentrate on areas where there has been increased incidence and suboptimal progress from a public health point of view. If an institution that could

not qualify for a traditional P30 proposed an exceptional idea and could field the team to work on it, they could become a national resource under this program. SPOREs can also provide a jump start in basic research, because as better research surfaces through SPOREs, grant applications will be successful in obtaining more funding.

Dr. Salmon asked Dr. Broder whether the decisions to accept SPOREs under these RFAs will be based on national priorities or on more subjective criteria. Dr. Broder replied that this is the area where it is necessary to be careful about diverting research monies from existing centers. He made it clear that no damage would be done to the centers budget line to allow for funding SPOREs. He stressed again the importance of national statistics in determining the direction of funding.

Dr. Bettinghaus asked what the motivation was for the modest increase in Minority Biomedical Research. Mrs. Bynum replied that the NIH convention in budget presentation can be very misleading, since it only allows an ICD to display its co-funding of MBRS grants with NIGMS. In actuality, a considerable amount of additional NCI funds are targeted to minority activities under other mechanisms. This budget line is only one measure of minority expenditures.

Dr. Temin expressed his concern over the training (NRSA) figure, as he sees this as the key to preparing the next wave of cancer researchers. He also expressed discontent over the intramural budget. He stated that it is receiving a smaller proportion of the total budget than it has in the past, and asked whether funds from the contract mechanism were supplementing this decrease. Mr. Hartinger replied that the intramural line includes both the program intramural funds that the NCI scientists have access to as well as the NIH management funds.

Dr. Jako expressed support for Dr. Broder's philosophy in regard to the SPORE program, stating that it is a fair balance between the National Cancer Program's investigators and new ideas and the public's need for research in high-incidence and high-mortality cancers. Dr. Jako also reported that a CNN program mentioned that the results of breast cancer treatment in the Northeast are better than in some other parts of the country. Dr. Jako suggested that this regional disparity be examined.

V. LEGISLATIVE UPDATE—MS. DOROTHY TISEVICH

Ms. Dorothy Tisevich, the NCI's legislative liaison, presented a brief update on recent legislative activities related to the NCI. Congress adjourned last November and began its new legislative session in the House on January 21 and in the Senate on January 22. Ms. Tisevich announced that the President was scheduled to deliver his State of the Union message on January 28, and that the President's fiscal year 1993 budget request would be transmitted to Congress on January 29. Hearings for the NIH budget are expected to take place around mid to late March.

Ms. Tisevich highlighted developments occurring at the end of the past Congressional session. Dr Healy, accompanied by Dr. Broder; Dr. James Watson, Director of the National Center for Human Genome Research; and Mr. Reid Adler from the NIH Office of Technology Transfer, attended a hearing on biotechnology development and the NIH patenting process held by Representative William Hughes (D-NJ), who chairs the House Committee on Intellectual Property and Judicial Administration. Mr. Hughes raised concerns about the cDNA patent, the protection of the taxpayers' investment in technology that ends up in the private sector, and other issues related to NIH Cooperative Research and Development Agreements (CRADAs). Mr. Hughes shares Representative Ron Wyden's (D-OR) concerns about the ability of NIH to enforce the reasonable price clause that is included in NIH CRADAs.

Representative Ted Weiss (D-NY) held a hearing on breast cancer on December 11, during which he released the results of a GAO study on NCI's progress against breast cancer over the last 20 years. Dr. Healy, accompanied by Dr. Broder and Dr. Vivian Pinn, the Director of the NIH Office of Research on Women's Health, testified at the hearing. Members of the committee expressed concern about the issues of access to health care by underserved populations, differences in cancer incidence and mortality between White and non-White populations, and NCI's effectiveness in disseminating new knowledge to the health care community.

Several briefings for Congressional staff were attended by NCI staff. These seminars, Ms. Tisevich stated, provide a valuable opportunity to inform Congress of the most important research and how it can be supported to improve the health of the citizens of this nation. Dr. Broder, while speaking at a seminar on new frontiers in cancer research held by the Congressional Biomedical Research Caucus, detailed the role of the NCI in cancer research and elaborated on some of the more exciting research. Other speakers included Dr. Michael Bishop from the University of California School of Medicine in San Francisco and Dr. Bert Vogelstein from the Johns Hopkins University School of Medicine.

Lawrence Kessler, a member of the Division of Cancer Prevention and Control, discussed technical aspects of the Breast Cancer Screening Safety Act of 1991 with Congressional staff and with representatives of the FDA and Centers for Disease Control (CDC). This bill was originally introduced by Senator Brock Adams (D-WA). Its intent is to maintain the quality of mammography procedures by establishing a certification and inspection program for facilities providing this service under the direction of the Secretary of Health and Human Services. The NCI has some reservations about the cost and feasibility of establishing a nationwide mammography registry, a provision in the proposed bill.

Ms. Tisevich reiterated that the NCI was appropriated $1.89 billion for fiscal year 1992. She directed members' attention to Attachment A in the legislative update package, which details the language that the House, Senate, and Conference reports concerning the NCI. Attention was also directed to page 3 of the update package, which lists all the other fiscal year 1992 appropriation bills funding cancer research, except those for the Department of Defense. Some $25 million was appropriated to the Department of the Army for breast cancer research, and $2 million was appropriated to Walter Reed Army Hospital to establish a center for prostate disease research.

Several new bills were introduced in the area of cancer prevention and control. In addition to the Breast Cancer Screening Act introduced by Senator Adams, a companion bill was introduced in the House by Representative Patricia Schroeder (D-CO).

Senator Kennedy introduced the Health Promotion and Disease Prevention Act of 1991 on November 7. Several of the provisions merit attention:

- The Centers for Disease Control would be renamed the Centers for Disease Control and Prevention (CDCP).
- New responsibilities in screening and early detection of prostate cancer would be authorized. CDCP would be able to award grants for studies to determine the prevalence, incidence, mortality rates, and stage at diagnosis of prostate cancer nationally, within regions, and within subgroups of the population.
- Studies would be conducted on the current state of screening and diagnosis and how effective these methods are in preventing prostate cancer.

The directors of CDCP and NIH would coordinate efforts in the following areas: evaluating existing methods of screening and diagnosis of prostate cancer; developing more sensitive, specific, and less expensive screening and diagnostic methods; examining and improving reporting of data on prostate cancer; distributing information concerning detection methods to help professionals; and hastening the review of research and development of technologies that ensure early detection of prostate cancer. In addition, this provision focuses attention on the leading causes of minority death, disease, and disability. It authorizes demonstration projects to prevent these diseases.

The bill also establishes the Centers for Disease Control and Prevention Foundation as a nonprofit corporation. This entity would be similar to the National Foundation for Biomedical Research, which was created by the NIH reauthorization bill that was enacted during the 101st Congress. It would support epidemiological studies, demonstration projects, and applied research in prevention or prevention effectiveness at CDCP and elsewhere.

Representative Mary Rose Oakar (D-OH) introduced the Breast Implant Surgery Informed Consent Act on November 4. This bill would demand that any State that receives funding from the Maternal and Child Health Services Block Grant Program, from Medicaid, or from the Preventive Health and Health Services Block Grant Program must require any State-licensed physician to inform patients considering implant surgery of any possible risks due to this procedure. This bill has been referred to the House Commerce Committee.

The Medicare Prostate Screening Act of 1991 was introduced by Representative Marilyn Lloyd (D-TN). This bill allows for prostate cancer screening tests to be covered under the Medicaid program. The NCI would aid the Secretary in identifying acceptable tests.

Ms. Tisevich mentioned several new bills being considered in the area of treatment. Representative Sander Levin (D-MI) introduced the Medicare Cancer Coverage Improvement Act of 1991. This bill would provide uniform coverage of anticancer drugs under Medicare. The term "drugs" would be defined so as to include drugs and biologics used in an anticancer therapeutic regimen for "a medically accepted indication." This phrase provides for the coverage of any drug that is approved by the FDA, appears in medical literature, or is either already included or approved for inclusion in one of the indices identified in the bill.

Taxol continues to be a topic of interest. Representative Gerry Studds (D-MI) has introduced the Pacific Yew Act of 1991, which would avoid waste of the trees by providing for the proper management of federal lands containing these trees. Furthermore, it has been learned that Mr. Studds plans to hold a hearing on taxol, possibly within the next month.

Ms. Tisevich outlined some expectations concerning Congressional activities as the second session begins. She reminded members of the stripped-down NIH reauthorization bill passed in the final days of the past session. It provided for the creation of the NIH Foundation that was mentioned earlier and the National Center for Medical Rehabilitation Research within the Child Health Institute. Controversy over this bill still exists, especially over the issue of fetal tissue transplantation research. Bills have been introduced in both the House and the Senate concerning NIH reauthorization. The House bill, H.R. 2507, was passed by the full House and referred to the Senate. Senator Kennedy introduced the Senate reauthorization bill, S. 1523. The Senate Committee on Labor and Human Resources will consider this bill shortly. Ms. Tisevich directed members to pages 5 through 7 of the update for details of the provisions. Differences between the two bills include the absence of fetal tissue transplantation, indirect costs, and conflict of interest provisions from the Senate bill. Senator Adams introduced a separate bill, the Research Freedom Act of 1991, which would allow the use of fetal tissue for specified research. This bill is expected to be worked into the Kennedy reauthorization bill. As

Dr. Broder mentioned, it seems likely that the White House would veto any bill directing funding for fetal tissue research.

The recent restrictions on receiving honoraria are expected to receive further attention. Representative Barney Frank (D-MA) introduced a bill relaxing the terms of the Ethics Reform Act of 1990. The House passed this bill, H.R. 3341. The Senate is expected to consider similar legislation early in this session; however, the outcome is uncertain. The House bill would only prohibit the receipt of honoraria for speaking and writing about topics related to an employee's official duties. Nonrelated activities would be determined by the three-prong test: 1) if the subject is not related to the interests of the office and does not necessitate the use of government time or resources; 2) if the reason for payment is unrelated to the employee's official duties or status; and 3) if the payer has no interests that may be markedly affected by the employee's duties. Additional information about this bill is in the update or may be obtained from Ms. Tisevich's office.

Dr. Temin asked Ms. Tisevich two questions. One question concerned whether the members of the National Cancer Advisory Board were considered federal employees and therefore restricted under the honoraria bill. Dr. Elliott Stonehill replied that only while working for the government are members subject to the restrictions. Board participants are otherwise considered independent. Dr. Broder expressed his concern over the effect these restrictions might have on the willingness of independent scientists to work as advisors to the government. He stated that these concerns have been voiced to the Office of Government Ethics. He did advise members to be cautious and to only accept honoraria for speaking or writing on topics not related to their work with the government. Dr. Salmon added that Dr. Temin had missed a meeting when the Board wrote a protest to the Ethics Committee.

The second question concerned travel reductions. Ms. Tisevich explained that it was an across-the-board reduction specifically for Public Health Service travel. She speculated that it may have been triggered by the controversy surrounding travel to the AIDS conference in Florence last year.

Dr. Bettinghaus expressed his concern for the proposed expansion of CDC responsibility to include prevention and activities related to prostate cancer. His fear is that these newly expanded duties may overlap with the responsibilities of NCI's Surveillance, Epidemiology, and End Results (SEER) Program.

VI. NEW APPROACH TO LABELING OF PRESCRIPTION DRUGS—DR. DAVID KESSLER

Dr. Broder, giving a brief history of the Food and Drug Administration and supplying biographical data, introduced Dr. David Kessler, Commissioner of the FDA.

Dr. Kessler began his talk by discussing the positive change in the relationship between the FDA and the NCI, and by introducing new FDA personnel who are responsible for helping to make this cooperative relationship happen. He went on to say that FDA has been able to decrease the approval time for cancer drugs from 40 months to 11 months while maintaining the same standards. From 1975 to 1985, the FDA approved one oncology drug every 2 years; for the last 5 years, the rate has climbed to nearly two drugs per year, and the number of investigational New Drug Applications for new cancer therapies has been increasing dramatically both from the industry and the NCI.

He then described the collaboration between the NCI, FDA, and the pharmaceutical company, Bristol-Myers, in conducting studies of taxol. He emphasized that the FDA cannot wait for oncology drug applications to come in. The FDA must be proactive and work with

sponsors, including the NCI, at the earliest stage of drug development. He described other collaborative tools such as the fellowship program that joins the FDA Center for Drugs and the NCI. This program prepares physicians for careers in research and regulatory science. Another formal interaction involves special meetings such as the meeting on cancer prevention agents and the workshop on monoclonal antibodies.

Dr. Kessler next spoke about biologics, saying there are developments in both biologic therapy and diagnosis. A granulocyte-stimulating factor was approved for use as an adjunct to chemotherapy, and a granulocyte macrophage-stimulating factor was approved for use in bone marrow transplants for lymphoma. The Biologics Advisory Committee recently recommended approval for interleukin-2 for the treatment of renal cancer. Dr. Kessler stressed that scientists at both the FDA and the NCI worked on this, and that he anticipates intense and extensive interactions with the NCI on biotechnology products for the treatment of cancer.

Dr. Kessler then turned to the topic of unlabeled uses of approved drugs, saying that a survey published by the General Accounting Office shows that off-label prescription for incurable cancers and for cancers without standardized treatment is very common—56 percent of patients receive at least one drug not labeled for that use. The FDA does not object to this but it does object to the promotion of unapproved uses of approved drugs—which is illegal. He stated that the FDA and those in the medical community feel this problem needs to be dealt with. The FDA's review could provide guidance on information not available for unlabeled use. Data on dosage, needed monitoring, and any caveats related to subsets of patients should be well established for every important indication, especially when dealing with drugs that are toxic.

The FDA is therefore planning to take steps to stimulate submissions for the labeling of at least the most widely prescribed secondary indications of approved drugs. He said that the FDA will be looking to the NCI, medical specialty societies, pharmaceutical companies, and FDA advisory committees to determine the scope of the phenomenon and identify the most medically important unlabeled uses. The next step, he said, is to scan the available information to see if the medical literature on the unlabeled use may contain all of the data needed for approval. When this is not possible, the FDA, he said, will have to seek further data and certain case records and will encourage the drug sponsor to develop the necessary information. All available resources will be used, including outside reviewers, to step up the processing of the submissions.

At this point, Dr. Kessler changed the topic and spoke on breast implants. He gave a history of the origin of silicone injections in Japanese women involved in prostitution approximately 50 years ago. The practice came to America and, in the 1960s, two physicians working with Dow Chemical developed an encasement for liquid silicone. He went on to say that there have been many variations and they have been on the market since before the enactment of the medical device law in 1976—these devices were grandfathered in. The FDA convened advisory committees to decide into which class these devices would go—Class I, II, or III—Class I being the least regulated and Class III requiring premarket approval applications. Breast implants were put into Class III. When Dr. Kessler arrived at the FDA, the agency called for premarket approval applications for breast implants to be submitted by July 1991. By this time, the agency had received seven applications. Three applications were denied because of a lack of clinical data, the other four are in the review process. The burden is on the manufacturer to prove safety. The data presented did not show safety, but the panel recommended continued availability of the products under the public health need exemption. At the time of this meeting, no industry information on breast implants had been made public.

Dr. Kessler closed on this subject, and his talk, by saying that women have a right to safe implants and asked for any questions from meeting attendees.

Ms. Brinker inquired about women who already have breast implants in place, and asked about a better alternative to saline implants. Dr. Kessler answered by saying that the advisory committee meeting in February will be focusing on women who currently have implants and, in response to her second question, he stated that taking unsafe products off the market will inspire the industry to create new and safer products.

Dr. Calabresi asked Dr. Kessler to comment on the current status of the proposed draft by the FDA to regulate CME programs sponsored by pharmaceutical companies. Dr. Kessler stated that the difficulty is distinguishing between scientific exchange (what the pharmaceutical companies claim their education efforts are) and product promotion. He said that the FDA is stepping up its enforcement actions in many areas and, in particular, dealing with promotion that is false or misleading. The FDA has also developed a first draft of a policy that distinguishes scientific exchange and promotion.

Dr. Davis then asked about the implications for reimbursement for off-label therapies—that once labeling changes occur, will reimbursement follow? Dr. Kessler replied that the label use as approved by the FDA should not be the basis for reimbursement. Some third-party payers use the label as an excuse not to pay; he feels that the FDA needs to send a strong message to the insurance community that the label should not be the basis for reimbursement.

Dr. Salmon inquired about the acceptability of company-sponsored exhibits but not company-sponsored symposia at national or academic institution meetings. Dr. Kessler replied that there is no problem with exhibits because they are clearly promotional; therefore, there is no confusion. The confusion comes in when the speaker at a symposium is a paid spokesperson—at what point that speaker actually engages in promotion.

Dr. Freeman asked about the FDA's relationship to tobacco. Dr. Kessler explained that tobacco is not in the jurisdiction of the FDA. He continued to explain that if tobacco were classified as a drug, it would never be found to be safe and, therefore, would be banned. He went on to say that there is a petition that has been filed with the FDA about the terms currently used to describe some cigarettes as "low tar" or "low nicotine." Dr. Kessler then asked for any advice about the tobacco situation. Dr. Freeman asked why tobacco is not considered a drug. Dr. Kessler replied that it is Congress that sets the mandate for the agency, so it is a Congressional decision.

VII. GENE THERAPY RFA—DR. MICHAEL FRIEDMAN

Dr. Bruce Chabner noted the existence of research within the NCI Intramural Program on treating cancer by transducing genes into host cells for the purpose of heightening the immune response to tumors. To provide support for preclinical and clinical research in outside institutions, the decision was made to establish an RFA for gene therapy. Dr. Chabner introduced Dr. Michael Friedman, head of the Cancer Therapy Evaluation Program (CTEP), to describe a proposal that had been reviewed and approved by the Board of Counselors.

Dr. Friedman used a series of slides to illustrate his introduction to the plan for issuance of an RFA for implementation grants for gene therapy. He defined gene therapy, for the purpose of this discussion, as the transfer of a functioning gene or genes into somatic cells to treat malignant disease.

Dr. Friedman reviewed several strategies for accomplishing this. The first involves the modification of normal host cells, usually immune cells or lymphocytes, to enhance antitumor efficiency. For example, cytotoxic T-cells, harvested from a cancer patient and shown to be reactive to that patient's tumor, would be transfected with cytokine genes or other genes to

increase their ability to either recognize, infiltrate, or, in fact, kill the tumor. These cells could be reinfused into the patient for possible clinical benefit.

A second possible strategy is the modification of autologous tumor cells to increase immunogenicity. Tumor cells that have been transfected with certain cytokine genes could be reinjected into the patient, resulting in cells that would produce the appropriate cytokines locally. It is hoped that there might be increased infiltration by the host effector cells, greater antitumor efficiency, and the development of some systemic immunity against that patient's tumor.

Other strategies briefly described by Dr. Friedman included the modification of normal host bone marrow stem cells to increase their resistance to the toxic effects of chemotherapy and *in vivo* treatment with genes to restore the function of tumor suppressor genes or to inhibit activated oncogenes to reverse the neoplastic process.

Dr. Friedman stated that certain protocols are being performed intramurally both for marker studies and for therapeutic studies. He added that there are also extramural studies demonstrating the feasibility of gene insertion techniques; these are limited to marker studies which at this time are not aimed at therapy.

Dr. Friedman explained that gene therapy requires an extraordinary review process before patients can receive this kind of treatment. He presented a slide that summarized the list of review committees and review boards that are involved. In addition to local institutional review boards that care for patient safety, there are institutional biosafety boards that look at employee and public safety. On the national level, he continued, there is the CTEP involvement when IND drugs or biologics are employed (in order to deal with concerns for patient safety or clinical trial design). There is also the mandatory interaction with the NIH Recombinant DNA Advisory Committee (RAC) on patient and public safety issues. The NIH Director has the overall sign-off authority on all such experiments. The Food and Drug Administration, primarily the biologics portion of CBER, is also concerned with these issues.

Dr. Friedman explained that the NCI is proposing a series of program project grants for gene therapy programs at a total cost of $5 million, with project periods of 4 years. It is expected that six to eight grants will be funded. The grants are called implementation grants because the focus is on establishing new programs to conduct gene therapy clinical trials for cancer patients. It is hoped that these grants will foster the process of implementation for institutions that are already proceeding along the continuum from early preclinical experiments to late clinical investigation. An important consideration is fostering interaction between basic scientists and clinical investigators, combining resources from different institutions that provide differing skills.

Support will be necessary for developmental preclinical studies, the formulation of clinical products and procedures, obtainment of regulatory approval, and for the clinical trials. The grants differ from many P01s in the recognition that some unique administrative costs must be dealt with, including substantial activities to meet regulatory requirements.

Dr. Friedman noted that many areas of research will be identified that will have significant potential for spin-off benefits. An important area of research will be the development of high-efficiency retroviral vectors, which appears to be the most efficient way to incorporate new genetic material. This does not rule out other considerations such as establishment of animal models, preclinical toxicology, and initial clinical studies. Collaboration with industry and with other investigators and other institutions will be supported and additional research areas should be uncovered as part of this activity.

Dr. Friedman moved on to a discussion of some substantial challenges in this dynamic scientific area. Gene therapy requires integral incorporation of expertise from three different collaborators: the basic sciences, including virology, genetics, and immunology; the clinical sciences, including oncology, clinical immunology, and bone marrow transplantation; and industry, which has been involved in vector technology and the availability of new cytokines.

The limited time available for grantees to develop complex program project applications is also a challenge, as well as the need to obtain reviewers for applications, considering the fact that applications are likely to be received from the people with the greatest insight into this area. Dr. Friedman also noted some of the unusual expenses that will be a part of this program: preclinical toxicology; cytokine availability; the administrative costs mentioned previously; and, potentially, patient care costs.

The RFA announcement was made on January 24th, and a special meeting is planned for February 28th to provide further information to investigators interested in the program. Representatives from the FDA, the NIH RAC, industry, and the NCI will be at the meeting. Letters of intent would be welcome by April 3rd, and applications are due by May 15th. The anticipated award date is September 30th.

Dr. Friedman stated that the CTEP will have many potential roles in the program, such as providing advice on regulatory issues and offering assistance in the design of clinical trials. The CTEP has access to investigational cytokines that are not commercially available. Annual meetings will be held to exchange information.

Dr. Calabresi opened the floor for questions. Dr. Temin asked whether applications would be accepted from investigators who were limiting their interest to marker studies. Dr. Friedman replied that this program is aimed at projects with therapeutic intent.

Dr. Temin noted that there has been some concern that there has not been sufficient animal work, and asked whether applicants will have to demonstrate some animal success before going on to humans with this technology. Dr. Friedman emphasized the necessity of a whole range of preclinical studies, including animal studies, studies of retroviral efficiency, and preclinical toxicology studies. He added that different institutions are at different points on this spectrum and stated that committees will not agree to the grant without good scientific underpinning.

Dr. Friedman, responding to a question from Dr. Durant, clarified the point that this program focuses on the use of genes, as opposed to gene products, in therapy.

Dr. Becker, noting that the RFA had been described as focusing on projects aimed at clinical applications, asked what would happen to applications from investigators who had done research on cell modification in animals and/or tissue cultures but who wanted to develop their techniques further before pursuing the goal of clinical studies. Dr. Friedman answered that such applications would be considered consistent with this RFA if they included specific tactical plans for moving from preclinical to clinical stages with specific clinical populations. He stated that the program is designed to capitalize on the efforts of investigators who are already moving toward clinical applications but are facing complex obstacles.

Dr. Broder added that a number of capable groups are already launched in trying to develop clinical applications from the revolution in genetic therapy and that this RFA is a user-friendly mechanism designed with special attention to the administrative hurdles faced by these groups. It is, in a sense, an attempt to facilitate a momentum that has already been gained. Dr. Broder observed that spin-off benefits of this work could go beyond the area of cancer research, including AIDS, cystic fibrosis, and other areas.

Dr. Broder continued by stating his personal view that there are strong advantages in moving to the clinical level early when there are a number of cancers for which no realistic options are available. This same philosophy, he noted, is related to the decision to enter clinical trials early with new drug applications.

Dr. Bettinghaus asked for clarification of the status of an application that stated that no clinical application would be included during the 4-year grant period but would be planned for a second phase. Dr. Friedman confirmed that an application that did not include patient treatment in the first 4 years would be considered if the investigator had identified a patient population, had a credible plan for treatment implementations, and had the necessary clinical resources lined up.

Dr. Salmon added that this RFA is a very important initiative and that the administrative component is an innovation in helping investigators deal with the daunting requirements for such research.

VIII. PROSTATE CANCER—AN UPDATE—DR. CHARLES MYERS

Dr. Charles Myers began his presentation with a discussion of suramin and its ability to antagonize growth factors of fibroblast tumors. A search for tumors dependent on the fibroblast growth factor was then initiated and prostate cancer emerged as a prime target. A Phase II clinical trial was conducted to test the activity of suramin in hormone-refractory metastatic prostate cancer.

He described the patients in the clinical trials who, as a group, were heavily pretreated and had poor prognoses. The only truly effective therapies for these types of patients are hormonal therapies. He noted that the prostate-specific antigen (PSA) showed what he termed as "huge" changes in many of the patients—with response to suramin correlating with improved survival.

He explained next that the PSA level in these patients needs to drop substantially and rapidly. Patients with a decline of 80 percent or more in the first 4 weeks have extraordinarily favorable prognoses. He said the two possible reasons for this are that: 1) suramin causes durable response; and 2) the ability of suramin to initiate a response is an indicator of indolent disease. Suramin, Dr. Myers believes, has a real effect on patient survival rates, but randomized control trial for proof of the effects will be necessary.

Dr. Myers mentioned that the toxicity and, therefore, the side-effects of the drug have been reduced. This was made possible because of the discovery that the toxicity is related to the peak plasma level of the drug and the antitumor effect is related to the duration of exposure to the drug at modest concentrations. Therefore, prolonged administration of the drug, with low peak levels, resulted in increased antitumor effects and decreased toxicity. These findings are supported by additional studies at the University of Maryland and the University of Arizona. He then posed the question, "What should we target for the next step in the development of this agent?"

He approached this issue by discussing the threat that prostate cancer presents to society. The disease is currently the number two cause of cancer deaths in males and the number one cause of cancer deaths in Black males, replacing lung cancer and, therefore, making prostate cancer a major public health issue. The grade and stage of the disease, he said, are equally as important in indicating overall survival, but that if a patient has clearly differentiated prostate cancer and "A" disease, he has a fairly grim prognosis—clearly differentiated carcinoma of any stage is bad. The two groups of patients to be considered the most critical are patients with Stage D2 disease and any patient with poorly differentiated disease regardless of stage.

Recently, randomized control trials have shown that hormone therapy has an impact on survival, but hormonal therapy is never curative. Hence, Dr. Myers decided to try to provide suramin in conjunction with hormonal therapy (using leuprolide and flutamide) in patients with metastatic prostate cancer who had bad prognostic features. He then described the procedure of administering the combined therapy.

Suramin has been much better tolerated in previously untreated patients than the hormone-refractory patients in his initial studies. Of those patients with elevated PSAs who had completed 1 month of therapy, 13 of 14 had an 80 percent drop in their PSAs within that 1-month period. Dr. Myers said these numbers don't express the true magnitude of these responses and proceeded to show "before and after" slides of the changes in a patient's prostate tumor. The patient, he said, is currently in complete remission.

Dr. Myers then stated that although the prospects for suramin are promising, it is cumbersome to administer and may have significant side effects. He and his colleagues are, therefore, launching a major effort to identify other therapeutic agents by looking at the biology of the disease. Their approach has been to look for receptor systems within prostate cancer that initiate growth arrest or cell death. He described the identification by one of his researchers of the extraordinary sensitivity of prostate cancer to intracellular cyclic AMP levels. If these cells are treated with dibutyl cyclic AMP (which is a nonhydrolyzable cyclic AMP analog), there is a dramatic decrease in initial tumor cell growth, and then, slowly, the cells die. He then described another way of increasing intracellular cyclic AMP using phosphodiesterase and methylxanthines. This work has been accepted for publication in the *Proceedings of the National Academy of Sciences*, and they have initiated a clinical trial in which they will use trental.

Dr. Myers then showed slides illustrating a consistent pattern being seen in prostate cancer cells which is a success in antagonists of various aspects of the signal transduction system. When an external receptor is coupled with G proteins, it results in activation of phospholipase C and formation of IP3 and release of intracellular calcium. He said an example of this is that prostate cells have prurinergic Type 2 receptors, and that if they put in a P2 antagonist, they have been able to demonstrate activation of G proteins and formation of IP3 and a dramatic increase in intracellular calcium. These signaling events, he said, are associated with growth arrest and death in hormone-refractory prostate cancer cells. The only hormone-sensitive prostate cancer cell line available was LNCaP, and its growth was unaffected. Dr. Myers said that these cells do have P2 receptors, but they are not coupled to G protein. It could be a specific finding for hormone-refractory disease or just an artifact of a relatively few number of cell lines available. He said they are investigating this in greater detail and are in the process of trying to decide which of this class of agents would make the most effective ones to bring to clinical trial.

Dr. Salmon asked if Dr. Myers had a drug sponsor in mind to introduce New Drug Application for suramin and also inquired if the data is significant to get a New Drug Application. Dr. Chabner responded that there are a number of interested companies and that a CRADA was advertised. Dr. Friedman noted that there is no pharmaceutical company prepared to make the drug available, hence there is a current supply problem.

Dr. Chan inquired as to the anticoagulant effect of suramin, asking if it is clearly shown that the toxicity and efficacy are related to pharmacokinetic effects. Dr. Myers responded that suramin is two sulfonated methylene rings and, in three dimensions, forms an alpha helix that matches heparin in a three-dimensional structure quite well, and binds to many of the same sites to which heparin binds. He said that early in the trials, they had serious problems with anticoagulation but that the problem tends to be prominent when suramin levels are near 300 micrograms per mil. At the low level at which they are working now, the anticoagulant activity of suramin is minor to nonexistent.

Dr. Broder commented that the drug requires exceptional skill on the part of the physician when being administered. He felt the drug should be available but should require a high degree of training and experience. His second comment was that suramin would have been dismissed as a drug if it had not been for the persistence of Dr. Myers and his coworkers and he stressed the need for strong clinical investigators.

Dr. Durant asked if there is subsequent protection for a drug company since this drug has been around for so long. Dr. Chabner replied that orphan drug status and a use patent which is currently in negotiation are two factors which can offer protection to a drug company.

IX. CALL TO ORDER—DR. JOHN DURANT

Dr. Durant began by calling the meeting to order and announcing that this portion of the meeting was open to the public. Dr. Durant then stated that Dr. Peter Greenwald, Director of the Division of Cancer Prevention and Control, would introduce the first speaker on the Women's Health Initiative, Dr. William Harlan, Associate Director for Disease Prevention in the Office of the Director of the NIH.

X. UPDATE ON WOMEN'S HEALTH INITIATIVE—DR. WILLIAM HARLAN

Dr. Greenwald opened his introduction by emphasizing the importance of studying factors that can influence the development of multiple diseases. Smoking, Dr. Greenwald stated, causes cancer, heart disease, and chronic lung diseases, and a low fat eating pattern affects heart disease, certain cancers, and other chronic diseases. These conclusions incited the NIH Director, Dr. Bernadine Healy, to begin the Women's Health Initiative. This program is a large trial and community study aimed at the prevention of heart disease, breast and colon cancers, and osteoporosis. These three diseases are the leading causes of death and disability among women. The initiative expands upon earlier work done by the NCI and other institutes of the NIH. Dr. Greenwald then introduced Dr. Harlan.

Dr. Harlan began his talk by describing the Women's Health Initiative as an integrated set of studies co-directed by himself and Dr. Vivian Pinn from the Office of Research on Women's Health. He stated that the issues the program will examine are the prevention of cancer, heart disease, and osteoporosis.

Dr. Harlan explained that there are three components to the study. The first is a large randomized clinical trial that seeks to prove or test the effectiveness of targeted interventions. Another aspect of the program attempts to identify new biomarkers and predictors of disease. The final portion of the initiative implements the use of a randomized community trial to examine the extent to which women may be motivated to adopt more healthful behaviors.

In all of these studies an assessment of risks and benefits for all of the organ systems will be carried out to help in balancing the two. In addition, the program will provide an opportunity to conduct a longitudinal observational study, which is actually similar to an epidemiologic study. This observational study entails the making of simple observations at the beginning of intervention and a mortality/morbidity followup. This study will provide a chance to determine predictors of disease. Finally, the randomized control trial of communities will be explored as a tool to test the varied approaches to the adoption of healthful behaviors.

Dr. Harlan explained that benefits and risks do not impact on one organ system only, but can have an effect on an entire individual. External factors, such as the environment and genetic background, need to be accurately measured and controlled for in these studies. Dr. Harlan also

pointed out the importance of measuring the physiological and psychological changes that occur as a result of preventive strategies, especially those that are adverse.

Dr. Harlan began his discussion of the components with the largest of the three, the clinical trial. He outlined three aspects of the randomized control trial: adoption of a low-fat dietary pattern, hormonal replacement therapy, and calcium/vitamin D supplementation. The dietary modification aspect of the program involves the randomized recruitment of 50,000 women who would either alter their diet to a low-fat eating pattern or continue prior eating habits as a control, and then be followed for nine years. The development of an overall benefit/risk ratio is one of the goals of this trial. Breast cancer has been cited as the primary outcome variable of interest, but the program also has strong applications for colorectal cancer and coronary heart disease. In addition, Dr. Harlan stated that the trial will also provide the opportunity to examine effects on some subsidiary disease outcomes. Dr. Harlan offered the example of diabetes mellitus. He explained that a low-fat diet is associated with a weight loss of 8.5 pounds, and that the chance of developing type II diabetes is diminished in women who experience a weight loss. Dr. Harlan also stated that differences in mortality would be examined.

Dr. Harlan explained that the dietary modification involves the reduction of total fat intake to 20% of calories. The saturated fat intake would be lowered to 7% of one's total calories. Dr. Harlan stated that this dietary alteration would naturally lead to an increased number of servings of fruits and vegetables to five a day and of grain to six a day. This diet, Dr. Harlan said, is the same diet that was used as the secondary prevention in the colon/polyp study. Women would also be encouraged to begin a daily physical activity program, although continued prompting would not occur.

Dr. Harlan then detailed the instructions that would be given to the control group, which represents 60% of the randomized group. They would be taught about basic nutritional principles; they would be provided with dietary guidelines for all Americans, which encourage a switch to 30% of calories from fat; and they would be given information on fruits, vegetables, and fiber. This group would also be advised to initiate a moderate physical activity program.

Dr. Harlan began his explanation of the hormonal replacement therapy by stating that this study involves the division of 25,000 post-menopausal women into three groups; one will be administered estrogen only (about 30% of the women), one will take estrogen plus progestin, and the last will receive a placebo. Dr. Harlan said that the participants would be followed for nine years while on therapy, and possibly for five years after that. This trial also would be evaluated for a benefit/risk ratio. Dr. Harlan stated that the primary effect is intended for coronary heart disease. The decrease in coronary heart disease is expected to be around 30%, although observational studies have shown as much as a 50% decrease in incidence. This trial also provides an opportunity to study cardiovascular disease (which includes stroke) and osteoporosis-related bone fracture differences in the three groups. The study will also examine the increased risk of breast cancer due to a regimen of estrogen; however Dr Harlan, noted that the results would be conclusive only if the risk increased by 30% or greater and the subjects were followed for a nine year period. If the participants were followed for an additional five years, then a 20% increased risk of breast cancer would be detectable. Dr. Harlan also mentioned that there is a proven risk for developing endometrial cancer in women with a uterus (an estimated 65% to 70% of the women in this group), and stated that the monitoring devices that would be used for this possible outcome would be detailed later.

Dr. Harlan then pointed out that observational studies suggesting any benefits to coronary heart disease or cardiovascular disease are based on estrogen only. The observational studies that have examined a combination estrogen and progestin regimen have been short and limited in number, consequently providing little evidence for the efficacy of the treatment. Dr. Harlan stated that it is even more important that reviews of these studies have returned no

significant findings of a reduced likelihood for developing endometrial cancer. He informed the group that the FDA had not licensed the use of progestin in combination with estrogen for osteoporosis because they are not convinced that it promises to deliver a greater reduction of risk for developing endometrial cancer than estrogen alone. Dr. Harlan also stated that a study is being conducted to determine what intermediate changes, if any, occur when estrogen or estrogen plus progestin is used. Already, studies have suggested that the use of the combination may lead to a less beneficial change in lipid pattern and blood clotting than estrogen alone.

Dr. Harlan acknowledged the doubt that surrounds this portion of the study and emphasized that participants would be monitored frequently for the development of endometrial cancer, which is generally a fairly low grade of malignancy and rather easily cured.

Dr. Harlan then provided an example of assessing benefits and risks. Dr. Harlan borrowed some information from an editorial by Lee Goldman in the *New England Journal of Medicine* to accomplish this task. Dr. Harlan explained that Mr. Goldman examined the risk of death for coronary heart disease, hip fracture, breast cancer, and endometrial cancer in a group of women between the ages of 65 and 74 years. Estimates of the changes that hormonal replacement therapy might provide were based on evidence that Mr. Goldman had gathered. Dr. Harlan listed the estimates as a decrease of 40% for coronary heart disease and of 60% for hip fracture; however, for breast cancer an increased risk of 30% was cited. This same risk/benefit assessment has been proposed for tamoxifen with respect to its ability to prevent breast cancer and possibly coronary heart disease, as well as its effect on osteoporotic fractures.

Dr. Harlan described the final component of the clinical trial, the calcium/vitamin D supplement. Some 45,000 women would receive calcium and vitamin D and then be analyzed in terms of a risk/benefit ratio. The primary effect will be on the prevention of osteoporotic fractures and possibly on colorectal cancer development.

Dr. Harlan said that all of these therapies would be examined in terms of quality of life and social changes that occur with these interventions. He also stated that some women would only receive the dietary therapy, others only the hormonal replacement therapy, and some only the vitamin supplementation, while many would receive some combination of the three.

Dr. Harlan then briefly explained the process for dividing the women who volunteer for the trial into groups. Any woman who does not wish to participate in the trial, is not eligible to participate, or came specifically to be in the observational study, will then be a subject for the observational study. The observational study will follow the same timeline. This group of women would provide estimates of risk factors for disease and would be used as a comparison for those in the clinical trial (in addition to the control group within the clinical trial that is not receiving active therapy). Dr. Harlan stated that this study will hopefully provide more reliable estimates of risk factors than are currently available, due to the large sample size of this study. Discovering new risk factors for these diseases is a goal of this study.

Dr. Harlan said that the procedure would involve the making of a few simple measurements on these women during the observational trial, storing biologic specimens for future analysis, and then conducting a followup for ten years. In the future, extended studies based on these women may be conducted, depending on the funding that becomes available. Dr. Harlan explained the value of such efforts by showing a slide with estimates for the cumulative number of events among 100,000 women between the ages of 50 and 79 years. These large numbers of events would make possible case control groups from within a large cohort that has been previously defined. Dr. Harlan stated that in the case of osteoporosis, plans for storage and future analysis of specimens already have been made.

Dr. Harlan commented that ancillary studies would be permitted on subsets of participants. He stated that on such a large cohort, even a five or ten percent sample would still constitute the largest number of women studied for most of these conditions. Certain requirements, such as not interfering with the overall study, separate consent, and separate funding, must be fulfilled to permit the outside study.

Dr. Harlan also addressed the issue of the size of the study. He said that due to its large size and complexity, it will be divided into phases to examine its feasibility. It has been decided to use a vanguard phase in which a coordinating center and about 15 supporting clinical centers would form the front line; develop the protocol, recruitment strategies, and materials; and examine feasibility. During the full phase, 30 centers would join the vanguard. All of the studies would be supported through the contract method. Dr. Harlan emphasized that the process that he has described is not yet definite. The final protocol is still being debated and modified, and will then be checked by the usual data and safety monitoring committees, before the final design is approved and begun.

Dr. Harlan stated that there are antecedent studies that deal with similar topics. The tamoxifen prevention trial relates closely to the hormonal replacement therapy; therefore, the assessments will be as similar as possible to allow a comparison of the results. Another study examines intermediate effects of hormonal replacement. In addition, an initial vanguard study was conducted for the dietary pattern study. Another study explored special problems that minorities may encounter with the diet. Dr. Harlan also stated that the diet being used for this study is the same as the one used for the colon/polyp trial, so it represents a complementary study. Most of the antecedent studies for the calcium/vitamin D supplementation were observational studies and conducted on a much smaller scale, with the exception of the Nurses Health Study in Boston which explored many of the same issues about risk factors and markers for disease.

Dr. Harlan then explained the last component of the Women's Health Initiative, the community randomized trial. Dr. Harlan identified the purpose of this study as the evaluation of strategies to achieve healthful behaviors. Separate communities will be targeted and used as the unit of intervention and of control. Women between the ages of 35 and 75 years will be the target population. Dr. Harlan said that the overall approach is very similar to that used in COMMIT. Dr. Harlan highlighted the fact that the study was including women in the transitional phase of their life, when women experience many changes and the adoption of healthful behaviors is crucial. Dr. Harlan emphasized that the endpoints of this study are to reduce risk factors and improve screening rates, not mortality or morbidity rates.

Dr. Harlan then described the structure of the study. Matched pairs of communities would be nominated by organizations. These communities would be randomly assigned either to receive intervention or to act as a secular control group. Since the study focuses on the adoption of healthful behaviors for medically underserved and minority groups, only communities with significant numbers of underserved and minority members will be chosen. Dr. Harlan explained that there would be three surveys done at the beginning, middle, and end of the intervention. Comparisons would be made between the first and last surveys, with the middle survey serving to indicate how fast changes occur or to indicate any necessary midcourse adjustments.

Dr. Bragg asked Dr. Harlan what the estimated cost per decade would be. Dr. Harlan said the total cost for 14 years of the study is $625 million. He said that the House and the Senate have approved the initial funding and allocated $25 million. Estimates of the costs for subsequent years have been made, although none can be made for funding. Dr. Bragg questioned the likelihood of an average American following such a diet. Dr. Harlan replied that the feasibility study for the Women's Health Trial showed that most women were able to follow

the diet. Dr. Harlan added that one reason for the large sample size is to allow for the number of women whose fat intake will either increase or decrease from the target percentage.

Dr. Bettinghaus asked what would happen if it were necessary to break the trial—if, for example, the study is successful for coronary heart disease, but has not been conducted long enough for another component. Dr. Harlan replied that no definite stopping points have been determined. Although he said that he expects the coronary heart disease study to take the full 9 years, he does feel that it is possible that osteoporosis study may end early, as they have very little information on the topic. If such a break became necessary, then a data and safety monitoring group would have to make the decision. Dr. Harlan suggested that perhaps an announcement would be made, stating that hormonal replacement therapy has been shown to prevent osteoporotic fractures, but that the study is being continued to reach the primary endpoint of coronary heart disease. He further suggested that one might not even use hormonal replacement therapy unless it could be shown to have other benefits, and might be decided against if other risks such as breast cancer were conclusively linked to it. Dr. Harlan stated that staff from 10 other institutes and many outside advisors were recruited to discuss the project, and that many of the women expressed a concern about a possible increase in the risk of breast cancer. This fact is one of the motivations for the extensive studying of breast cancer in relation to this study. Dr. Harlan then mentioned that there was a meeting that was being held simultaneously to discuss the issues of nonstatistical rules for data and safety monitoring of trials.

Dr. Durant asked Dr. Harlan what his requirements for stopping the study would be. Dr. Harlan replied that if the researchers could not get the women to take the pills and follow the diet, then the study would be halted. He said that he feels the feasibility for the diet has already been addressed. Dietary compliance will be monitored, and if it is not being adhered to then the study will be altered or halted. After one year, if the results for the specialized diet and pill intake that were received in the Women's Health Trial were not matched by the current ones, then the study would be modified or reevaluated.

Dr. Durant asked whether these guidelines would be documented and then publicized. Dr. Harlan replied that a document had already been compiled. Dr. Bettinghaus commented that he agreed that the vanguard women's health trial had established the feasibility for that particular group of women (primarily upper/middle income level and White) in being able to maintain the specialized diet. Dr. Bettinghaus, however, did express concern over whether low income women and minorities would have equal access to such a diet.

Dr. Harlan replied by providing the details of the minority feasibility study that was just about to begin. Dr. Harlan explained that this study would be approximately one year ahead of the full study, and that the intention was to continue the participation of the subjects of the minority study into the full study. Dr. Salmon asked what the impact would be if the trial design proves that the minority and lower income components are not feasible. Dr. Harlan replied that minority participation in this study is crucial; if the appropriate representation and compliance cannot be achieved, then the study will not be conducted.

Dr. Chabner asked whether women at high risk for breast cancer or heart disease would still be randomized into groups, despite the fact that they may be put on hormone replacement therapy (and create an even greater risk of breast cancer) or put on a placebo (receiving no protection against heart disease). Dr. Harlan replied that the women would be well-informed about the study and could make the decision not to participate. In addition, some exclusions of women are made, but they are rare; for example, a woman with a previous history of breast cancer would not be allowed to participate. Dr Chabner asked whether women with a strong family history of breast cancer would be included in the study. Dr. Harlan answered that they would be permitted into the study and that an informed consent would be obtained. The informed consent would detail all the risks, and explain the potential effects that a family history

of a specific disease may have on one's chance for contracting that disease. Dr. Durant questioned whether some of these women should be excluded rather than being allowed to choose. Dr. Harlan replied that this policy had not yet been finalized, and that some exclusions would be made (although very few). He further stated that there was even some pressure to include women at a high risk for breast cancer in the hormonal replacement therapy to determine whether it was dangerous, in attempt to demonstrate the range of views held on this topic. Dr. Harlan said that his group had concluded that these women should be excluded. Dr. Salmon suggested that the process for evaluating eligibility that was used by the tamoxifen breast cancer prevention trial would be a good model for this study. Dr. Salmon also expressed his concern that women in the high-risk group would not be able to accurately assess their increased risk from only an informed consent or a family history. Dr. Harlan replied that almost all of the women in the study would be at a high risk for breast cancer, as most of them are over 50 and postmenopausal. Dr. Harlan stated that age is the main risk factor for breast cancer, and that the additional risk conveyed by other factors are marginal in effect.

Dr. Durant commented that he hoped the study merited the funds that were being allocated to it. Dr. Harlan replied that the money is being funded separately and that it will not compete with the R01 pool.

Ms. Brown expressed her concern over the implications of this study for women at high risk for breast cancer due to any factor, including age. Ms. Brown also criticized the feasibility of monitoring the diet of the low income minority group member, whose food habits have not been previously studied. Dr. Harlan said that these feasibility issues were the main reason for conducting the minority feasibility trial. Dr. Harlan explained that a food frequency and four day diet record were currently the method of choice, but as data began to be compiled modifications to this method would be made.

XI. UPDATE ON DIETHYLSTILBESTROL—DRS. G. IRIS OBRAMS AND RUTH ANN GIUSTI

Dr. Adamson prefaced the presentations with some background information on diethylstibestrol (DES). DES was introduced in 1938—a time when naturally occurring estrogen was both scarce and expensive. DES is a synthetic, orally active drug; while it is not a hormone, its structure has features in common with steroid hormones. For nearly three decades, DES was used to prevent miscarriages and premature births, even though there were questions about its efficacy. The NCI has funded research on DES because it has been shown to be a transplacental carcinogen, which induces clear cell adenocarcinoma of the vagina and is a risk factor for the daughter of exposed mothers.

Dr. Giusti began her presentation by showing a slide of an advertisement from a 1957 issue of the *American Journal of Obstetrics and Gynecology* describing DES as safe and effective (advocating the prophylactic use of DES in all pregnancies). However, Dr. Giusti stated, several studies in the 1950s raised questions about the drug's efficacy, including a large randomized trial that showed no decrease in spontaneous abortions, neonatal deaths, or premature births among 840 women compared with 806 women receiving a placebo.

Estimates of DES exposure in the United States, Dr. Giusti said, are very rough, with one estimate coming from the National Prescription Audit putting the number of prescriptions at 1 million annually during the late fifties and early sixties and about 500,000 annually for the period between 1963 and 1971. Assuming that 50% of the prescriptions were for completed pregnancies, 13% of the completed pregnancies between 1948 and 1971 were DES exposed.

Dr. Giusti reported that in 1971 a classic case control study noted an association between DES and the subsequent development of clear cell carcinoma of the vagina. This finding was soon confirmed by Dr. Greenwald, and the use of DES in pregnancy was banned later that year.

Dr. Giusti then turned to discussing the effects of DES exposure on daughters in utero. A followup study of daughters exposed during pregnancy suggests that the risk of clear cell carcinoma of the vaginal is low—1 case per 1,000 exposed women. One study has reported a two-fold increase in dysplasia and carcinoma in situ of the cervix and vagina in DES-exposed women. No studies have shown any increases in invasive squamous cell carcinoma among DES-exposed women. Mothers who took DES during pregnancy have been found to have a small increased risk of breast cancer and no increased cancer risks have been shown in men exposed in utero to DES.

Prenatal exposure to DES, Dr. Giusti mentioned, has been associated with anomalies in the uterus, cervix, and upper vagina, and a three-fold increase in genital tract anomalies has been reported among men with prenatal exposure.

As the cohort of individuals exposed to DES ages, questions remain about the risks of breast ovarian, and prostate cancer. In September 1991, Dr. Broder met with two DES-related groups because it was felt that there was a real need to review current data on the long-term health effects of DES-exposure and to develop recommendations for future research. In April, 1992 a workshop will be held to do just that.

Dr. Obrams then made a presentation on the epidemiological studies conducted by the NCI on DES. The NCI, Dr. Obrams said, has been doing epidemiology studies on DES for 20 years. Since 1972, the NCI has supported studies of several cohorts of DES-exposed women and their offspring. One study is focusing on the reproductive function of DES-exposed daughters and sons. Another study is addressing the breast cancer risk of women exposed to DES during their pregnancies approximately 30 years ago. A third study of 5,000 daughters, 4,000 of whom were exposed to DES, is also being funded.

Investigators representing these studies, Dr. Obrams reported, have been invited to the April meeting and will present summaries of the data collected on DES exposed mothers and their children over the past 20 years. Because continuing grant support for these studies is unsure, the NCI will hold a special meeting in April during which these key investigators will try to reach a consensus on the best way to continue to followup these mothers and their children. In the event that no grant application is submitted, Dr. Obrams stated, DCE will support these cohorts by contract. If this happens, a concept will be prepared for review by the Board of Scientific Counselors of DCE.

A question was raised by Dr. Durant on whether any evidence has been found in the grandchildren of DES-exposed women that would suggest that the drug has gotten into the genome. Dr. Giusti replied that there have been no reports of increased cancer risk in the third generation. However, she noted, those children are still quite young and this group has not been systematically studied.

XII. CANCER PREVENTION RESEARCH FACILITY—DR. BARRY KRAMER

Dr. Peter Greenwald brought to the Board's attention the concept of a proposed cancer prevention research facility, to be funded if possible through the Division of Cancer Prevention and Control (DCPC). He noted that the Division's intramural program is the smallest within the NCI, representing about 2 percent of the overall intramural activities. While the DCPC is intended to be primarily an extramural division, Dr. Greenwald stated that a "critical mass" of hands-on scientists is needed to be able to effectively lead a large national program. He also observed that intramural and extramural programs growing in parallel would benefit each other. Thus, the NCI is seeking space to house a somewhat larger intramural prevention effort.

Dr. Greenwald introduced Dr. Barry Kramer, Associate Director for Early Detection and Community Oncology, to further describe the proposed facility.

Dr. Kramer stated that the development of a cancer prevention research facility was approved unanimously and identified as a top priority in October by the Board of Scientific Counselors of the DCPC. He explained that the concept of the facility is based on three premises: 1) the impact of diverse approaches, such as studies of cellular events and epidemiologic studies of risk factors, on the science of cancer prevention; 2) the potential of emerging disciplines, such as molecular epidemiology, to provide a synthesis of orientations; and 3) the need to train future scientists in cancer prevention. Progress could be expedited by the development of a facility that combines the strengths of various institutions. Dr. Kramer cited a recent article in the *Journal of the National Cancer Institute* describing a similar effort in France by that country's Association for Research on Cancer, which plans to set up a comprehensive research center for cancer prevention, detection, and early diagnosis.

The proposed NCI facility, Dr. Kramer continued, is planned as a means to accomplish two important goals for the Institute's intramural program: 1) to build on the scientific base of cancer prevention and remain at the cutting edge in this field; and 2) to build upon the NCI research infrastructure for meeting future space needs as the prevention field expands.

Dr. Kramer used a slide to illustrate the concept of the cancer prevention research facility as a nucleus of activity drawing on a variety of expertise. While the DCPC would play a key role in the facility, other divisions of the NCI, including the Division of Cancer Biology, Diagnosis, and Centers and the Division of Cancer Etiology, have expressed interest in becoming involved. Other Federal research institutions have also expressed interest, including the Department of Energy. Academic cancer centers and schools of public health also should play a major role.

Each group in the facility would be funded by its own traditional mechanisms; for the NCI, this would be its intramural budget. These mechanisms would be subject to the usual review process, including site visits. The involvement of academic centers would be funded by competitive awards through the research project grant pool.

Dr. Kramer detailed four main areas of rationale for the facility: 1) such a center would bring together a broad range of expertise for daily interactions; 2) progress in specific areas of importance could be accelerated (for example, markers of high risk for direct screening); 3) the facility could identify leads that could then be evaluated and transitioned into definitive, large-scale extramural trials; and 4) no model currently exists in the United States specifically devoted to cancer prevention.

Most of the floor space in the facility, Dr. Kramer stated, would be devoted to bench research, especially in the areas of molecular biology, immunology, and biochemistry. An

ambulatory clinical unit would also be available for small-scale pilot trials that could then be scaled up in the extramural community. There would also be applied disciplines in the fields of epidemiology and computer science, as well as training and biometry facilities. A core of activities for routine tests, such as DNA sequencing, protein synthesis, monoclonal antibody production, tissue culture, and flow cytometry is anticipated. Finally, there is the possibility that a core facility would house a metabolic kitchen that would be useful for nutrition studies.

Dr. Kramer explained that the NCI has estimated a need for about 25,000 square feet for the facility; as more partners express interest in participating, this estimate may have to be increased. Within the NCI space, the Division of Cancer Biology, Diagnosis, and Centers has expressed interested in having some laboratory facilities for vaccine research; biomarkers would be addressed by the newly formed branch in the Division of Cancer Prevention and Control; the Laboratory of Nutrition and Molecular Regulation has expressed interest in using the facility; and the Division of Cancer Etiology (DCE) has expressed interest—DCE labs that could participate include Molecular Oncology, Viral Carcinogenesis, Cellular Carcinogenesis and Tumor Promotion, and Comparative Carcinogenesis.

Dr. Kramer explained that several mechanisms for operating such a facility have been explored. The ideal would be a cooperative agreement with one or more academic institutions. A precedent for this type of partnership is the Center for Advanced Research in Biotechnology, a joint venture in Gaithersburg, Maryland, between the National Institute for Standards in Technology and the University of Maryland. Discussions with the NCI Office of Space Management and the Office of General Counsel indicate that this type of arrangement is feasible. A less ideal solution would be a straightforward long-term lease arrangement for the NCI from an academic institution that would offer to build the facility.

Dr. Kramer concluded by explaining that, if a lease arrangement is the mechanism chosen, the institution that builds the facility will be selected in open competition based on several criteria, including proximity to the NIH campus and expertise in critical research areas.

Dr. Temin asked whether research on cancer vaccines would include viral vaccines, from the point of view of both development and getting people to use them. Dr. Greenwald responded that efforts are underway on the development of viral vaccines, and that the NCI is working to define an appropriate role for the DCPC in this effort. One question is whether a structured process is needed to facilitate progress on one or two more promising targets in addition to the usual investigator-initiated research.

Dr. Temin again expressed his concern that there are good vaccines, such as the vaccine against HBV, which people are not using. Dr. Durant asked whether the nonuse of the hepatitis vaccine was a sufficient subject for a clinical alert. Dr. Temin noted that an estimated 30 percent of all health care workers are not immunized and that as many as 30,000 cases of hepatitis occur among such workers in a year.

Dr. Bettinghaus expressed concern that, frequently, the existence of an intramural facility tends to help guide the direction of the RFAs issued by a particular Division. He asked whether the existence of this facility might begin dictating the nature of the direction in which the DCPC might go, a development that might not be in the best interest of the larger goal of preventing many kinds of cancer—through the reduction of tobacco use, for example. Dr. Greenwald acknowledged this concern. He argued, however, that there are few resources for training in fields related to prevention research, and suggested that having an intramural program helps build training based on solid science as a means of promoting the field.

Dr. Kramer pointed out that the facility's involvement with academic centers would give people in the facility a larger view of potential areas to move into around the country.

Dr. Jako spoke in support of the facility, noting that the primary mission of the Public Health Service relates to the prevention of disease. He added that, if other institutes are to be involved, a larger facility will be required.

Dr. Salmon asked whether the DCPC was considering moving its headquarters in conjunction with the establishing the facility, making the point that administration should not be too far detached from the science. Dr. Greenwald agreed on this point, suggesting that ideally administrators and scientists would work together.

XIII. SUBCOMMITTEE REPORTS—DR. PAUL CALABRESI

Women's Health and Cancer Subcommittee Report

Mrs. Pollin began by noting the eager positive responses she received from various Senators and Congressmen regarding their interest in working with the Subcommittee. She then proceeded to discuss the fact that 83% of medical decisions are made by women. This, she said, raises questions such as: "What happens to a family when the woman becomes ill? Who cares for the caretaker?" Therefore, a support system seems crucial to recovery. Citing Dr. Spiegel's study as an example, Mrs. Pollin pointed out that, among the differences between women and men, women with cancer require a different kind of psychosocial support than men as part of their treatment. She suggested that the sources for such support be considered as part of women's health issues studies.

The Subcommittee's guest, Dr. Vivian Pinn, Director of the NIH Office of Research on Women's Health (ORWH), described the activities and plans of the office. Dr. Pinn reported to the Subcommittee that ORWH has indeed stressed the bio-behavioral aspects of disease and cancer in women's health. Dr. Pinn also stated that she needs more staff support to enable the office to carry out its mission and to disseminate information about women's health activities at NIH throughout the community. In addition, ORWH budget increased from $1.8 to $10.5 million within fiscal year 1991-92, allowing for more research on women's health. In 1991 alone, ORWH supplemented 20 NIH grants with $800,000 for the purpose of increasing the representation of women, particularly minority women. Dr. Pinn explained that ORWH does not have its own grant authority. Supplements must conform to an internal NIH selection process, which is in development. She also intends to fund research on new and current issues. For instance, Dr. Pinn expressed interest in assisting NCI with its request for partial funding to cover costs of blood tests for effects on women's immune systems for the planned NCI study of breast implants.

Dr. Pinn is also the Co-Director of the NIH Women's Health Initiative Study. At the Subcommittee meeting, she described plans for a public hearing, March 2-3, to receive topic recommendations for a conference in June on recruitment, retention, and advancement for women in biomedical research careers. Dr. Becker pointed out that there is a need for accurate data and that Dr. Pinn's office should provide such data as a valuable service, which Dr. Pinn assured is forthcoming. Dr. Bragg suggested that Dr. Pinn's office network with the women's committees of professional societies to obtain information. It was noted that while female investigators have a comparable award rate to men, they apply for and receive smaller grants.

Dr. Pinn acknowledged the recommendations made and closed her report to the Subcommittee with mention of a forthcoming conference report on research opportunities in women's health and funding of an IOM study on the ethical, legal, and medical barriers to the inclusion of women in clinical trials.

Cancer Centers Subcommittee Report

Dr. Durant reported that the Subcommittee had met to decide what to do with a limited budget and an increasing number of funding requests.

Several financial models that had been presented to the Subcommittee were reviewed, resulting in the recommendation that there should be a cap on the Cancer Center Support Grant award to any center based on the size of its research base. This amount would only increase if the rest of the grant support in the research base grows. The size of the research base would be determined from all NCI research support; all NIH research support in which there is a secondary NCI assignment; all American Cancer Society support; and all other support submitted by the center directors that comply with NCI Grant Referral Guidelines and eligibility requirements of the Cancer Centers Program. As Dr. Durant noted, this method enables other centers to grow and results in a more equitable distribution of funds, which may in turn breed new support. Dr. Temin asked Dr. Durant whether or not the T32 grants are included and suggested that training be included in any model for research. Dr. Durant added that the Subcommittee emphasized flexibility in how to deal with the issue of funding.

Information and Cancer Control for the Year 2000 Report

Dr. Bettinghaus reported that the Subcommittee approved two concepts for contracts for NCI's Office of the Director: $40,000 for support of activities of the U.S. National Committee and the International Union Against Cancer; and the start-up funding of $600,000 to continue and complete the local area network service NCI is currently developing, with a maintenance contract thereafter of $400,000 annually.

Mrs. Pollin, Dr. Bettinghaus continued, gave the Subcommittee an exciting report about the National Basketball Association (NBA) and the NCI mammography initiative. Approximately 80 wives of NBA players and wives of staff members of NBA teams attended an all-day meeting; they were instructed on how to assist their local cancer centers in disseminating information about cancer. Dr. Bettinghaus added that the Subcommittee suggested to Mrs. Pollin that it become an ongoing event.

The Subcommittee, Dr. Bettinghaus further reported, suggested last fall that it would be useful to collect sample materials from various cancer centers throughout the United States. The NCI has since collected a large amount of material. The Subcommittee agreed that this educational information directed at cancer patients and the community at large can become available to medical libraries if it is placed in the Combined Health Information Database (CHID). NCI staff will let each center know how to add their materials to the database.

Planning and Budget Subcommittee Report

Dr. Fisher reported that the subcommittee discussed the 1992 budget. He noted that Dr. Wells was concerned about the effect the flat training budget would have on the pool of trained investigators. The explanation was that the National Research Service Awards have not been reauthorized, and therefore the appropriations committee has not increased the funding.

Dr. Fisher mentioned that the NIH Financial Management Plan would limit the increases to the biomedical research and development price inflator (BRDPI), which would keep down growth. He also reported that members of the subcommittee felt that it would be a good idea to hold the January Board meeting after the President's State of the Union Address, although they did understand that the NCAB meetings are planned far in advance of the State of the Union Address.

The subcommittee approved a draft of the NCAB Biennial Report for 1991-1992 and thought that it was a good document. They then moved on to a discussion of NIH's Framework for a Strategic Plan. Dr. Temin suggested that the document should contain some mention of health care practice and costs. It was also noted the Framework contained no indication of strategies to deal with the deteriorating infrastructure of biomedical research.

Another topic of discussion at the subcommittee meeting was an analysis of the support to individual investigators. Dr. Fisher noted that in fiscal year 1990, NCI funded 2,600 different investigators with more than 3,000 grants. Ninety investigators received more than $500,000 for research. Dr. Temin raised this issue in an attempt to discover whether some of the monies in the larger grants could be recaptured and used to fund additional R01 or R29 awards. In this way, more and better training opportunities would be supported by keeping more laboratories functioning. This led to discussion of investigators reporting all sources of funding, including outside of NIH sources such as the Howard Hughes Medical Institute and the American Cancer Society. The question was then raised, Dr. Fisher said, if there is any auditing. The discussion as to what to do regarding this issue drew no conclusions, except that it was determined that this issue should be more thoroughly explored. The fear is, he explained, that as these grants get bigger and bigger, that there will be less care about training, which is supposed to be an integral part of the grants. This area may be appropriate for consideration by the entire NCAB, he added. NCI staff will provide more information at the next meeting about what information could be provided about total support to investigators who receive a large amount of NCI funding.

The final topic of discussion at the subcommittee meeting was the future use of OIG and MERIT awards. They discussed phasing out the T1 OIGs and limiting OIG investigators to one renewal with the added requirement that they develop a transition plan to other mechanisms relatively early in the renewal period. A few members expressed the opinion that, while it is nice not to have to prepare a detailed application, the need to recompete promotes scientific quality. A suggestion was made to hold MERIT and OIG awards to 13 percent rather than 15 percent, and if the OIGs are phased out, then the MERIT awards should be held to a lesser proportion, such as 10 percent. The Subcommittee will consider this topic at its next meeting.

Dr. Broder asked that members of the Board who wished to make comments regarding the Bypass Budget, do so as soon as possible. Secondly, he said, they would like to further address the issue of the MERIT and OIG awards with the Board and would like the Board's input either from subcommittee or the full Board. Dr. Broder raised a third point, concerning the size of awards. He stated that NCI is generally opposed to caps on funding, and that perhaps a better focus would be the amount of time the investigator will spend on the grant. He offered the example of an investigator who has committed 25 percent of his or her time to a grant, then, after the grant has been awarded, trying to reduce the committed time to be able to allot time to another grant. In this situation, Dr. Broder noted, it may be that the grant was approved on the strength of that investigator's time commitment and reviewers might feel that a smaller commitment would not be sufficient.

It was then recommended that Dr. Fisher's subcommittee could prepare a survey of some sort asking the members their views on the MERIT and OIG awards. Dr. Calabresi then asked Dr. Fisher to have his subcommittee prepare some proposals for the NCAB to react to.

Dr. Salmon noted that NCI does not have a system to check the accuracy of data on investigators' support from outside agencies.

XIV. NEW BUSINESS

Dr. Calabresi opened the meeting's new business portion with a call to approve the minutes for the November meeting. The minutes were unanimously approved as written.

Mrs. Bynum followed with a note on her report of the regional meetings on preparing the "Framework for a Strategic Plan". She reported that additional meetings have now been scheduled in response to increased interest. She then invited the various committee members to attend the meetings, as well as to submit any comments or testimony.

Dr. Calabresi brought up two issues to be voted on and discussed, both of which dealt with the effects of newly-mandated travel restrictions. The NCAB, he reported, strongly advocates that Congress remove the imposed travel restrictions and has drafted a resolution to that effect. In the discussion following, changes in the resolution's wording were decided upon to specify that these restrictions apply only to domestic travel. The resolution was then approved by the Board, unanimously.

The second issue concerned site visit allocations as described in a proposal prepared by DEA. There was an extensive discussion regarding whether any revisions to this plan are necessary. It was stressed that appropriate judgment, rather than automatic action, be the basis for site visits, and that no one site visit was more important than another. It was then agreed that a formal Board resolution was not needed on this matter, because the appropriate NCI staff were in attendance and received the message.

Dr. Broder continued the meeting with his report on the press conference launching the Regional Mammography Summits, cosponsored by the Komen Foundation. Nine comprehensive cancer centers received NCI conference grants to conduct eight summits. He noted that all the grantees attended the press conference, and special awards were presented to Ginger Sullivan and the Komen Foundation. Dr. Broder will report back the results from the summits after seeing how effective the Comprehensive Cancer Centers are serving as local information outlets for outreach activities. Mrs. Malek, NCAB liaison and National Chairman of the Summits, added that the press conference was well attended.

Dr. Calabresi turned to Mrs. Bynum, who offered a motion giving cognizant NCI management grants specialists the authority to negotiate actual award amounts, a duty the Board would otherwise be responsible for. Board approval was unanimous.

This portion of the meeting ended with Mrs. Bynum's suggestion that, for their information, Board members review the newly revised manual issuance (4513) describing policy on board and council operations.

Future Agenda Items

Since questions had been raised regarding the basis upon which foreign grants are decided, Dr. Becker requested that Mrs. Bynum gather informational materials on the matter for discussion at a future meeting.

XIV. ADJOURNMENT—DR. PAUL CALABRESI

There being no further business, the 81st National Cancer Advisory Board was adjourned at 2:17 p.m., January 28, 1992.

Date

Dr. Paul Calabresi, Chairman