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

Summary of Meeting
May 5-6, 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]
May 5-6, 1992

The National Cancer Advisory Board (NCAB) convened for its 82nd regular meeting at 8:00 a.m. May 5, 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. Phillip Frost
Mrs. Brenda Johnson
Dr. Walter Lawrence, Jr.
Mrs. Marlene A. Malek
Ms. Deborah Mayer
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. Benjamin Barnhart, DOE
Dr. Roy Fleming, NIOSH
Captain Bimal Ghosh, DOD
Dr. John Johnson, FDA
Dr. Theodore Lorie, DVA
Dr Hugh McKinnon, EPA
Dr. Dr. Lakshmi Mishra, CPSC
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

---

[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

Dr. Eve Barak, Associate Director for Cell Biology, Division of Cellular Biosciences of the National Science Foundation, representing the National Science Foundation, Washington, DC

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

Dr. Robert W. Frelick, representing the Association of Community Cancer Centers

Dr. Edward P. Gelmann, Chief, Division of Medical Oncology of the Vincent Lombardi Cancer Research Center, representing the American Society of Clinical Oncology

Dr. Marston W. Linehan, Head of the Urologic Section, Surgery Branch, Division of Cancer Treatment, representing the Society of Urologic Oncology

Dr. Elaine Locke, representing the American College of Obstetricians and Gynecologists

Dr. Edwin A. Mirand, representing the Association of American Cancer Institutes

Ms. Linda O'Connor, representing the Oncology Nursing Society

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

In addition to NCI staff members, meeting participants, and guests, a total of 35 registered members of the public attended the meeting.

TABLE OF CONTENTS

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) and members of the President's Cancer Panel. 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.

II. FUTURE BOARD MEETING DATES AND CONSIDERATION OF MINUTES OF PREVIOUS MEETING—DR. PAUL CALABRESI

Dr. Calabresi addressed the topic of future Board meeting dates. Meetings scheduled to occur in 1992 and 1993 were previously confirmed by Board members and are listed on the agenda. Dr. Calabresi turned the Board members' attention to the confirmation of the 1994 meeting dates. He explained that, as mentioned during previous meetings, the meetings are scheduled to last 3 days; however, whenever it is possible, the meetings will adhere to a 2-day agenda. Dr. Calabresi added one correction to the list of scheduled 1994 meeting dates. He asserted that to comply with a previous Board decision regarding the May-June meeting, the meeting that was scheduled to occur on May 30-June 1 must be moved to May 31-June 2. This decision was based on a conflict of times with the Association of Physicians of Medicine Meeting. As there were no further corrections, Dr. Calabresi announced that the 1994 meeting dates were confirmed.

Dr. Calabresi reminded members that the January minutes have been mailed to members and that copies are also included in their Board books. Dr. Calabresi then announced a motion to approve the January minutes. The motion was seconded and approved.

Dr. Calabresi stressed to all members the importance of attending the entire 2-day meeting. He explained that a quorum of Board members is required for a vote to be considered official. A quorum consists of a minimum of 12 Board members. Dr. Calabresi added that as it is impossible to predict the time or occurrence of all motions, members are requested to be present at all times. He also emphasized the need to abide by the scheduled timeframes for all items on the agenda.

Dr. Calabresi announced that any Board member who would like to have a grant application discussed must inform Mrs. Bynum by the end of the morning coffee break to allow time to alert the necessary staff and gather the appropriate materials.

Dr. Calabresi informed members that the closed session of the day's meeting would begin at exactly 3:00 p.m., following the subcommittee meetings. He stressed the urgency of all members attending this session to ensure a quorum.

Dr. Calabresi pointed out that this meeting was being covered by closed circuit television. He also requested that guests avoid taking seats marked "Reserved."

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

Dr. Freeman reported that the Panel had held four panels in four different cities within the last year. He stated that a fifth panel was scheduled to occur in New York in early June.

Panel topics have included poverty and cancer, breast cancer, technology transfer, the education of the scientist, and, next month, prevention of cancer.

Dr. Freeman updated members on the status of various Panel activities. The annual report, Dr. Freeman said, is nearly finished and will be delivered to the President upon completion. Dr. Freeman informed members that the subpanel on breast cancer, which is chaired by Nancy Brinker, will convene their first meeting on May 28 at the National Institutes of Health (NIH). Mrs. Marilyn Quayle and Dr. Bernadine Healy, Director of NIH, will both be present at the initial meeting. Vice President Quayle had requested that the Panel form a subcommittee on breast cancer to conduct an extensive review of breast cancer research, detection, and treatment in the United States and around the world. The 17 members of this subpanel were chosen from a broad spectrum of disciplines.

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

Dr. Broder began his report with some announcements. He informed members that the President had announced that day his intention to appoint Charles B. Wilson a member of the NCAB for a term that would expire on March 9, 1998. Dr. Wilson will succeed Dr. Ken Olden, who assumed *ex officio* status due to his appointment as head of the National Institute of Environmental Health Sciences (NIEHS). Dr. Broder reported that Dr. Wilson currently serves as the Director of the Brain Tumor Research Center at the University of California in San Francisco.

Dr. Broder, with the assistance of Mrs. Bynum, thanked and distributed certificates of appreciation to five Board members whose terms of service have expired, including Dr. Bernard Fisher (in absentia), Dr. John Durant, Dr. Phillip Frost, Mrs. Irene Pollin, and Mrs. Zora Brown. Dr. Broder stressed that they will continue to serve as Board members until the President appoints their successors.

Honors, Awards, and Staff Changes within the NCI

After a brief overview of the highlights of the meeting's agenda, Dr. Broder proceeded to announce recent award recipients. Dr. Calabresi, NCAB Chairman and Chairman of the Department of Medicine at Brown University, received the Oscar Hunter Memorial Award in Therapeutics. Dr. Lou Staudt, a member of the NCI, was given the Arthur S. Flemming Award, which is an extremely prestigious award given to government employees of exceptional promise. Dr. Steve Katz, Dr. Claude Klee, and Dr. Tom Waldmann were all elected to the Institute of Medicine. Dr. Ira Pasten was elected to the Academy of Arts and Sciences. Dr. Brian Kimes, Dr. Claude Klee, and Dr. Eli Glatstein received the Presidential Executive Rank Award. Dr. Broder reminded members that Dr. Glatstein left the NCI to become Director of Radiation Oncology at the Southwestern Medical School at the University of Texas at Dallas.

Dr. Broder then announced some staff changes. Mr. Donald Christoferson, the deputy associate director for administrative management, will serve as the acting assistant director and deputy agency ethics official for the NCI. Ms. Iris Schneider, assistant director for program operations and planning, will serve as the acting executive secretary for the President's Cancer Panel and for the Panel's special commission on breast cancer.

New Developments within the NCI

Dr. Broder reported that the President's Cancer Panel convened on February 21 in San Francisco to discuss the issues of cancer research and technology transfer. Dr. Broder added that future meetings will consider the causative relationship between poverty and cancer.

Dr. Broder announced that the NCI participated in the House appropriations hearings on March 16. Representative William Natcher (D-KY), who served as chairman, and other members of Congress expressed concern over cancer incidence and mortality rates. Dr. Broder stated that Congressional members also focused attention on information dissemination and public awareness, breast and prostate cancer, vaccines against cancer, and activities targeted to minority and undeserved populations. Dr. Broder noted that Congress also explored the topic of outreach activity in the cancer centers. He indicated that he is extremely pleased with the efforts of the cancer centers in response to the new criteria of comprehensiveness, which require that the center define the community it serves and engage in meaningful community service and outreach activities, in addition to numerous other requirements. He said that he believes these efforts have elevated the entire quality of the Centers Program. Dr. Broder reported that Congressional members asked questions concerning the implementation of the NIH strategic plan, the importance of the Cancer Institute in AIDS research, the NIH-wide Women's Health Initiative, and technology transfer. Dr. Broder said that Ms. Tisevich could probably obtain transcripts of the hearing for Board members who want them.

Dr. Broder informed members that the Senate appropriations hearing was scheduled for May 13, with Senator Tom Harkin (D-IA) presiding. He indicated that efforts will be made to update Board members concerning this hearing.

A number of new programs relating to breast, prostate, ovarian, and cervical cancer were initiated since the fiscal year 1992 appropriations committee report urged, "in the strongest way that the National Cancer Institute make breast, prostate, ovarian, and cervical cancer its top priorities and treat these diseases with the utmost urgency." Dr. Broder emphasized that efforts have been made to develop new specialized programs of research excellence (SPOREs). NCI also issued a program announcement for new and competing applications targeting research in these areas. Dr. Broder expressed extreme satisfaction regarding the number of applications that have been received in response to the program announcement. Dr. Broder also indicated that another important aim of the program announcement has been achieved, which is to prompt funded cancer researchers to expand their activities to include these cancers. Dr. Broder added that the breadth of the response and high level of quality of the SPORE applications in breast, prostate, and lung cancer is highly commendable. Members of the National Cancer Program have rallied to respond to these major concerns.

Breast cancer is a topic of primary importance at the Institute. The Women's Health Initiative has commenced, which will explore a number of issues including dietary fat reduction as an applied variable in a large-scale preventive trial. Dr. Broder stated that a study to explore the role of tamoxifen as a possible chemopreventive agent for women in certain risk categories has also been initiated.

Dr. Broder then highlighted some statistics regarding breast cancer to emphasize the importance of this topic. Beginning with women who are in their 20s, a noticeable rate of breast cancer is apparent. Starting at age 30 and for every age group thereafter, the incidence of breast cancer dominates the graphical representation of cancer statistics. Dr. Broder summarized the results of the statistical analysis, which indicate the prominence of breast cancer and that the risk of developing breast cancer dramatically increases as a function of age. By the time an American woman reaches age 60, for every 100,000 women in that age group, approximately 300 will develop breast cancer in any given year, and if she continues to live until age 65, the incidence for that age group increases to 400 new cases of breast cancer in any given year.

Dr. Broder reported that on April 29 an announcement was made that Dr. Fisher would be the principal investigator in a study being conducted at approximately 300 sites in the U.S. and Canada to explore whether tamoxifen can prevent breast cancer among women in certain risk categories. Dr. Broder emphasized that tamoxifen is not a panacea for breast cancer. It has been shown to prevent the development of a new primary tumor in the contralateral breast in women

who already have had one primary. Some studies have shown it reduces the risk of developing a new primary by 30 to 40 percent. However, there are side effects that have been linked to the use of tamoxifen; the most probable risk is the development of endometrial cancer or thrombophlebitis. There has been an indication that it may cause liver cancers in rats.

Dr. Broder discussed some of the criteria for entering this trial, which vary depending upon the age category of a potential subject. The younger a woman is, the more significant her risk for developing breast cancer must be to qualify for the study. Issues such as whether a mother, sister, or daughter has breast cancer; whether there have been previous biopsies (especially with atypia), age of onset of menstruation, and age of first full-term delivery determine an individual's risk for developing breast cancer. An automatic eligibility condition is a diagnosis of carcinoma or lobular carcinoma *in situ*. Dr. Broder added that if a woman has multiple risk factors, her chance of developing breast cancer is a cumulative product of all these factors. A risk profile would be developed for each woman to determine if she is at a level of risk that would qualify her for entry into this placebo-controlled trial.

Dr. Broder stressed that NCI does not recommend that doctors prescribe tamoxifen as a chemopreventive agent. The intent of the study is to determine the role of tamoxifen in cancer prevention. A possible link between tamoxifen and a lowered cholesterol count and positive effects on osteoporosis will also be explored.

In addition, the National Heart, Lung, and Blood Institute and the National Institute of Arthritis and Musculoskeletal and Skin Diseases will be collaborating with the NCI. Dr. Broder emphasized, however, that the tamoxifen study is not the only approach the NCI is utilizing to address breast cancer. The dietary fat reduction study, studies of certain micronutrients or synthetic vitamin A analogs, and research examining the role of 4HPR are other efforts regarding breast cancer treatment and prevention. NCI is also working to expand the basic research program on vaccine development

Dr. Broder announced that the first of the regional breast cancer summits were held in Tucson at the Arizona Cancer Center and in Detroit, Michigan, at the Mary Ellen Prentiss Comprehensive Cancer Center. Over the next several months a total of eight summits will be convened, which are cosponsored by the NCI and the Susan G. Komen Foundation and hosted by NCI-designated comprehensive cancer centers. The summits gather businesses, community organizations, and health service providers to learn about the importance of early detection of breast cancer and methods for establishing cancer screening activities. These programs place special emphasis on reaching undeserved women in the community through outreach activities. Dr. Broder added that Marlene Malek is the National Chair of the summits and that Mrs. Quayle is the Honorary National Chair. Dr. Broder remarked that Nancy Brinker is the "spiritual chair" for many of these activities and thanked her for her hard work.

The President's Cancer Panel established its special commission on breast cancer, chaired by Nancy Brinker. The 17-member commission will study the status of breast cancer research, prevention, detection, and treatment and will report on methods to enhance efforts to reduce morbidity and mortality rates for breast cancer.

Dr. Broder informed members that he would be leaving the meeting at noon to attend a special breast cancer coalition meeting. This coalition is composed of women from across the nation who have joined together to focus on new and more effective methods for preventing and treating breast cancer.

Dr. Broder stated that a National Minority Cancer Awareness week was recently announced. A Spanish version of the film, *Once a Year for a Lifetime*, was created as part of the effort to focus attention on minorities and cancer. Dr. Broder reported that at the same press

event, Mrs. Ginger Sullivan announced the beginning of Project Awareness, a public/private partnership created to provide undeserved women with breast cancer education, mammography, clinical breast exams, and follow-up. The project will be initiated this year in eight U.S. cities by a coalition of organizations, including the NCI.

Dr. Broder also mentioned that the National Basketball Association is continuing the NBA Wives Save Lives initiative that was conceived of and facilitated by Irene Pollin. He thanked Mrs. Pollin for her hard work.

Taxol Update

Dr. Broder described taxol as having a solid role in helping to induce partial and, in some cases, complete responses in people with end-stage cancer and without other options. He emphasized that it is not a magical cure but is certainly active in breast and ovarian cancer. A major issue of concern related to the drug is availability. Currently, the only source of taxol is the Pacific yew tree; however, ecological issues are involved, as stripping the bark to extract the drug kills the trees. These concerns have hampered efforts to obtain an adequate supply. One possible alternative being explored is the development of synthetic or semisynthetic versions of taxol. Dr. Broder noted that a semisynthetic version of taxol, called taxotere, has been developed and will be studied, and that he expects promising findings regarding the total synthesis of taxol will soon be available. Dr. Broder informed members that many prominent scientists have expressed doubt concerning the development of a total synthesis of taxol, but that recent research makes this prediction premature.

Discussion of the NCI Budget

Dr. Broder reported that the actual obligations for 1991 were approximately $1.7 billion. The appropriation for 1992 was about $1.989 billion when the year began, which was a little more than a $275 million increase; however, numerous reductions have resulted in an adjusted appropriation estimate of $1.951 billion. The primary reduction was in the area of travel and was NIH-wide. Dr. Broder explained that in order to protect patient travel to the NIH Clinical Center for individuals on protocols, larger cuts will be made in other travel such as staff travel to scientific meetings and site visits. The appropriation estimate reflects a salary and expense reduction of approximately $22 million and the NIH Director's authority to move about $15 million out of the Institute. A further reduction of $16 million has been proposed by the NIH Director, which would leave the budget at slightly over $1.935 billion. Dr. Broder commented that the President's budget for fiscal year 1993 for the NCI is approximately $2 billion.

Dr. Broder summarized the breakdown of the fiscal year 1991 obligations. Expenditures in the Research Project Grant (RPG) category totaled approximately $792 million. Research Project Grants, which include traditional investigator-initiated grants, P01s, FIRST Awards, and Outstanding Investigator Grants (OIGs), are always the largest component of the NCI grants budget.

Dr. Broder initiated a discussion regarding the Outstanding Investigator Grants. He indicated that a poll of the members was taken by phone concerning the establishment of a temporary moratorium on this type of grant. Twelve of the 17 members were reached, and all those available agreed to the moratorium. Dr. Broder then explained that this means that any new applications for this particular grant will be held. Dr. Broder then presented the details of the debate surrounding Outstanding Investigator Grants, explaining that these grants were implemented at a time before the current cost containment policies of the NIH were initiated and when there was no focus on limiting out-year award length or commitments. Congress has specified that the average length of an award must, for all Research Project Grants, be 4.0 years. Since the Outstanding Investigator Grant lasts 7 years, this grant poses a problem. In addition,

the Board has requested that a cap be placed on the total percentage of the RPG pool that is devoted to long-term awards, such as the Outstanding Investigator Grant. Dr. Broder indicated that a fair method for dealing with this mechanism is being developed and that any input on the topic would be appreciated.

The fiscal year 1992 adjusted appropriation for the Research Project Grants is about $891 million and for fiscal year 1993 the President's budget request is $953 million. These figures indicate that an increase of approximately $62 million has been allocated to the Research Project Grant line. Dr. Broder observed that this category is the only budget area that has been proposed for an increase in funding.

Dr. Broder stated that cancer centers funding increased from $110 million in FY 1991 to $125 million in FY 1992, and will remain at this funding level for fiscal year 1993. The SPOREs program, which was created in fiscal year 1991 for initial funding in FY 1992, received $17.5 million. Although these two programs are classified as separate categories, for administrative purposes they are considered as the two elements of the total centers line, which has a budget of about $143 million. Dr. Broder stressed that, in his opinion, the SPOREs program does not divert funding from other programs. He added that he believes that the SPOREs program will be extremely important.

Dr. Broder indicated that several budget categories were not allotted an increased amount of money for fiscal year 1993, including the research career programs, cancer education programs, and the minority biomedical support grants. He added that the cooperative group line, which received an increase of $17 million (from $61 million in 1991 to $78 million in 1992) after experiencing a loss of 33 percent of its constant dollars over many years, was not proposed for an increase for 1993. In addition, he stated that the budget request for National Research Service Awards (NRSAs) was not increased for fiscal year 1993. NRSAs require special authorization as part of a larger NIH package, and the appropriations committee has taken the position that it will not increase the budget for this activity until a higher amount is authorized.

Dr. Broder noted that there are some reductions included in the 1993 President's budget request. From fiscal year 1991 to fiscal year 1992, the cancer prevention and control line enjoyed a $21 million dollar increase (from $85 million to $106 million); however, this item is targeted for a 14 percent reduction in the President's budget. In addition, the construction line is completely eliminated from the budget for fiscal year 1993.

Dr. Broder presented a breakdown of the competing and noncompeting grants as part of the Research Project Grant pool. He indicated that an increase is estimated in noncompeting funded grants from 2,200 in 1991 to nearly 2,500 in fiscal year 1993. Regarding the competing line, 840 grants were awarded in fiscal year 1991, and this figure will be in excess of 1,000 for 1992. NCI expects to fund more than 3,300 grants in fiscal year 1992. Dr. Broder added that he expects the figure for the total number of competing and noncompeting grants to reach a bit under 3,400 for fiscal year 1993.

The total success rate of all Research Project Grants is expected to increase from about 28 percent in fiscal year 1991 to 34 percent in 1992, and the figure will decrease slightly in 1993 to a 30 percent total success rate.

Dr. Broder indicated that he expects that the Shannon Award system will be implemented at the NIH-wide level, as in the previous year. He informed members that the NCI will have an integral role in the NIH-wide strategic plan and that numerous community-based meetings regarding this topic have been convened. Dr. Broder stated that Board members will be apprised of developments related to the NIH strategic plan.

Dr. Broder mentioned that during the day's Budget Subcommittee meeting, general principles of the bypass budget would be discussed. He stated that input concerning this matter would be appreciated. Specific figures for the professional needs, or bypass, budget are not yet available.

Dr. Jako stated that he agreed with the current funding focus on breast cancer and other primary cancers mentioned earlier. He asserted that respiratory cancers, especially lung cancer, must also be addressed. He suggested that methods for early detection in breast cancer may be applicable to lung cancer. Dr. Broder responded that he agreed that the NCI must focus on lung cancer. He added that as lung cancer is the number one cancer killer among men and women, it is impossible to make progress against the incidence and mortality of cancer without addressing lung cancer. Dr. Broder pointed out that it is one of the diseases included in the Specialized Program of Research Excellence Program. He stressed that he believes progress is being made in reducing the incidence of lung cancer in certain groups; for example, White men in certain age categories. Among women, however, the mortality rate due to lung cancer has increased in excess of 100 percent over the last 20 years. This increase, Dr. Broder asserted, is largely linked to changes in smoking practices and the fact that women have been specifically targeted by commercial organizations with messages that induce them to smoke. Dr. Broder stated that efforts addressing lung cancer must be increased, but must not only focus on smoking cessation. Effective programs for individuals who have already begun to develop lung cancer are also essential.

Dr. Bettinghaus expressed his concern regarding the approximately $15 million reduction in cancer prevention activities. He noted that the Board has made numerous comments that are on record in support of prevention efforts at the Institute. Dr. Broder responded that the reduction in the fiscal year 1993 budget is not yet definite.

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.

NCI-Related Hearings and Briefings

Ms. Tisevich stated that several hearings and briefings involving NCI staff have occurred since the last NCAB meeting. On March 4, Dr. Bruce Chabner, Director of the Division of Cancer Treatment (DCT), testified at a joint hearing on taxol, which was chaired by Representative Gerry Studds (D-MA). This hearing focused on legislation introduced by Representative Studds, the Pacific Yew Act of 1991, which was designed to prevent waste of the Pacific yew resource by providing for proper management of federal lands containing these trees. A follow-up briefing for subcommittee staff on the annual plans for the Pacific yew harvest was delayed due to ongoing negotiations between Bristol-Myers Squibb and the Bureau of Land Management. The briefing was finally held on April 22, with Dr. Saul Schepartz from the Division of Cancer Treatment representing the NCI. Congressional interest in taxol is high and has resulted in active support from several members to make this drug available to patients.

On April 30, Dr. Richard Adamson, Director of the Division of Cancer Etiology, testified at a hearing on breast implants chaired by Representative Marilyn Lloyd (D-TN). Representative Lloyd chairs the House Aging Subcommittee on Housing and Consumer Interest. Dr. Adamson testified on the proposed NCI study of augmentation mammoplasty and stressed the NCI's commitment to discovering a cure for breast cancer.

Two recent events in Massachusetts regarding women's health issues have been attended by Dr. Broder. Dr. Broder was present at a forum on breast cancer on April 30, which was

sponsored by Representative Joseph Early (D-MA) and held at the University of Massachusetts Medical School in Worcester. Members of the community, researchers, patients, and advocacy groups attended this gathering. In addition, on May 4, Dr. Broder participated in a field hearing on breast cancer and women's health issues, which has held by Senator Edward Kennedy (D-MA) at the Faulkner Hospital in Boston.

Ms. Tisevich noted that several other briefings and meetings are included in the Board's legislative update package. Many of these meetings are related to breast and prostate cancer, two topics that Congress considers extremely important.

NIH Reauthorization Bill

Ms. Tisevich informed members that breast and prostate cancers were extensively discussed in the recent Senate action on the NIH reauthorization bill. To ensure that Board members fully understand the discussion of the NIH reauthorization bill, Ms. Tisevich provided some background information related to the bill. Authorizing committees provide the legal authority for a federal agency or program to operate. In addition, these committees authorize levels of funding proportional to the scope and responsibilities of the agency. These recommended figures serve as guidelines for appropriations committees, in combination with the President's budget, agency testimony, and testimony by outside advocacy groups. Ms. Tisevich reminded members that the Subcommittee on Health and the Environment of the Energy and Commerce Committee has jurisdiction over NIH programs. This subcommittee is chaired by Representative Henry Waxman (D-CA), and Representative John Dingell (D-MI) presides over the full committee.

The House passed H.R. 2507, the NIH Revitalization Amendments of 1991, last July. At that time, the fiscal year 1992 appropriation was still under consideration and, therefore, the bill addressed the authorization of NIH programs for fiscal years 1992 to 1994. The current appropriations cycle, however, is focused on fiscal year 1993; therefore, the time period will probably be changed to begin with fiscal year 1993. The Senate bill addresses this issue.

Ms. Tisevich continued her discussion of the House bill with an overview of the controversial provision directing that meritorious research projects on fetal tissue transplantation be funded. She commented that this item will probably induce a Presidential veto of the bill. Ms. Tisevich added that the margin of approval in the House on the original bill was 13 votes short of the required two-thirds majority for an override of the veto.

In terms of specific NCI appropriations for fiscal year 1992, the House authorized a total of $2 billion in funding. They directed the NCI to allocate not less than 10 percent of this total to the prevention and control line. In comparison, of the actual total FY 1992 appropriation of nearly $2 billion dollars, $106 million was directed to the prevention and control line. Ten percent would have been about $200 million, which indicates that the percentage directed to the prevention and control line was only slightly more than 5 percent of the total NCI budget.

Ms. Tisevich stated that the House bill also provides for a transition in the first year of the reauthorization bill. It requires that prevention and control be funded at 75 percent of the recommended level in the bypass request. The 1992 bypass request for prevention and control was $182 million. Seventy-five percent of this figure would be $136.5 million. Ms. Tisevich explained that if this bill had been enacted in fiscal year 1992, since only $106 million was appropriated to the prevention and control line, the NCI would have been directed to move $30 million out of other programs and into this mechanism to fulfill the requirement. Ms. Tisevich stressed that the prevention and control line constitutes only a portion of the NCI's cancer prevention research and cancer control activities. In sum, approximately $645 million will be spent on prevention in fiscal year 1992.

Another provision requires that at least $50 million of the total NCI budget be allocated to basic research on breast cancer and the development of a method of early detection for ovarian cancer.

Ms. Tisevich informed members that the Senate committee with jurisdiction over NIH is the Committee on Labor and Human Resources, chaired by Senator Kennedy. The full Senate approved an NIH reauthorization bill on April 2 by a vote of 87 to 10, which is more than enough for a two-thirds majority to override the expected Presidential veto of the bill. Ms. Tisevich said that this bill overturned the current moratorium on fetal tissue transplantation research.

Provisions within the Senate bill that directly affect the NCI include the authorization of appropriations for research and the prevention and control line of $2.218 billion and $156.8 million, respectively. Ms. Tisevich explained that these two line items are traditionally included within the NIH reauthorization bill. Additional provisions within the Senate bill include an increase of $400 million for breast and women's reproductive cancers, an increase of $72 million for prostate cancer, and an increase of $30 million for a new program on State cancer registries. Ms. Tisevich stated that these figures extend the total NCI budget to $2.876 billion. She added that the Senate bill covers a period of 5 years, beginning with fiscal year 1993, while the House bill only includes a 3-year period.

Ms. Tisevich highlighted some new responsibilities with which the NCI has been charged, including the development of a national program of State cancer registries. This item was originally proposed by Senator Patrick Leahy (D-VT) as a companion bill to a House bill introduced by Representative Bernie Sanders (D-VT). Ms. Tisevich emphasized that this program was deliberately established as an independent project that was separate from NCI's Surveillance, Epidemiology, and End Results (SEER) program. This distinction is intended to protect the SEER program from resource shifts to the new program. Ms. Tisevich added that the original Leahy bill included a provision that required the NCI to conduct a study of the elevated breast cancer rates in the Northeast. This requirement is included in the reauthorization bill.

Ms. Tisevich informed members that a new section on breast and women's reproductive cancers requires that the NCI develop and submit a research plan for these cancers, which the NCI has already created in anticipation of this provision. A final directive of the Senate bill requires the NCI to conduct an expanded and intensified research effort regarding prostate cancer. The bill includes a mandate for the creation of an inter-Institute task force to coordinate research efforts across NIH.

Ms. Tisevich mentioned that the Kennedy bill directs the Centers for Disease Control (CDC) to initiate a breast cancer mortality prevention program modeled after the breast and cervical cancer mortality prevention program that already exists. An additional $20 million would be authorized for CDC for that effort.

Ms. Tisevich reported that the 1993 President's budget recommended $2.010 billion for the NCI and the 1993 bypass budget request totaled $2.775 billion. Ms. Tisevich reminded members that the House bill is based on fiscal year 1992 and, therefore, cannot accurately be compared to any of these different authorization levels.

New Cancer Prevention and Control Bills

Ms. Tisevich announced that several new bills regarding cancer prevention and control have been introduced. These bills, she said, are listed in the legislative update package.

Senator Bingaman (D-NM) and Representative Synar (D-OK) introduced the Tobacco Health and Safety Act of 1992. This bill would regulate the sale and distribution of tobacco products containing tar, nicotine, additives, carbon monoxide, and other potentially harmful constituents. Under this bill, the Secretary of the Department of Health and Human Services (DHHS) would have the authority to regulate nontobacco products that contain nicotine. The bill would also require that tobacco manufacturers fully disclose all chemical additives in tobacco products and would prohibit the dissemination of free samples or coupons for cigarettes.

Ms. Tisevich reported that Senator Leahy and Representative Sanders introduced bills directing the Secretary of the DHHS to declare breast cancer a public health emergency.

Regarding cancer etiology, bills were introduced by Representative George Brown (D-CA) and Representative Frank Pallone (D-NJ) directing the Department of Energy to establish an electromagnetic fields interagency committee to coordinate federal research efforts on the health effects of electromagnetic fields and to create an information dissemination program. These items were incorporated into the comprehensive National Energy Policy Act, which will move forward when several issues are resolved by the two subcommittees with jurisdiction over these bills.

Two bills related to the effects of DES exposure have been introduced. Senator Riegle (D-MI) introduced a bill last January that would authorize the Secretary of DHHS to provide federal grants to States for programs to identify and aid individuals who have been exposed to DES. The bill authorizes $6 million per year for this program. Representative Louise Slaughter (D-NY) proposed the second bill, the DES Education and Research Amendments of 1992. This bill directs the Secretary of DHHS to establish a program to conduct and support research and training, disseminate health information on DES, and provide for longitudinal studies regarding individuals who have been exposed to the drug. The bill authorizes $1 million in appropriations for fiscal year 1993 and $500,000 per year for the next 2 years.

Ms. Tisevich concluded her presentation by announcing that Senator Alan Cranston (D-CA) introduced the RU-486 Regulatory Fairness Act to invalidate the import alert initiated by the Food and Drug Administration (FDA) and to require that the FDA consider applications regarding RU-486. As there were no questions regarding the legislative presentation, Dr. Calabresi thanked Ms. Tisevich and moved on to the next agenda item.

VI. GLIOBLASTOMA SUICIDE GENE—DR. MICHAEL BLAESE

Dr. Rabson introduced Dr. Blaese by providing some biographical details of Dr. Blaese's life, including his opportunity to train with Dr. Robert Good, a leader in clinical immunology; his arrival at the NCI in 1966, where he began working in the Metabolism Branch of the NCI with Dr. Thomas Waldmann; and his development of one of the major programs in the study of immunodeficiency diseases in conjunction with Dr. Waldmann. Dr. Rabson praised Dr. Blaese as one of the world leaders in the physician/scientist technology transfer approach.

Dr. Blaese began his presentation by defining gene therapy as the introduction of a gene or genes into cells to provide a set of permanent or temporary instructions for those cells. He indicated that the purpose of his presentation is to discuss potential applications of gene transfer in the treatment of cancer. Dr. Blaese described the original intent of gene therapy as an effort to treat genetic disease by correcting an inherited or genetic defect. Initial research in this field revealed that the applications of gene therapy went beyond correcting inherited or genetic defects to potentially being able to reverse an acquired gene defect or somatic mutation such as the mutation in tumor suppresser genes that lead to malignancy. Dr. Blaese added that this technology could possibly be used to program cells to perform new functions or exhibit new

properties; for example, to be able to program vascular endothelial cells to produce factor 8 in hemophilic children or to modify T-cells to be make them resistant to HIV infection.

Dr. Blaese stated that he divided gene transfer for cancer treatment into two general areas, based on the approaches employed by the research team to accomplish the desired outcome. He termed the first "indirect approaches," which use gene transfer for biologic response modification, such as enhancing the cytotoxic activity of tumor infiltrating lymphocytes (TIL) by inserting genes that would keep those cells activated or using the homing activity of TIL to deliver a cytotoxic product directly to the malignancy. Another possible indirect use of gene therapy is to introduce cytokine genes into the tumor itself, thereby inducing the tumor itself to produce immune activating compounds to immunize the host.

Dr. Blaese asserted that if a mechanism for directly delivering genes to cancers could be developed, this technology could lead to a direct therapeutic approach of gene modification as a treatment of cancer. Dr. Blaese explained that if genes could be delivered directly to all malignant cells in the body, one could potentially reinsert tumor suppresser genes into the tumors *in situ,* or other genes that would kill the tumor cells, for example, by inducing apoptosis. Another possibility would be to couple a toxin gene with a tissue-specific promoter, which would ensure that it only integrates into the tumor and then activates the production of a poison to kill the tumor.

Dr. Blaese indicated that he would be devoting most of the remainder of his presentation to a discussion of introducing susceptibility genes into the tumors *in situ,* which would render the tumors more vulnerable to treatment with other agents. Dr. Blaese emphasized that there are many techniques for gene transfer and that the choice of method should be dictated by the particular application under consideration. To achieve a long-term, stable expression of a gene to treat an inherited disease, Dr. Blaese said, it would be preferable to use a method of gene transfer, such as the use of a retrovirus vector, that would integrate the gene into the genome of the host cell.

Dr. Blaese commented that there are several problems with the use of retroviruses. Retroviruses integrate randomly. Therefore, if they integrate at the wrong site on the genome, they could potentially activate an adjacent oncogene. He added that safety systems that would allow the elimination of these vectors or the transformed cells are being explored. Another disadvantage is that they require the target cell to be synthesizing DNA for integration to occur. They do not integrate into cells that are in G-0 state, the usual state of the totipotent bone marrow stem cell. Dr. Blaese reported that, thus far, no one has been successful in using a retrovirus to insert a gene into these totipotent bone marrow stem cells.

Dr. Blaese began an explanation of the regulatory gene systems, or suicide genes. The basic concept is to introduce into a cell a gene that would remain relatively neutral until the cell is exposed to a prodrug, which would then be converted by the inserted gene into a cytotoxic agent. One possible approach is to introduce 5-fluorocytosine (5-FC) into host cells. This antifungal drug is nontoxic at usual doses. The mechanism by which this drug works is through the presence of an enzyme, cytosine-deaminase, in fungi that converts 5-FC into 5-fluorouracil (5-FU), a potent cytotoxic agent. If the enzyme is inserted into mammalian cells, the affected cells could be selectively eliminated by treating the organism with 5-FC. This technique is termed a selective suicide system and it allows for intracellular generation of 5-FU.

An alternative approach involves the insertion of a gene that codes for the enzyme herpes thymidine kinase (TK), which converts the antiherpes drugs ganciclovir and acyclovir into toxic compounds. Dr. Blaese commented that this system has been extremely useful. He presented slides of a mouse with two cancerous lumps. One lump was a wild type cancer and the other tumor was exactly the same except that the TK gene was inserted into it. When the animal was

treated with ganciclovir, an efficient elimination of the malignant cells occurred. Dr. Blaese remarked that some people might question the effectiveness of this system for use in systemic therapy, as the lump that did not carry the gene was not affected by the ganciclovir. Some data suggest, however, that it may not be necessary to insert the gene into every malignant cell to achieve the desired effect. To illustrate this point, Dr. Blaese summarized the findings of an experiment his team conducted in which they mixed herpes-modified cells with wild type tumors in various proportions. They used these mixtures to establish tumors, allowed them to grow, and then treated the animals with ganciclovir. When the animals with 100 percent wild type tumors were treated with ganciclovir, all the animals developed cancer. If 100 percent of the tumor cells carried the TK gene, then approximately 90 percent of the animals were cured by treatment with ganciclovir. The crucial finding was that when only 50 percent of the cells carried the selected gene, 90 percent of the tumors were still killed by treatment with the drug, and when only 10 percent of the cells were modified, over half of the malignant tumors were destroyed. Dr. Blaese noted that they termed this effect the bystander effect.

Dr. Blaese stated that the challenge is to develop a method to clinically apply this knowledge. The problem with bone marrow stem cell transduction is that the cells are not in cycle, and therefore not taking up the gene when retrovirus vectors are employed. Dr. Blaese explained that when one considers a patient with a brain tumor, the only mitotically active cell in the brain is the tumor. If a retrovirus vector could be delivered to the site of the tumor, only the malignant cells should integrate the gene and thus be susceptible to the drug. Dr. Blaese reported that his team stereotactically injected fibroblasts that were producing a herpes TK retrovirus vector into the tumor site of a rat. This rat was treated with saline as a control, and it was apparent that the injection of the retrovirus producer cells had no effect on the malignancy. A rat from the same litter was treated with ganciclovir a week after the gene insertion. This animal experienced a total elimination of the tumor. Dr. Blaese said that of the first 14 animals treated, 11 animals were completely cured of their malignancy.

Dr. Blaese commented that his team is waiting for approval from regulatory committees to try this approach in the treatment of human brain cancers, both glioblastomas and potentially metastatic tumors. Dr. Blaese offered one final comment regarding efforts to develop retrovirus producer cell lines, which have focused on optimal virus production *in vitro*. Research must now concentrate on optimizing systems of delivery of virus *in situ* or *in vivo* for this clinical application to be effective.

Dr. Salmon asked whether Dr. Blaese had been able to estimate the number of cells that were transfected within the tumor to determine how important the bystander effect is in this model. Dr. Salmon asserted that he believes that the proliferative fraction would be relatively small in human glioblastomas, probably about 5 or 10 percent. Dr. Blaese estimated that in the rat model, approximately 20 to 75 percent of the tumor cells are experiencing transfection. Limited information regarding the proliferative fraction has been obtained. Dr. Salmon suggested that Dr. Wilson, the new Board member, might be able to provide good estimates of the proliferative fraction that Dr. Blaese should expect, as he has been studying this subject for a long time.

Dr. Calabresi asked whether Dr. Blaese had any information on how the gene gets to the bystander cells. Dr. Blaese responded that the gene is definitely not being transferred. He stated that there is a product that is released from the transduced cells that has an effect on the bystander. It was determined that in some *in vitro* experiments, the TK enzyme is released by the transduced cell, which then may catalyze the formation of a monophosphorylated ganciclovir that the bystander cells absorb and are eventually killed by. Dr. Blaese said that the *in vivo* mechanism has not yet been discerned.

Dr. Frost commented that it might be possible to enhance the bystander effect by pretreating the cells with methotrexate to cause them to fixate in the S phase. Dr. Blaese

responded that this is an interesting idea and that there are many approaches they need to explore in the future.

Dr. Salmon asked Dr. Blaese to estimate the duration of survival of the fibroblasts once they are injected. Dr. Blaese responded that they survived for an average of 2 weeks in the studies conducted in rhesus monkeys.

Dr. Blaese reported that this proposed clinical trial will be considered by the Recombinant-DNA Advisory Committee (RAC) on June 1, and if the committee approves the study, then clinical trials will begin in the late summer or early fall.

Dr. Salmon asked whether Dr. Blaese would use a human fibroblast producer line. Dr. Blaese responded that they will use a murine fibroblast producer line, as there is concern about the potential side products of a human line. Dr. Blaese added that further research regarding human lines needs to be conducted.

VII. OVERVIEW OF EFFORTS TO SYNTHESIZE TAXOL—DR. PAUL WENDER

Introduction

Dr. Chabner introduced Dr. Wender, noting that 1½ years ago, it was one of his fondest dreams that someone would synthesize taxol. Much has been done to make taxol available, he said, from working with other federal agencies to gain access to trees to supporting grant-related research on synthesis and semisynthesis. While all of these efforts have been of theseproductive, he said, the most exciting and most important development in terms of availability is the work of Dr. Wender.

Overview

Dr. Wender began his presentation with a brief description of the evolution of taxol from its initial extraction, to the isolation work that led to the elucidation of its complex structure, to the discovery of its potential for treating ovarian, breast, and other cancers.

With some 170,000 women per year being diagnosed with either breast or ovarian cancer, the impact of this drug could be enormous, he said. Dr. Wender showed a slide of a patient who, 2 years ago, was diagnosed as having stage IV ovarian cancer and was told to get her personal effects in order. The patient is still alive 1 to 1½ years past expectations which, he commented, is a fantastic testimonial to the significance of taxol.

With regard to the supply of taxol, Dr. Wender noted that there are now two taxol compounds in clinical trial. The difference between the two is a relatively small piece of a large and complex molecule. This leads one to believe, he said, that there could be many compounds that are as good or better than taxol. Both compounds can be made from a tricyclic precursor.

Dr. Wender then discussed the various methods for producing taxol. He called the first method a macro approach of digesting trees to isolate taxol and taxol precursors. It is hoped that this can be replaced by natural harvesting of needles and stems. Plant tissue culture is the second method that could be used to generate taxol. The third method would be to use the specific enzymes that are responsible for biological construction of taxol in the cell. The fourth way—synthesis—is abiological. Dr. Wender emphasized that the interesting aspect of synthesis is that it is not biosynthesis based—it is need based.

Taxol Synthesis

Comparing the synthesis of taxol to mountain climbing, Dr. Wender remarked that science is at the base, trying to get to the peak. Ever since Mt. Everest was defined as the highest mountain, people have wanted to get to the top, and, after many people had failed, the mountain was finally scaled. There is a parallel between that story and the effort to synthesize taxol. One difference between the synthesis of taxol and the climbing of Mt. Everest is that the goal is not just to be first, but to build a superhighway to the top so that the synthesis of taxol is not a struggle.

The road to synthesizing taxol began 10 years ago with a plan to develop methodology for the construction of eight-membered rings. Taxol was chosen at that time because it presented an interesting structural challenge. Many groups had made progress constructing eight-membered rings with an approach that formed one bond of the central eight-membered ring. Dr. Wender stated that they thought it would be interesting if two bonds were formed at once—bring a four-unit piece together with another four-unit piece.

They were able to demonstrate the synthesis of an eight-carbon ring by putting two four-carbon rings together in the presence of a transition metal catalyst, effecting a 4+4 cycloaddition. This was the first synthesis of an eight-membered ring containing sesquiterpine. This was pertinent to the construction of the BC rings of taxol, Dr. Wender explained. Another member of Dr. Wender's group was working on using a low-valent iron to catalyze the cycloaddition reaction. This produced a BC system that very closely resembled the BC system of taxol. At that point, the team decided to try to synthesize taxol, but before doing any laboratory work, they would develop, on paper, a practical synthesis of taxol and its analogs. From his experience as a consultant to the pharmaceutical industry, Dr. Wender said, he knew that 15 to 25 steps would be practical.

To make the core ring of taxol, Dr. Wender noted, they wanted to take an A ring precursor and a C ring precursor and combine the two by forming bonds between carbon 10 and carbon 11 and between carbon 3 and carbon 2.

Dr. Wender stated that they saw the possibility of constructing the C ring precursor with a variety of methods. The key, then, was to find an A ring precursor on a practical level. It turned out that the answer was turpentine, or paint thinner. Turpentine is the product of the pine tree—a readily available, abundant source. Seventy-six percent of the material found in turpentine is pinene. Because pinene is used as an industrial solvent, it is available in large quantities and is inexpensive. Pinene also contains 10 of the 20 carbons needed to synthesize taxol. Another favorable attribute of pinene is that it comes in the same chirality as taxol.

Upon further examination of the structure of pinene, it was discovered that it had the wrong connectedness—that is, the carbons did not connect in the same order as they do in taxol. To reconnect the carbons so that they matched those of taxol, C11 was activated first, because that is where the C ring precursor is attached. The process was done in two phases—oxidation at C2 and alkylation at C11—to form the C11-10 bond. Then, using photochemical techniques, the C15 was removed from the C13 and attached to the C11. The C2-C11 bond was then broken in one of two ways. It took five steps to get to an A ring precursor from pinene.

Dr. Wender said he would describe the science behind the strategy. The first step was to explore a process that had already been developed—the air oxidation of pinene. He reminded the audience that the C2 carbon in pinene needed to be activated and explained that simply blowing air through the reaction mixture in the presence of a catalyst would activate the C2 carbon. Dr. Wender emphasized that this process can be done on a large scale. However, at their laboratory they are limited by their equipment to quantities of hundreds of grams. Once the

basic chemistry is mastered, then, with the help of chemical and process engineers, it should not be a problem to scale up the process.

Dr. Wender then discussed the addition of the C ring precursor. He described the value of one particular precursor that carries oxygen in the C9 position and contains eight more carbons. When this eight-membered precursor is added to pinene, with its 10 carbons, 18 of the 20 carbons needed to make taxol are present. With this addition, one of the two key bonds needed to make taxol has also been formed. At this point, Dr. Wender said, they ran into some trouble. They had difficulty adding a carbonyl group. However, computer modeling helped. The computer showed that the molecule is so congested in the target region, it is very difficult to get C3 to add to C2. With this discovery, they decided to revise the strategy to add to C2 first and then put the epoxide in later to get the fragmentation to occur. This results in the A, B, C tricyclic core of taxol in five steps from pinene.

Everything fit in well except one part, said Dr. Wender. Pinene doesn't have an oxygen at C1. This problem was circumvented by oxidating the carbon-hydrogen bond with air, much the way air turns butter rancid. Now a complete A ring system and a B ring in exactly the right configuration for taxol is formed. The C2 needs to be reduced to get the alpha-oriented benzoloxy group, and the C9 needs to be elaborated into the ketone. The C8 methyl group is then added, which is required for the C ring elaboration.

Dr. Wender then recapped the synthesis up to this point, noting that the carbon-oxygen double bond at C9, the carbon-oxygen single bond at C10, and the carbon-oxygen single bond at C1 and C2 are all complete. Everything in the B ring is now complete with the exception of adding the methyl next to C8, and that is accomplished by treating the molecule with metal ammonia, which causes reduction of the C ring.

Summarizing, Dr. Wender said that with five steps, commercially available pinene converts into the tricyclic core of taxines; with three more steps, the pinene atoms are arranged in the same order as taxol; and, with three more steps, entry into the C ring is allowed. It is a total of 13 steps, Dr. Wender said, to what they consider the final phase of synthesis. Dr. Wender explained that it is possible to convert an aromatic C ring into the CD ring of taxol. Applying this knowledge, they can add the A ring to the CD ring to achieve a taxol-like molecule. In this process, absolute and relative stereochemistry are controlled, and, for the purposes of medicinal and biochemical studies, analogs are available from steps five forward.

Conclusion

Referring to the earlier stated goals, Dr. Wender said they are in the final phase. They have a way of making analogs and they are in a position to start doing systematic studies on taxol. The molecular basis for the medicinal activity of taxol can be probed using these analogs. These studies would compliment the work being done by laboratories that are degrading taxol by stripping away substituents to find the active portion of the molecule. Their additive approach, combined with others' subtractive approach, will someday yield what is and is not required to trigger the medicinal activity of taxol. This could simplify the targeted molecule.

Dr. Wender then praised the work of the people in his laboratory and the dedication and enthusiasm they have all shown. He also thanked several people from NCI and from Bristol-Myers Squibb.

Questions and Answers

Dr. Jako asked if there are alternative ways of deriving the chemical material and if taxol is being tried in any of the lung cancers.

Dr. Chabner replied that it has been tried in lung cancer and shown to be active in small-cell lung cancer in 40 percent of the patients tested; however, this was in a very small number of patients.

Dr. Wender responded to the first part of Dr. Jako's question, stating that synthesis is just one of many approaches contributing to the science in this area of study.

Dr. Chan asked about the economics of synthesis versus semisynthesis and also asked if the biosynthetic pathway is known.

Dr. Wender answered that to compare the two technologies would be inappropriate at this time because synthesis is so new to the problem. He did add that synthesis is driven by the need to provide a low-cost solution. As to the biosynthetic pathway, Dr. Wender said that subject is being investigated in many laboratories.

Dr. Becker noted that he thought the D ring was required for activity.

Dr. Wender agreed with Dr. Becker and informed him that the experiment had been done where the D ring was removed and no activity was shown. However, the study was not detailed enough to show if the absence of the D ring alone was the sole factor in the loss of the medicinal activity.

VIII. EVALUATION OF THE NATIONAL CANCER PROGRAM— DR. SAMUEL EPSTEIN

Dr. Calabresi introduced Dr. Samuel Epstein, Professor of Environmental and Occupational Medicine at the School of Public Health, University of Illinois Medical Center. Dr. Epstein began his talk on the evaluation of the National Cancer Program by stating that the evaluation was based on positions expressed in a press statement endorsed by more than 65 national experts in the public health and cancer prevention areas.

The statement read, in part:

> "Over the last decade some 5 million Americans have died of cancer, and there is growing evidence that a substantial proportion of those deaths were avoidable. Now we express grave concerns over the failure of the war against cancer, whose failure is evidenced by the escalating incidence of cancer to epidemic proportions over recent decades, and the absence of any significant improvement in the treatment and cure of the majority of all cancers. We express further concerns that the generously funded cancer establishment, the National Cancer Institute and the American Cancer Society (ACS), has misled and confused the public and Congress by repeated claims that we are winning the war against cancer. In fact, the cancer establishment has continually minimized the evidence for increasing cancer rates, which is largely attributed to smoking and dietary fat, while discounting or ignoring the causal role of avoiding exposures to industrial carcinogens in air, food, water, and the workplace. Furthermore, the cancer establishment and major pharmaceutical companies have repeatedly made extravagant and unfounded claims for dramatic advances in the treatment and cure of cancer. Such claims are generally based on initial reduction in tumor size, tumor response, rather than on prolongation of life, let alone on the quality of life, which is often devastated by highly toxic treatments."

Dr. Epstein explained that this statement recommends that the NCI provide cancer cause and prevention funds equal to that of its other programs. This major shift, he said, should be initiated immediately and completed within the next few years. He said that the NCI's response is that it allocates 17 percent of its total budget to primary prevention.

Dr. Epstein began his slide presentation, stating that in 1991 the NCI has cut its 1986 objective of reducing cancer mortality from no more than 84 deaths per 100,000 by the year 2000 to no more than 130 deaths per 100,000—a reduction of 50 percent. He then discussed incidence and mortality trends in the general U.S. population by stating that: from 1950 to 1988 there was a 44 percent increase in cancer incidence; the mortality from 1962 to 1982 increased approximately 8.7 percent; from 1975 to 1984, for all ages, the incidence of cancer increased from 162 deaths per 100,000 to 171 per 100,000—a 5.2 percent increase; and for persons under age 20, there has been a 4 percent decrease in mortality.

He then talked about what he called the near static survival rates for common cancers, saying that the General Accounting Office in 1987 concluded that for the majority of cancers, actual improvements have been small or have been overstated by the published rates. He quoted a review of the literature on chemotherapy (Abel, 1990) that summarized that there is no clear evidence that patients, as a whole, have prolonged survival, let alone a better quality of life with chemotherapy. He said that although this is the opinion of many well-known oncologists, ongoing studies do not take the quality of life issue into account.

Dr. Epstein next addressed conflicts of interest involving the past Chairs of the President's Cancer Panel, and his perception of current conflicts of interest at the Sloan Kettering Cancer Center. He showed slides of Sloan Kettering's holdings in various pharmaceutical and industrial companies, the data coming from Sloan Kettering's annual financial report. He also showed ties to drug and industrial companies of members of Memorial Sloan Kettering's Board of Overseers. These types of companies, he added, would be far more interested in cures than in prevention.

He gave another example of conflict of interest when describing the NCI/American Cancer Society joint Breast Cancer Detection Demonstration Project with average mammogram doses of 2 rads per woman. The National Academy of Sciences Committee on Biological Effects of Ionizing Radiation in 1971 emphasized that the risk of cancer increases approximately 1 percent for every rad. He reported that the senior NCI official in charge of this demonstration project did not warn women of this risk in order to gain positive publicity and, therefore, more funds for research. Dr. Epstein stressed, however, that this was in the past. Dr. Epstein reiterated that Memorial Sloan Kettering is an excellent example of how the "major decision-making body in the prototype National Cancer Center is dominated by industrial and drug company interests."

He also emphasized that the current composition of the NCAB is in violation of Section 407 of The National Cancer Act which requires that no less than five Board Members be "knowledgeable in environmental carcinogenesis." He urged that this violation be remedied.

He then introduced the topic of the relevance of basic research to cancer in general. He recounted Dr. Broder's testimonies before Congress that basic research is a major priority. Dr. Epstein disputed this by quoting the negative response of several leading molecular biologists on their thoughts regarding the relevance of their work to cancer in general. He then quoted Rep. Obey (D-WI) who said that many of the most important discoveries in basic research originated in Institutes other than NCI, particularly at the National Institute of General Medical Sciences (NIGMS). Dr. Epstein said that Rep. Obey was concerned about the disproportionate increase in funding for the NCI and the decrease for NIGMS.

Dr. Epstein next quoted NCI's estimate on the contribution of lifestyle and environmental factors on cancer mortality, which, he said, were based on tenuous and flimsy evidence: diet causes 35 percent; tobacco, 30 percent; reproductive and sexual behavior, 7 percent; occupation, 4 percent; alcohol, 3 percent; geophysical factors, 3 percent; pollution, 2 percent; industrial products, 1 percent; and medicine and medical procedures, 1 percent. He claimed that these NCI data were from Doll and Peto's 1981 paper based on obsolete and scientifically flawed analyses of *Trends in Cancer Mortality from 1933 to 1977*.

He then addressed primary cancer prevention. The NCI, he said, defines primary prevention as those research activities designed to yield results directly applicable to the identification of risk and interventions to prevent disease, or the progression of detectable but asymptomatic disease. Dr. Epstein specified that NCI's definition also includes chemotherapy, and that chemotherapy plays a significant role in the budget of primary cancer prevention, and a wide range of programs unrelated to primary prevention. He feels that including chemotherapy in the category of preventing cancer is stretching the definition of prevention too far. He reported that the panel he represents formulated a definition of primary cancer prevention as research on avoidable chemical and physical carcinogens in air, water, food, home, and the workplace, as well as education and other practical applications of currently available information on such exposures.

He went on to discuss the subject of cancer prevention appropriations. The total budget, he said, is about $2 billion. Cancer prevention is allotted $645 million, of which $335 million is allocated to primary cancer prevention, which is 17 percent of the total appropriation. Dr. Epstein believes the figures are misleading and erroneous and that the true figure is well under 5 percent.

He next addressed occupational cancer and what he feels to be an egregious example of underfunding to the National Institute of Occupational Safety and Health (NIOSH). He said that the NCI has systematically trivialized the evidence for occupational and other causes of lung cancer. He then gave some facts regarding nonsmoker-related lung cancer, which he said have been ignored by the NCI: the incidence of lung cancer has more than doubled in recent decades; lung cancer rates in Black men are 40 percent higher and have been increasing more rapidly than in Whites over the last few decades, even though Blacks have smoked less and have started smoking later in life; and the incidence of adenocarcinoma of the lung, which is less clearly related to smoking than squamous cell carcinoma, has increased sharply over the decades.

He went on to say that the role of occupation as a major cancer-causing variable was ignored in nearly all of the 30 retrospective studies associating lung cancer with smoking. He contended that there are strong associations between lung cancer and occupational exposures to a wide range of carcinogenic products such as arsenic, chrome, nickel, BCME, and carcinogenic processes such as copper smelting; uranium, zinc, and lead mining; spray painting; and tanning. He also spoke about air pollution in industrial communities, saying that U.S. industries in 1991 discharged nearly four billion pounds of chemicals into the environment, including a wide range of carcinogens.

Dr. Epstein then claimed that the NCI has grossly exaggerated the role that a high-fat diet plays in causing cancer. He charged that the estimate that high-fat diets are responsible for 35 percent of cancer incidence is among the most inadequately documented scientific positions that the NCI has ever developed, and the NCI claim is based on a weak, outdated (1981) study by Doll and Peto. He also pointed out that Peto retracted these unfounded claims in 1987. The results of cohort studies, he said, have produced, at best, inconsistent results. He continued that the NCI has ignored the role of a wide range of carcinogenic pesticides and other carcinogenic dietary contaminants.

Dr. Epstein turned next to breast cancer. He noted that a wide range of carcinogenic pesticides such as DDT, chlordane, and dieldrin, which are concentrated in animal fats, induce breast cancer in rodents. DDT, he continued, promotes breast cancers induced in rodents by aceto-amido phenanthrene, a highly potent carcinogen. This may be contributing to the high incidence of breast cancer, as DDT and PCB are concentrated in breast tissue. Breast cancer deaths in premenopausal Israeli women declined sharply following reductions in use levels of DDT and other pesticides, in spite of increasing fat consumption and decreasing parity.

Regarding mammography, Dr. Epstein said that the NCI and ACS have failed to investigate the relationship between increasing breast cancer rates and high-dose mammography programs, and that the NCI has failed to aggressively explore safe alternatives to mammography, especially for premenopausal women.

Dr. Epstein next broached the topic of environmental carcinogens. He stated that the U.S. currently produces nearly 500 billion pounds of synthetic organic chemicals per annum, including a wide range of known carcinogens; however, only 10 percent of the chemicals have been tested for carcinogens. He then focused on pesticides, which, he said, have been associated with 20,000 excess cancer deaths annually, while the NCI has failed to conduct any epidemiological studies on the great majority of pesticides known to induce cancer in experimental animals. He then referred to pesticides used in lawn care, stating that 10 of the 34 pesticides used in lawn care are carcinogenic and one of them, 2, 4-D, induces lymphomas in humans. Studies have shown, he contended, that dogs living in homes receiving regular lawn care service have shown a greater incidence of lymphomas. He reasoned that children and infants playing on the treated grass may also be at risk for lymphomas from the pesticides.

Dr. Epstein next spoke about chlordane and heptachlor, two of the most common carcinogens in the U.S., used in pesticides to treat homes for termites. It was found that routine termite treatment resulted in air contamination causing from 300 to 3,000 excess deaths per year.

He next discussed his feeling that the NCI trivializes causes of occupational cancer. He noted that the NCI allocates 1 percent of its budget for occupational cancer and that its position is that occupational cancers account for 4 to 6 percent of all cancer deaths in industrialized countries. Other, divergent views hold that the range of deaths from occupational cancer may be as high as 40 percent. He gave the example of cancer deaths in New York State—of 47,000 cancer deaths, 10 percent are estimated to be due to occupational cancer. Dr. Epstein said that this is too high a rate to receive only 1 percent of NCI's budget.

Dr. Epstein next made recommendations to the NCI. First, the need for NCI to publicize on a large scale, a cancer prevention program to inform and educate the public, the media, Congress, the administration, and industry that much cancer is avoidable and due to past exposures to chemical and physical carcinogens in air, water, food, and the workplace, as well as lifestyle factors, particularly smoking. His second recommendation is for the NCI to provide scientific expertise on primary cancer prevention to Congress, federal regulatory agencies, and other authorities regarding a wide range of avoidable carcinogens in air, water, food, and the workplace. His final recommendation calls for a large-scale expansion of primary cancer prevention programs, about which he did not go into detail.

He then posed several questions to the NCI, including: To what extent are future plans and programs inflexible or can the NCI respond to concerns on new perspectives such as those presented today? Would the NCI be willing to organize a public debate that would focus on its definition of primary cancer prevention and would offer alternative perspectives? Would the NCI publish the statement of the 65-plus scientists in the *Journal of the National Cancer Institute* and offer a critique or rebuttal? Would the NCI be willing to assist with funding of and

participate in the analysis of their primary prevention programs? Finally, Dr. Epstein asked that the response to his presentation not be what he described as "scientific McCarthyism."

In response to Dr. Epstein's presentation, Dr. Richard Adamson made a few remarks, asserting that the NCI places a priority on and has significant research in cancer biology, cancer causation, cancer treatment, and cancer prevention and control, and applies the results of this research to fulfill its mission in reducing the incidence of mortality and morbidity of cancer in humans.

He repeated the NCI budget figures that Dr. Epstein reported, and then defined total prevention research. Total prevention research, he said, includes research with a high probability of yielding results that will be applicable to disease prevention or health promotion. Also included are studies aimed at clarifying the chain of causation—the etiology and the mechanism. He then defined primary prevention as research that is designed to yield results directly applicable to identification of risk or intervention to prevent disease or the progression of detectable but asymptomatic disease.

Dr. Adamson then discussed the total budget for environmental carcinogenesis, which was $270.4 million in fiscal year 1991. He defined carcinogenesis research as research to identify or characterize the mechanism of action of exogenous agents, conditions, or procedures that initiate, promote, or otherwise contribute to the development of cancer.

He described some of the current studies being conducted, including a study on agricultural workers and farm families, involving 80,000 people who have been exposed to chemicals, pesticides, herbicides, and fertilizers. The study also takes into account dietary conditions and lifestyle habits. He pointed out that the study dictates taking dust and food samples in the home and soil samples in the fields and barns. Dr. Adamson cited other studies on silica exposure, jewelry workers, miners, photographers, laboratory workers, pottery workers, etc. In addition, he said, the NCI is supporting additional studies in conjunction with the National Institute of Occupational Safety and Health. The NCI also has numerous studies that link the laboratory with epidemiologic studies, so good measurements of exposure and effect can be obtained.

He listed the environmental agents that are being studied, including outdoor air pollution, diesel exhaust, gasoline exhaust, PAHs, smelter emissions, arsenic, cadmium, chromium, lead, nickel, cooking oil vapors, environmental tobacco smoke, radon, organic phosphates, fumigants, and organic solvents.

He next spoke on heterocyclic aromatic amines which occur when meat is cooked, particularly at high temperatures. These are among the most potent carcinogens occurring in food. One of these compounds, he said, has induced tumors in nonhuman primates. Ninety percent of the animals under treatment developed tumors within a 4-year period of time. He said that not only are studies being conducted at NCI, but NCI is also funding studies elsewhere, particularly at Lawrence Livermore.

Dr. Adamson then addressed PCBs and PBBs. He explained that the NCI has a workshop on this topic and they are following cohorts who are exposed to transformers in the workplace. He said the NCI follows populations with PBBs in conjunction with other agencies—they have followed approximately 4,000 families for 15 years. He said that they do not include biological agents in their studies on environmental carcinogenesis, but they have learned that biological agents also contribute to human cancer. He noted that the vaccine for hepatitis B may be the first vaccine to prevent cancer.

He then showed a series of slides showing publications on prevention of smoking, cancer tests, and nutrition, many of which are available to the public. Dr. Adamson concluded by stressing that the NCI works in cooperation with a number of agencies, and that the NCI has in place a comprehensive and balanced program of experimental, epidemiologic, clinical, and prevention research that gives NCI credibility at both the national and international level.

Dr. Epstein responded to Dr. Adamson's presentation with five points: 1) It should not be suggested that heterocyclic carcinogens in food, always present, are related to the massive increase in cancer incidence and mortality in the last few decades. 2) The wide range of chemical carcinogens are largely included in the studies on occupational cancer for which 1 percent of the NCI budget is allotted. 3) No reference was made to the issue of carcinogenic contaminants, pesticides, and other agents in fats. 4) No reference was made to the imbalance of funds made available for avoidable carcinogens in air, food, water, and the workplace, as opposed to the high percentage of allocations related to clinical research. 5) No reference was made of NCI's failure to provide scientific information and testimony to Congress, regulatory agencies, and decision-making bodies on methods of avoiding exposure to avoidable carcinogens in air, water, food, and the workplace.

Dr. Calabresi next called on Dr. Greenwald to respond. Dr. Greenwald began by noting that he feels the NCI has unfunded research opportunities in cancer prevention, basic research, therapy research, early detection, prevention, facilities, and training, but that, overall, the Institute has a balanced approach.

In response to Dr. Epstein's comments on changing the goals for reducing cancer mortality by the year 2000, Dr. Greenwald explained that the 1986 exercise looked at what could be achieved if all cancer knowledge could be fully implemented. It was a goal, not a promise. He reminded the audience, that at that time NCI felt that the goals would have to be periodically reassessed and that the first reassessment would be done when the 1990 data were collected. That reassessment, Dr. Greenwald added, is under way. After the reassessment the mortality line will probably be more modest; however, signs of progress are present. As evidence, he stated that: smoking has decreased from 33 percent in 1980 to about 25 percent presently; colon cancer incidence, rising until 1985, has shown 4 consecutive years of decline; and mammography use has improved.

Dr. Greenwald then responded to Dr. Epstein's comments on the Doll and Peto estimate of cancer mortality due to diet. Dr. Greenwald stated that last year Dr. Doll updated his estimate on diet's contribution to cancer mortality. The 35 percent figure remained the same, but the range of uncertainty of this figure was narrowed from 10 to 70 percent to 20 to 60 percent. He said the claim that 35 percent of cancer mortality is caused by diet will continue to be controversial until the Women's Health Initiative is completed with trial evidence.

Regarding environmental causes of breast cancer, Dr. Greenwald noted that in industrial Japan, incidence of breast cancer is one-fifth that of the United States, and in relatively clean, rural New Zealand and some Scandinavian countries, the disease is common.

He then spoke about mammography for 40- to 49-year-old women. He said the NCI has definitive trial evidence of the efficacy of mammography for 50- to 65-year-old women. The NCI believes for women 40 to 49 years old and 65 years and older, the recommendations for both of these age groups should be based on medical judgment. Breast cancer rates for women age 64 and over are still increasing, he added. Mammography still obtains good contrast at this age, and there is every reason to believe it will be useful. Referring to definitive trial evidence for mammography use in this group, Dr. Greenwald said there just were not enough women over age 65 in the trial to establish that fact.

In the 40- to 49-year-old group, Dr. Greenwald said there were three lines of evidence supporting the recommendation. First was the Health Insurance Plan study, which he noted was very well done and showed a mortality rate of 76 percent in the screened, as compared to the unscreened, group. He also noted several studies from other countries that did not show the benefit for women age 40 to 49.

The second line of evidence is from the Breast Cancer Detection Demonstration Project started in 1973 in which 280,000 women were offered mammography. The stage at diagnosis was the same for women age 40 to 49 as compared to women ages 50 and over; there was a larger proportion of early-stage disease than is obtained from the population at large.

The third line of evidence Dr. Greenwald presented was the incidence and mortality of breast cancer for women age 40 to 49 from 1973 to 1989. The results show a 10 percent drop in mortality. Dr. Greenwald stressed that it would take very compelling evidence to change the NCI policy.

He pointed out that the Surveillance, Epidemiology, and End Results study and the Breast Cancer Detection Demonstration Project to promote early detection both began in 1973, and that Betty Ford and Happy Rockefeller discovered their breast cancers in 1974. This time period saw a rise in the number of early diagnoses, although the majority did not occur through mammography. He said it is speculated that these factors contributed to the later decline in mortality for breast cancer.

Dr. Greenwald stated that in 1976, an article entitled *Mammography: A Contrary View* was published, which raised alarm about radiation from mammography that then reached Senate hearings and was widely debated in the press. It is speculated that this may have led to a decrease in early detection due to a radiation scare. In the early 1980s, a major rise in breast cancer incidence was seen, probably due to the increased use of mammography. NCI's prediction is that this higher incidence rate of early detection accompanied by a movement toward early-stage detection will be reflected in a lower breast cancer mortality rate that will be demonstrable by 1996. He added that there is a 3-year lag and that the data will be from 1992. He also noted that if the rate of early detection goes down, mortality will go up.

Dr. Greenwald then described an early detection trial currently being conducted in Canada. Approximately 90,000 women, age 40 to 49, were put into two categories: those who received a mammography plus physical exam, and those who received only a physical exam. He then stated that it is not fair to draw conclusions currently, because the study has not yet been published—however, the Principal Investigator published in his own book a chapter in which he showed the prevalence mean. The prevalence mean is defined in the study as the first time a study participant goes in for her exam and is randomized to mammography plus physical exam or physical exam only. The investigators observed that there were more detections for women who had no nodes in the mammography group. In the one to three node positive group, there was no difference, but in the women with the most advanced cancers at time of detection, there were almost four times as many tumors in the mammography group as the physical exam only group.

Dr. Greenwald noted that the results from this experiment are strange. At the first exam a high number of cancers should not be found in the mammography group if it were a true, unbiased randomization. In true randomization, the numbers should be about equal. Dr. Greenwald said that it is either a very rare statistical fluke or somehow women with symptomatic cancer or a family history of breast cancer were placed in the mammography group. This raises questions about the study, he said.

Dr. Calabresi opened the floor, and Dr. Broder requested that the following discussion be kept on a scholarly level, noting there is merit in having a position tested with scholarly discussion.

Discussion

Dr. Epstein responded to Dr. Greenwald's statements. He pointed out again that he feels the 35 percent figure regarding diet is a gross estimate with little or no scientific basis, that the Breast Cancer Detection Demonstration Project was an invalid study, and that the Health Insurance Plan Program did not show efficacy. He thinks it highly questionable that the NCI recommend that high-risk premenopausal women have a mammography every 2 years. He said that receiving radiation from a mammogram is adding yet an extra risk. He pointed out that there has been little or no reference to the importance of occupation as a major cause of cancer, and the role of environmental carcinogenic contaminants in fat, pesticides, and estrogens.

Dr. Jako asked if Dr. Epstein has any scientific evidence to show that occupational causes of cancer are greater than 4 percent. Dr. Epstein replied that in 1978 he was asked, indirectly, by the Occupational Safety and Health Administration (OSHA) to try to come up with some analysis as to how the 4 percent figure was derived by industry and the NCI. This was based on the totally unfounded assumption that 35 percent of cancers were attributed to diet, 40 percent to smoking, and another amount to sunlight and medicine, totaling 96 percent, leaving a balance of 4 percent which, simplistically, was attributed to occupation. These estimates, he said, were based on obsolete data from 1933 to 1977, times during which occupational exposures were very low. He further explained that Peto admitted that the divergent estimates could account for up to 20 to 40 percent, as opposed to 4 to 6 percent.

He then reported that other investigators have done a detailed analysis of occupational cancer deaths in New York, and their conservative estimate is 10 percent, as opposed to the 4 to 6 percent attributed by NCI. He continued that even if the NCI estimate were correct, it deemed more funding than 1 percent of the entire NCI budget.

Dr. Jako replied that Dr. Epstein's Institution did not seem to have scientific data that would change the estimate.

Dr. Becker asked Dr. Epstein to clarify his definition of prevention. Dr. Epstein replied that the primary emphasis on cancer prevention should be to reduce avoidable exposures to carcinogens in the first place rather than to let people be exposed and then try to cure cancer once it has developed. Dr. Epstein agreed that chemoprevention is important but is irrelevant to primary prevention.

Dr. Becker noted that the tone of some of Dr. Epstein's remarks was highly adversarial, and said that he thought Dr. Epstein came perilously close to using scientific McCarthyism himself. He pointed out that Dr. Epstein used the negative term "cancer establishment." Dr. Becker said if they are going to Congress to plead for more money, let it be distributed equally among the disciplines, because the plight of those who are suffering with cancer now cannot be ignored. He concluded by asking Dr. Epstein to please refrain from using adversarial terms and suggestions of accusation, and to provide the data to identify the proper targets.

Dr. Salmon spoke next. He identified himself as the director of one of the nation's comprehensive cancer centers whose largest research program is a cancer prevention program, the largest component of which is cancer prevention intervention trials. He said that he found Dr. Epstein's separation of primary prevention and chemoprevention to be specious.

He reminded Dr. Epstein that the NCI's mission is to overcome cancer as a problem and to do it as quickly and as effectively as possible, be it with treatment or prevention. He also objected to what he thought was Dr. Epstein's denigration of the effects of cancer treatment by addressing tumor shrinkage as fallacious. Complete remission, he said, is accepted as an intermediate marker for improved survival. Other approaches for cancer treatment include improved quality of life, he said.

In his own program, Dr. Salmon said, the search for approaches to primary prevention in the study of nutritional factors is done in an interventional fashion. This includes discovering the roles of dietary fat, dietary fiber, retinoids, carotenoids, and selenium. Given the strength of the estrogen hypothesis, they fully support participating in the tamoxifen breast cancer prevention trial, and feel that it may cause a major reduction in breast cancer incidence. He said that the tamoxifen trial could give a faster result than the longer-term approaches to primary prevention which may be very difficult to conclude.

Dr. Adamson reiterated that the $270 million funded for environmental carcinogenesis studies does not include any monies for chemoprevention. He added that the NCI has ongoing and future plans for studies addressing the role of pesticides in regard to breast cancer.

Dr. Epstein next made his concluding remarks. He explained that his approach, which was perceived as adversarial by the NCAB, was carefully considered by the 65-plus scientists he represents. He also emphasized that he had never made personalized ad hominem attacks on individual scientists in NCI. In striking contrast, following the February 4th press conferences, he was personally attacked by named and anonymous NCI spokesmen using terms such as "menace," "gadfly," and "unethical." In spite of requests to Dr. Broder, NCI has not seen fit to withdraw these charges. This is clear scientific McCarthyism, he said. He then explained that regarding the New York studies he quoted earlier, he had an extensive discussion with the author, and quoted from language used in their conversation.

He defended his use of the term "cancer establishment" by noting that the 65-plus scientists believe there is a strong basis for the viewpoint that there is a cancer establishment fixated on diagnosis and treatment. He also defended his quotes from the General Accounting Office, Rifkin, Chabner, and Abel, that there has been no significant advance in cancer treatment and cure for the majority of cancers. At this point, Dr. Chabner asserted that he was quoted out of context.

Dr. Epstein then addressed the tamoxifen studies. Tamoxifen, he said, is a potent carcinogen and the evidence for its ability to prevent breast cancer is highly questionable, and women should not be given tamoxifen without a warning. He closed his remarks by stating that he is glad to have finally gotten the attention of the NCI, and he looks forward to dialogues with the NCI in the future.

Dr. Calabresi then adjourned the meeting for lunch.

IX. CLOSED SESSION

A portion of the first day of the meeting was closed to the public because it was devoted to a meeting of the Special Actions Subcommittee. A total of 1,075 applications were received, requesting support in the amount of $200,052,559. Of these, 1,075 were recommended for funding at a total cost of $173,578,264.

X. MINI-SYMPOSIUM: *LIVING WITH CANCER*— MS. DEBORAH MAYER

Dr. Calabresi called the meeting to order and introduced Ms. Deborah Mayer, who organized the mini-symposium, *Living with Cancer*. She pointed out that the NCI needs to look at people who currently have cancer, because it has such a profound impact. She said she asked the presenters to not only speak on what is known in their fields, but also about what there is yet to learn. With this, she introduced the first speaker, Dr. Mellette from the Medical College of Virginia.

Cancer Rehabilitation—Dr. Susan J. Mellette

Dr. Mellette spoke of cancer rehabilitation as paving the way for cancer patients in the physical, psychosocial, and vocational areas. Cancer rehabilitation is aimed at the prevention of physical, psychosocial, and vocational dysfunctions that may result from cancer. These categories, she said, do include preventive, restorative, supportive, and palliative care.

Dr. Mellette described many changes in cancer surgeries, especially those that have become less severe. She showed slides displaying the changes in breast cancer and extremity sarcoma treatments, where there are now limb-sparing procedures. She noted, also, that there has been a decrease in colostomies.

An increasing trend, she said, is restoration. She showed slides of breast reconstruction, and of a man who suffered from a maxillary sinus cancer. This man had prostheses, both intraoral and extraoral. She explained that he needed not only the prostheses, but speech pathology as well for his rehabilitation. She displayed other slides showing that lymphodema and lower extremity edema are present problems. She showed other slides of disfiguring surgeries, explaining the procedures and results.

Dr. Mellette then described a task force set up by the Office of the Director of NIH, which met in June of 1990. The task force held several panels, including one on cancer rehabilitation. One of the charges of the panel was to develop priorities, the first of which was to develop instruments and measures for assessing functional outcomes. She discussed a select few of these, including activities of daily living and physical measures of rehabilitation patients. Very recently, she said, there has been an attempt at developing better psychosocial scales; however, many of these seem to emphasize nausea, vomiting, and side effects rather than actual physical well-being. She added that there are so many things within the cancer experience that affect moods, though other factors affect moods at the same time—she said these profiles of moods need to be better standardized.

Another priority for the panel was to develop new materials and bioengineering techniques for prostheses—very important in the area of physical rehabilitation. She emphasized that not only do new prostheses need to be developed, but testing needs to be done on existing prostheses. She expressed that she would like to spend the majority of her time on another priority, the use of existing clinical trial mechanisms for evaluating rehabilitation outcomes. Some cooperative groups, she said, are already incorporating quality-of-life measures, which, however, have been optional, because many personal questions must be asked which can create discomfort.

The next issue she spoke about was that of long-term results involving early studies, particularly involving breast cancer. She spoke of a volunteer program provided by the American Cancer Society that deploys "Reach to Recovery" volunteers who demonstrate exercises to postoperative women, but, she said, the program needs to be updated. For example, no one is really sure which exercises a woman needs after a lumpectomy, or what

should be done after radiation. She stressed that physical therapists and physical medicine rehabilitation workers insist that problems with lymphedema are greater in patients with lumpectomy with axillary dissection and radiation than in those with modified radical mastectomies, but that it takes time to occur. More data are needed on this, she said.

Dr. Mellette turned to nutrition and the role it plays in functional outcomes. She said much more work needs to be done in this area and questions must be addressed, including: Does nutrition make any difference to a patient with a limb-sparing procedure? Do those with better nutritional status recover better? Do their muscles regain any more strength? Another example is that women gain weight with breast cancer during and even after chemotherapy. Is this metabolic, she wanted to know, or is it nutritional?

She then spoke of sexual dysfunction, mentioning that there is work being conducted in potency-sparing procedures, e.g., penile prostheses, and even prostheses to put in empty scrota. She said they are embarking on a long-term study of tamoxifen in women who don't have breast cancer—many of these patients complain of vaginal dryness and visit their gynecologists, who give them estrogen cream, which antagonizes the effects of tamoxifen. She said that more data on this are needed.

She then spoke about current interventions in metastatic diseases. She mentioned replacing cervical vertebrae in patients with cancer metastasis. Dr. Mellette lamented the fact that not a great deal of money is spent on patients with metastatic disease even though they may live for long periods of time. She said more work needs to be done in this area. Dr. Mellette closed her presentation by emphasizing that, many times, rehabilitation problems can present opportunities for advances in treatment.

Status of Center for Rehabilitation—Dr. David B. Gray

Dr. Gray, Acting Deputy Director of the National Center for Rehabilitation Research, provided the Board with an update on the Center's activities. He briefly explained the history of the Center, the creation of which was signed into law by President Bush in November of 1990. Upon its creation, the Center met with some resistance because each of the Institutes comprising the NIH had an interest in rehabilitation. Also, Dr. Gray related, challenges such as selecting a staff and arriving at a consensus of what constitutes rehabilitation were encountered. As a result, the Advisory Board, made up of 18 public and 13 *ex officio* members, has attempted to "give medical rehabilitation a focus." This focus differs from the traditional approach taken by the NIH in that it concentrates on function rather than on organ, organ system, or impairment. Dr. Gray explained the rationale for this approach by citing the example of immobility—a function—which can be caused by many things (e.g., cancer, paralysis, head injury, and various types of inborn errors and anomalies).

Dr. Gray then discussed the Center's initial funding and the projects for which these funds would be used. During the first year of the Center, Dr. Raub, Acting Director of the NIH, allocated $600,000 to fund eight training sites at various universities throughout the United States. The Center received an appropriation of approximately $9.2 million, of which $8.3 million was slated for the funding of grants and contracts; the remainder was for operations and an intramural program. These funds will be used this year to support regular R01s and, potentially, some program projects and additional training grants.

The Center, Dr. Gray informed the Board, is considering funding rehabilitation-related grants originally assigned to other Institutes. He noted, especially, those grants that are close to the funding line and those that the other Institutes currently cannot fund. Dr. Gray indicated that the Center would cofund or accept grants submitted to the Centers for Disease Control, the

National Institute for Occupational Safety and Health, the National Institute on Disability and Rehabilitation Research, and NIH Institutes and Centers.

In addition to the preceding projects, the Center issued a program announcement in the January 21 edition of the *NIH Guide to Grants and Contracts*. The Center has also submitted two Requests for Application: one on reproductive fitness for people with a physical disability; the other on prosthetics and orthotic devices. A third Request, focusing on bowel and bladder management, should be issued soon.

In the future, Center activities will be funded according to seven basic categories: 1) mobility; 2) behavior adaptations to disability; 3) whole-body response to physical impairment; 4) development of a new generation of technical devices; 5) measurement and the development of measurement tools for assessment and new epidemiology studies of disability; 6) treatment effectiveness and clinical trials for existing or new rehabilitation treatments; and 7) training a new generation of rehabilitation scientists. The long-term plan is to develop centers of excellence in each of these seven areas.

Dr. Gray closed his talk by mentioning a 12½-minute videotape produced by the Center. He recommended that if the Board had the time, they should view the videotape.

Questions and Answers

Dr. Mellette inquired about the role of cancer rehabilitation in the Center's activities. Dr. Gray responded by acknowledging the conspicuous absence of a representative from the cancer field on the Advisory Board. He elaborated on the importance of including cancer patients in rehabilitative studies sponsored by the Center. Dr. Gray pointed out that these cancer patients do survive and they need to be able to readjust their work or have their work suitably adjusted to them. He reiterated that the focus of the Center's activities is function, and cancer does, indeed, reduce function. Dr. Gray concluded by encouraging all Board members to contact him or Dr. Alexander, the head of the Center, to share ideas on how they can work together to improve the lives of people with disabilities.

Pharmacologic Pain Aspects—Dr. Diana Wilkie

Ms. Mayer introduced the next speaker, Dr. Diana Wilkie, Assistant Professor, Department of Physiologic Nursing, University of Washington.

Dr. Wilkie began her presentation by pointing out that the magnitude and significance of the cancer pain problem is enormous. In 1992, she continued, more than 1 million Americans will be diagnosed with cancer, and as many as 850,000 will experience moderate to severe pain during the course of their diseases. Approximately 250,000 Americans will die this year, with severe, unrelieved cancer pain.

Significant morbidity is associated with unrelieved cancer pain. Chronic pain may lead to compromised immune function and early death. Anxiety, depression, fatigue, anorexia, insomnia, and feelings of helplessness, hopelessness, fear, and anger interfere with the will to live and willingness to tolerate cancer therapy. These factors combine to compromise functional status and quality of life. She pointed out that cancer pain experts estimate that 85 to 95 percent of people with cancer could have adequate pain control if existing therapies were used appropriately.

She next described the analgesic ladder advocated by the World Health Organization (WHO). In step one, therapy includes use of a nonopioid, such as aspirin, Tylenol, or other nonsteroidal anti-inflammatory drugs like Motrin, with or without an adjuvant drug. If pain

persists, at step two a weak opioid such as codeine or a hydrocodone such as Vicodin, or an oxycodone such as Percodan is added to the nonopioid, and adjuvant drugs are continued. If pain persists, a strong opioid such as morphine, a hydromorphone like Dilaudid, or methadone, is advocated and used with or without the nonopioid and the continuance of adjuvant drugs.

She continued that findings suggest that step-one drugs can provide adequate analgesia until death for 5 to 27 percent of the patients with mild to moderate pain. Unfortunately, she said, these drugs are underused by oncology, family practice, and internal medicine physicians—physicians who usually provide first-line treatment to patients with cancer pain. Reasons for underuse have not been established.

Although evidence supports the general efficacy of nonopioids in the management of cancer pain, several areas of research are needed. Because research data are available to guide the selection of drugs and the maximum dose that can be tolerated, it is important to identify individual characteristics that affect response to nonopioid therapy. Current clinical practice is to conduct sequential drug trials to find the effective nonopioid—but, she said, this practice delays optimal analgesia and consumes the patient's energy while adding to the costs of care.

She added that investigations are needed to elaborate the mechanisms of analgesia and specific types of cancer pain, to consider the importance of prostaglandin and leukotrien synthesis, and peripheral versus central nervous system sites of action. She added that controlled clinical trials are needed to evaluate the safety of using nonopioids for pain management in patients undergoing active cancer therapies.

Some clinicians, she said, are reluctant to use these drugs because the antipyretic effect could mask fever, an early symptom of infection, and because the relative risk of gastrointestinal bleeding is three times greater with nonopioid users. Given the neutropenia and thrombocytopenia seen during cancer therapy, she said, nonopioid side effects are worrisome where research data are not available to guide clinical practice decisions. Frequently these agents are not being used when active cancer therapies are being undertaken, although the patients are in severe pain.

In addition to nonopioid analgesics, step one of the analgesic ladder calls for use of adjuvant drugs, such as tricyclic antidepressants like Elavil, anticonvulsants like Tegretol, and antianthioletics and steroids. All but the antianthioletics are advocated for the treatment of pain associated with lesions of the peripheral and central nervous system. She noted that few placebo-controlled clinical trials have been published to evaluate these drugs as adjuvant therapies for cancer pain. Study findings of nonmalignant chronic pain need confirmation in well-designed studies of patients with cancer pain and tumor involvement of neural tissues.

She pointed out that, recently, other nonopioid agents have shown efficacy in the treatment of cancer pain. Oral and spinally-administered membrane-stabilizing drugs, such as mexiletine, and lidocaine with papivocaine, are being used in clinical practice with evidence of superb analgesia. However, controlled clinical trials are unavailable to evaluate the role these drugs should play in the management of cancer pain.

Methylamphenadate, a short-acting amphetamine, was recently shown to reduce drowsiness, confusion, and other signs of cognitive impairment associated with continuous infusion of morphine. However, studies are needed to confirm the duration of these improvements and the best amphetamine and dose needed to combat opioid-induced sedation. The effects of coadministration of amphetamines and opioids on sleep, appetite, and quality of life are needed.

She described calcitonin, a hormone secreted by the thyroid to control serum calcium concentrations—calcitonin is also produced by some lung tumors. It is now being examined in several studies and one controlled trial. Although results are promising for the analgesic effect of calcitonin on bone and phantom limb pain, she said, controlled clinical trials are needed to evaluate the mechanisms of action and analgesic efficacy, the appropriate route, the toxicity, and the tumor response associated with the exogenously administered calcitonin. She said it is not known if the exogenously administered calcitonin might actually promote tumor growth; therefore, this needs to be studied.

Dr. Wilkie reported that 6 to 32 percent of the patients with cancer could be maintained on step-two weak opioids until death—some patients have been maintained as long as 40 weeks using step-two drugs without escalating to step-three drugs. Research is also needed in step-two drugs because they are often used inappropriately.

Dr. Wilkie next spoke of step-three drugs, which include morphine, methadone, and a number of other agents. She reported that findings from descriptive studies suggest that about 35 percent of the patients with cancer pain require strong opioids to effectively manage pain, especially in the terminal health phase. The WHO's guidelines recommend morphine as the drug of choice, with oral administration. However, recent evidence raises questions about its use as the drug of choice, particularly in high doses and in patients with compromised renal function. Morphine administered in high doses orally and intrathecally have been associated with hyperalgesia and myoclonus. However, the extent and characteristics of this phenomenon have not been determined. Furthermore, she said, it is well established that the hepatic-formed morphine metabolite morphine-6 glucuronide is pharmacologically active with analgesic and side-effect properties.

She explained that the morphine-6-glucuronide passes the blood/brain barrier and accumulates when renal function is impaired. A recent study in a sheep model indicates that morphine-6-glucuronide may be produced as well as cleared by the kidneys. She said that controlled studies are needed to evaluate the effects of high-dose morphine therapy and the role that morphine-6-glucoronide plays in producing analgesia in patients with cancer pain, especially considering hepatic and renal function. She said that studies are also needed to evaluate the metabolites of other strong opioids and to examine the relative potency of opioids in repeated dose conditions, which are more representative of the clinical needs of patients with persistent pain. Research is also needed to address the optimal drugs or combinations of drugs and the administration routes for the management of specific types of pain, such as nociceptor and neuropathic pain.

She noted that there is considerable debate among the cancer pain experts regarding the opioid responsivity of neuropathic types of pain and that additional research is needed to clarify the debate. Research is also needed to establish the most appropriate use of drug administration technologies.

Dr. Wilkie addressed several problems in drug therapy at all steps of the analgesic ladder. The first is that investigators studying drug therapies for cancer pain recognize the variables with potential to explain the great interindividual differences seen in response to analgesic therapies. She said that a review of the literature would suggest that in cancer research, pain variables do not receive adequate description or control, and in pain research, the cancer variables do not receive adequate description or control.

She stressed that when evaluating drug effects in cancer pain management, it is important to consider the type of cancer, because pain patterns may be quite different for various cancers. Other variables that need to be considered include the metastatic pattern, the antitumor therapies that have been used that may influence permeability of the blood/brain barrier, the location of the

pain, the pain intensity both at rest and in movement, the pain quality, and whether the pain is constant, intermittent, or transient.

Finally, she said, it is important to evaluate the effects of beliefs and attitudes held by clinicians, patients, and family members regarding the use of drug therapy for cancer pain management. She continued that use of the WHO's drug therapy guidelines to combat the unnecessary suffering associated with cancer pain would not be maximized until clinicians, patients, and family members understand the difference between tolerance, dependency, and addiction, and realize that cancer pain control is viable. She said that 50 to 60 percent of the patients should not be experiencing excruciating pain, and believes that an 85 to 90 percent pain relief incidence can be reached. She also believes research is needed on disseminating what is known about cancer pain management in the face of the war on drugs and the "Just Say No" campaign. She explained that patients are not taking their prescribed analgesics because of this particular campaign and the prevalent antidrug attitude. She reinforced that research is vital to patients in order that they receive adequate prescriptions for cancer pain.

Questions and Answers

Dr. Temin asked if the general attitude toward drug abuse affects practitioners as well. Dr. Wilkie responded that in some States where triplicate forms are used, there is a decrease in the number of opioid prescriptions written. She continued that clinical practice anecdotes suggest that if a physician writes a triplicate in error, rather than writing a second prescription, the physician would leave it for fear that a State official would be concerned about the potential for abusing the prescription of those opioids. Dr. Temin asked whether it would be useful if the NCAB made a statement to a particular audience regarding this issue, to which Dr. Wilkie replied that it would be very helpful to make a statement to the WHO.

Dr. Durant inquired about a drug administration schedule. Dr. Wilkie answered that the pattern of the pain must be considered. For constant pain, a schedule has been very effective, but for intermittent pain scheduled dosing can create problems.

Dr. Calabresi asked Dr. Wilkie to address the anticipation of pain in reducing the amount of pain medication. Dr. Wilkie responded that cancer pain is multidimensional, and that it is difficult to adequately judge the dosage of pain medication. She indicated that her goal is for all of her patients to have zero pain on a 0 to 10 scale. She continued that research findings indicate that clinicians are willing to let their patients tolerate pain up to the point where it impedes functional status. She said that clinicians' goals for pain must be congruent with patients' goals for zero pain to be reached in clinical practice.

Dr. Chabner asked where most pain research is being conducted, how it is supported, and if much support is coming from the private sector. Dr. Wilkie answered that much support comes from the private sector. Bristol-Myers Squibb has been supporting renowned pain researchers throughout the U.S. and are now extending it to England. She then named several other prominent researchers. Dr. Chabner inquired as to whether any support came from the NCI, to which Dr. Wilkie said she did not know how much support originated from NCI.

Nonpharmacologic Pain Aspects/Agency on Health Care Policy and Research Guidelines—Dr. Betty Ferrell

Ms. Mayer introduced the next speaker, Dr. Betty Ferrell, from the City of Hope National Medical Center in Duarte, California. Dr. Ferrell announced that she would be focusing on the guidelines for pain management from the Agency for Health Care Policy and Research (AHCPR) and nondrug interventions.

She began by noting that the guidelines were released on March 5th of this year, and focused on acute pain management, both postoperative as well as procedural- and trauma-related pain. She said that in the U.S., 23 million surgeries are performed each year. It is estimated that 50 percent of these patients do not get adequate pain relief. She stressed that a great many surgeries are cancer related.

The first goal of the guidelines is to reduce the incidence and severity of patients' acute postoperative or posttraumatic pain. The second goal is to educate patients about the need to communicate unrelieved pain so they may receive prompt evaluation and effective treatment. The third goal is to enhance patient comfort and satisfaction, and the fourth goal is to contribute to fewer postoperative complications and, in some cases, shorter stays after surgical procedures.

She explained that the guidelines promote a collaborative, interdisciplinary approach to pain control, including all members of the health care team, with input from patients and patients' families. The goals emphasize an individual, proactive pain control developed pre-operatively by patients and practitioners.

The guidelines, she said, emphasize assessment and frequent reassessment of the patient's pain. From this process, they hope to get a detailed report of the patient's pain; an intervention, giving medicine and using a nonmedical approach; an evaluation of the drug and nondrug therapies; and development of a formal institutional approach to management of acute pain.

The guidelines contain suggestions and also include certain requirements. The first requirement is that pain intensity must be assessed and reassessed at regular intervals. The second requirement is that patient preferences must be respected when determining pain management. The third is that institutions must develop and organize programs to evaluate the effectiveness of pain assessment and management.

Dr. Ferrell described the development process of the guidelines. The process included a review of scientific evidence and expert opinion. The panel consisted of nurses, physicians, an ethicist, a patient, a pharmacist, a physical therapist, and members of a number of other disciplines.

Twelve databases were searched which resulted in 2,400 drug citations, 7,000 nondrug citations, descriptive studies, and studies of hypnosis, relaxation, heat, cold, etc. However, the panel found that only 1,000 of the drug studies and 800 of the nondrug studies were of a quality that could be reviewed. She next showed a copy of the four-part guidelines and said that she would distribute copies to the NCAB.

Dr. Ferrell then provided highlights of the guidelines, including: 1) pain assessment; 2) pain caused from procedures such as surgeries, biopsies, treatments, etc.; 3) the issue of known or suspected substance abusers, who are particularly troublesome in pain management; 4) pain management for the elderly, particularly relevant because the majority of cancers are in the elderly; and 5) pain in children.

She addressed nondrug interventions and noted that the panel is currently writing guidelines for chronic cancer pain. Nondrug interventions are described as being either cognitive or physical. Cognitive interventions include imagery, relaxation, and hypnosis; physical agents are treatments such as heat, cold, acupuncture, and acupressure.

A review of the same 12 databases showed only 25 published studies related to nondrug interventions in cancer pain. Sixteen of the studies were based on cognitive techniques and nine of the studies were related to physical intervention. Most of the studies used very small sample

sizes. She described the studies as using weak methodology instead of randomized, controlled trials. There is very little science, she said, to support nondrug interventions, and very little funding to support these kinds of studies.

Dr. Ferrell emphasized that the most important nondrug intervention is education—so patients know their pain can be relieved. She said we must overcome patients' fear of addiction, tolerance, and respiratory depression. She pointed out that presently, institutions designated as NCI cancer centers may have no formalized pain management program, no ongoing pain assessment, inadequate use of drug modalities, and outdated and inadequate pharmacologic interventions. This, she said, has widespread implications for cost. In her own institution, they found that unrelieved pain was the number two reason for hospital admissions.

The AHCPR has, therefore, indicated their research priorities as: 1) to increase the quality of intervention studies; 2) to compare drug and nondrug interventions; 3) to advocate the need for models to study postoperative pain and its outcomes; 4) to conduct studies on nondrug interventions; 5) to conduct multisite studies to determine the effects of variation in practice; 6) to conduct studies on patient preferences for specific interventions; 7) to conduct studies on how to resolve the causes of unrelieved pain; 8) to conduct studies on pain prevention and management in special groups, (e.g., children, the elderly); 9) to conduct studies on pain management in ambulatory surgery centers; 10) to conduct studies on effectiveness of different assessment tools; 11) to examine the costs of pain management; and 12) to conduct studies on legal issues such as regulatory issues.

Dr. Ferrell closed with several comments. First, pain management does not occur in acute care settings, she said, it occurs at home, and is given most often by family caregivers who are often frail and elderly and have their own health problems. Second, the cancer pain document that will come from the AHCPR will demonstrate the widespread health policy implications of the problems of pain in cancer. Third, because guidelines for chronic pain in cancer were not available, she included in her handout three papers that summarized the status of chronic cancer pain management. Finally, she said, it is very important to remember that the relief of cancer pain is awaiting no scientific breakthrough. The drugs to reduce and relieve the majority of cancer pain already exist. What is needed is support for dissemination and evaluation of available information.

Questions and Answers

Dr. Becker asked if there are any methods of pain measurement. Dr. Ferrell replied that there is not a standard biological measure for pain, and that the guidelines suggest using the patient self-report as a standard pain assessment scale. They suggest that the patients be asked to rate their pain on a scale of 1 to 10. After a dose of medication is administered, the patient is reassessed approximately 45 minutes later. Dr. Becker responded that this seems totally inadequate because there are some patients who are quite tolerant to pain, and some who are not tolerant at all. He mentioned having some sort of standard measure of inflicting pain to measure the patient's response. Dr. Broder interjected that, on the record, Dr. Becker did not mean this comment. Dr. Becker replied that this has been done to measure response of analgesic agents on volunteers. Dr. Ferrell responded that, ultimately, a patient's pain cannot be judged—that the patient must be listened to and evaluated by using the scale. She elaborated by stating that there have been studies that have demonstrated pain assessment. What needs to be done is to uniformly ask patients about their pain and measure it in a quantifiable way.

Dr. Salmon added a few comments to Dr. Ferrell's presentation. He clarified that when Dr. Ferrell addressed nondrug approaches to pain, she did not include existing clinical modalities. He stated that neurosurgeons and radiotherapists play major roles in pain management in many areas such as cordotomy for intractable pain in a specific location or

radiation therapy for localized bone pain. He said these are very dramatic and effective approaches that do not require drugs and often allow a patient to go from a step-three drug back to a step-one drug or less.

He then said that he suspects that most NCI-designated clinical and comprehensive centers do, indeed, have pain teams. He then remarked that he understood Dr. Ferrell's remarks on the need for research, when she said what is truly needed is education about existing therapies. Finally, he said, a large part of patient cancer pain is managed by physicians in their offices and not at cancer centers. He feels that oncologists are familiar with the steps of pain management; however, internists or generalists who don't deal with cancer patients and their problems are a significant part of the educational issue.

Dr. Ferrell acknowledged that she did not refer to radiation therapy and certain anesthetic and surgical procedures because the postoperative guidelines do not deal with these modalities. She pointed out, however, that the three papers she included in the syllabus all refer to the importance of radiation therapy and surgical procedures. She disagreed with Dr. Salmon's suggestion that oncologists are practicing optimum pain management. She referred to an ECOG survey (a survey of practicing oncologists) that indicated that practicing oncologists still have very little knowledge in the use of the steps in the WHO ladder. She emphasized that practicing oncologists still have fears of addiction, tolerance, etc. Dr. Salmon said the point that he was originally trying to make was that pain management is largely an outpatient issue and may involve physicians in their offices as opposed to institutions.

Dr. Broder commented that an expectation of the cancer centers is that they serve their communities as focal points for the transmittal of knowledge. He asked for advice from the Board as to the correct expectations of comprehensive cancer centers in disseminating and transmitting knowledge to the communities they serve.

Dr Calabresi asked about the status of self-medication regarding pain control. Dr. Ferrell responded by stressing that the best way for patients to self-medicate is via oral medications. Self-medication involving more complicated methods such as a PCA pump is recommended by the AHCPR when patients cannot swallow—the pump provides them better control and allows them to relieve the pain before it becomes severe.

Dr. Ferrell also spoke of the high cost of PCA morphine (approximately $4,000 per month). She said that the benefits of these types of procedures should be scrutinized.

Psychosocial Intervention Issues—Dr. David Spiegel

Dr. Spiegel began his discussion by pointing out the need to rethink current strategies for assisting cancer patients. He indicated that medical research in the twenty-first century will derive some benefit from twentieth century science and technology developments (e.g., genetics, immunology, and brain imaging). However, researchers are also approaching the next century with a poor understanding of what this technology means. Dr. Spiegel explained that previous methods of facing the problem of cancer have tended toward the mechanistic in a way that fails to take advantage of the rich possibilities for helping cancer patients or to advance medical techniques. He then proposed that the best medical treatment for cancer patients involves psychosocial as well as surgical, medical, and radiological intervention. Dr. Spiegel elaborated on three specific psychosocial variables purported to be of great value in treating patients with cancer: behavior, i.e., risk behavior, and early detection; compliance with medical treatment; and the effects of psychosocial support.

Proceeding to explain why a shift in focus is needed, Dr. Spiegel described two extreme schools of thought related to illness. The first he called "endless materialism," which supports

the belief that the way people feel or react is an epi-phenomenon, not necessarily influencing the disease itself. The other extreme, disembodied spiritualism, promotes the notion that once problems or illnesses have been solved in the mind, they will magically be fixed in the body. Both of these theories, Dr. Spiegel stated, are incorrect. He reported that the latter method may result in serious side effects, especially if patients are blamed for poor management of their mental states, or for either succeeding or failing to control their cancer.

Dr. Spiegel moved on to discuss current literature linking social support and health outcome. James House, whose article appeared in *Science* (1988), demonstrated a strong relationship between social integration and age-adjusted mortality, after controlling for health risk behaviors such as alcoholism and smoking. This study, which surveyed approximately 8,000 individuals, showed that a strong relationship exists between lower social integration (having day-to-day contact with other people) and mortality. Dr. Spiegel pointed out that the link between social isolation and age-adjusted mortality is as strong as the well-known links between high cholesterol and mortality and smoking and mortality.

As an aside, Dr. Spiegel mentioned that both men and women appear to find protection against disease progression in relationships with other women. For most women, that involves cultivating relationships with their sisters, friends, and mothers. For men, that protection is found most often within a marital relationship.

Dr. Spiegel proposed that, assuming there is a relationship between psychosocial support and disease status, perhaps there are specific ways in which psychosocial intervention can improve response to disease progression. He indicated that there is cancer literature that identifies social isolation as a risk factor for earlier mortality, and psychosocial stress as a risk factor for early recurrence of illnesses like breast cancer.

Dr. Spiegel then shifted the talk to a body of research begun at Stanford University in the 1970s, which looked at the relationship between psychosocial support for cancer patients and both psychological as well as medicinal outcome. He also acknowledged his collaborators: Joan Bloom, University of California at Berkeley; Helen Kraemer, Stanford University; Ellen Gottheil; Irving Yalum; and the women who participated in the study. These 86 women had been diagnosed with metastatic breast cancer and were comparable on background demographics. All were randomly assigned to either an intervention group or to routine and excellent oncological care. In terms of prognosis, all had equivalent disease-free intervals (38 months for the control group, 36 months for the intervention group) from initial diagnosis to first metastases, and they were, on average, 5 years beyond initial diagnosis.

Dr. Spiegel then described the methodology of the study, which had as its goal to help the women cope with and deal more effectively with their cancer. This was to be accomplished by helping the women reorganize their views of their lives by enabling them to change their priorities. One exercise in which the women participated assisted them in directly facing their fears of dying. Dr. Spiegel explained that most cancer patients frequently think about death, but they tend to be more concerned about the process of dying than death itself. They fear loss of control, being unable to dictate their medical treatment, pain, and isolation. The exercise, commonly known as "detoxifying dying," also helped the women adjust to the loss of group members throughout the study—27 percent of the sample died within the first year. Dr. Spiegel indicated that when faced with the loss of a group member, the other women tended to gather strength. They were reassured by the grieving of the other group members because they knew that they, too, would be grieved. They also identified with the dying member's strength and ability to cope. Dr. Spiegel relayed another critical aspect of the support group: not only did the members give strength to each other, they had practical advice for each other on how to handle their fears, how to interact with their doctors, or how to manage their medical treatment. This "helper therapy principle," Dr. Spiegel stated, is a powerful part of any support group.

Support groups such as the one described in the study should be made available to all cancer patients, Dr. Spiegel said, because of their potential to provide benefits to all members. Aside from the give-and-take of supporting each other, group members also reorganized their life priorities. They changed their plans for the precious time they had left. The women also improved their communications with family members and doctors, and exhibited a significant reduction in mood disturbance, as measured by the Profile of Mood State scale. The control group actually got worse.

Dr. Spiegel went on to speak about the role of hypnosis in teaching patients to control their pain. In the Stanford study, women were taught a simple self-hypnosis exercise that Dr. Spiegel compared to concentrating deeply on a good movie or book so that one's surroundings seem to fade. He elaborated that the cognitive component of pain is very important, citing the work of Ronald Melzac at McGill University, who found that top-down influence from the cortex can influence pain perception in the thalamus and the brain stem, where it is processed.

Dr. Spiegel also mentioned that there is a surprising direct relationship between the use of analgesics and pain. Often, patients experience significant levels of pain but the drugs do not help. In his study, Dr. Spiegel and his colleagues found that two factors determined how much pain a given patient would experience: mood disturbance and a belief that the pain signified a worsening of the illness. Site of metastasis did not even enter the regression equation. Therefore, Dr. Spiegel explained, mood and other cognitive variables seem to account for a great deal of variance in pain experienced.

As part of the self-hypnosis exercise, participants in the study were asked to imagine they were floating in a hot tub, concentrating on their areas of pain, making them warmer and cooler. At the end of the initial year of the study, both intervention and control groups reported their levels of pain sensation according to a scale numbered 0 through 10. Reported pain levels for the intervention group were just half the reported levels for the control group. Interestingly, the frequency and duration of pain attacks did not change; the patients in the intervention group were simply managing them better.

Dr. Spiegel then described the physiological responses to this type of pain management. Through a process called brain electrical activity mapping, one can actually observe the brain's response to various pain stimuli. It involves taking a computerized electroencephalogram, which records electrical activity on the scalp resulting from a series of shocks to the wrist. In the normal condition, the patient shows activation over the parietal cortex in response to the shocks. A patient who has been hypnotized and told that her hand is cool and numb, however, will show a substantially reduced response to the same shock. Similarly, if the patient is instructed under hypnosis to pay close attention to the stimulus, she exhibits a significant increase in response.

Dr. Spiegel stated that when people change the way they experience pain, they actually change the way their brains process the associated information. He referred to comments made by Alan Lechner, the Acting Director of the National Institute on Mental Health (NIMH), at a conference sponsored by the Coleman Foundation: that studies with PET scans on brain glucose metabolism demonstrate that mental processes actually influence the way the brain processes information. Dr. Spiegel reiterated that the interaction between mind and body is significant.

The women in the Stanford study were later followed up by Dr. Spiegel and his colleagues. By that time, 83 of the 86 women had died. Median survival did not differ between the intervention and control groups. In fact, half the intervention sample died just the same way the control group did. However, in the second half of the sample, there was an enormous difference: by 48 months, all of the control patients had died, while one-third of the intervention group was still alive. Mean survival for the control group was 19 months; for the intervention group it was 36.6 months. There was also a statistically significant, 15-month time difference

among the two groups between first metastasis and death. Dr. Spiegel pointed out that, much to the surprise of the staff, the intervention seemed to affect the progression rate of the illness in at least some patients.

Another study has shown consistent results. In 1990, there was a published report in the *Journal of Cancer Oncology* showing that lymphoma and leukemia patients who received home visits and educational interventions lived significantly longer than members of the control group who received only routine care.

Dr. Spiegel moved on to discuss possible mechanisms like the grandmother effect—one's grandmother admonishes one to eat well, sleep well, and get exercise. Patients who are less depressed and have adequate support may be able to meet these daily needs. Another possibility is improved interaction with their doctors. Perhaps patients who receive psychosocial support and whose lives have meaning to them will elicit more vigorous treatment from their doctors.

Two other classes of mechanisms that Dr. Spiegel thinks warrant further investigation are psychoendocrine and immune responses. The former is of interest because of the endocrine system's responsiveness to stress, which is facilitated by the hormones cortisol and prolactin. These hormones also have immunosuppressive qualities, and some, especially prolactin, may have a proliferative effect on endocrine-sensitive tumors, like those characteristic of breast cancer. Dr. Spiegel then quoted from Seymour Levine's study in which a squirrel monkey was stressed under different conditions. When he was alone and placed under stress, his cortisol levels increased predictably. However, if he was placed with another monkey and placed under the same stress, his cortisol level raised only half as much. If there were five monkeys with him, there was no increase at all in the level of cortisol. Dr. Spiegel mentioned that psychosocial support could potentially serve as a buffer that protects the body from the physiological consequences of stress.

The relationship between the body's immune response and cancer progression is complex, stated Dr. Spiegel. However, he emphasized, Dr. Fauci's study at UCLA indicates that patients who are diagnosed with malignant melanoma and who have access to a support group show a significantly augmented response (compared to controls) in terms of natural killer cell cytotoxicity after 6 months.

Dr. Spiegel mentioned that preliminary data from his own laboratory show that after a successful interaction, cancer patients exhibit a transient reduction in NK cytotoxicity, which returns to baseline 24 hours later. He explained that this might be another mechanism by which the group interaction helps patients deal with their problems. However, he cautioned, it is not yet clear the extent to which NK or other *in vitro* tests are indicative of how the body responds to cancer.

Concluding his talk, Dr. Spiegel outlined three areas for further research and clinical activity. The first includes randomized prospective clinical trials of the psychological and medical effects of psychosocial intervention for cancer patients. These group studies should have homogeneous patient populations that are well characterized and stratified on important prognostic variables. He mentioned the human genome project, which is spending 5 percent of its total budget on the ethical and psychological implications of the genome project, and expressed his hope that clinical medicine would do the same for cancer research. The second area requiring more attention, according to Dr. Spiegel, is improving early detection of disease incidence or recurrence among patients who are at high risk for specific kinds of cancer. This population would ideally include not only smokers, but those who are socially isolated or who are subject to severe and adverse life stresses. Finally, Dr. Spiegel stated that studies of the

psychosocial variables related to the identification of women with family histories of breast cancer and how those variables interact with outcome would be of tremendous value.

Dr. Spiegel conveyed his hope that this type of research will at least raise questions about whether the best medical care should include a combination of surgical and medical psychosocial interventions.

Hospice and Palliative Care Issues—Drs. Ken Miller and Michael Levy

Dr. Ken Miller and Dr. Michael Levy delivered presentations on hospice and palliative care issues. Both doctors are on the board of the Academy of Hospice Physicians. Dr. Miller is a community hospice director in Montgomery County and Dr. Levy is the medical director of Palliative Care Services at Fox Chase Cancer Center.

Dr. Miller began his presentation with a commentary on the lack of communication between the community and academicians. Dr. Miller is a community oncologist and the director of a local hospice, which cares for over 100 outpatient hospice patients each day. Dr. Miller explained that hospice care does not use a great deal of technology such as epidural narcotics. It utilizes a more personal approach to pain control, which involves a thorough understanding of the physiology of pain, pharmacology, and clinical assessment. Dr. Miller remarked that little attention is devoted to pain control and patient comfort issues during the training of doctors. In fact, in 14 years of training, Dr. Miller stated that he only heard one lecture on pain control and that was delivered by Dr. Levy. Despite the dearth of pain-control training he received, Dr. Miller estimated that he dedicates approximately 30 percent of his time to dealing exclusively with palliative care and another 30 percent on the interface between palliative care and curative therapy. Dr. Miller noted that even while he was training at the NIH, no palliative or hospice training was provided. Dr. Miller suggested that if the NIH would institute aggressive palliative programs for patients who are at the NIH for temporary therapy, this program would serve as a national model for community programs.

Dr. Miller commented that he constantly must weigh the risks and benefits of curative therapies in terms of short-term side effects, long-term toxicity, and data regarding disease-free survival. Statistics related to chances of survival also must be considered in the decision to implement certain protocols.

There are many goals of treatment, including cure, long-term palliation, short-term palliation, psychological support, and research. Dr. Miller stated that support and palliation are the hardest goals to achieve, while cure is one of the easiest. He supported this statement with two assertions: if these two goals are not achieved, physicians tend to personalize the failure; and many physicians have never learned about or become proficient in palliative care.

Dr. Miller remarked that it is very difficult to tell patients that their cancer has continued to progress despite the treatment they are receiving. It is much easier to start a new protocol or add a new drug to their regimen. The transition from curative therapy to palliative care is difficult, as are the everyday problems of palliative care such as intractable pain and nausea, anorexia, and constipation.

Oncologists tend to undermedicate their patients, devote little attention to pain alleviation, and fail to treat other symptoms. Dr. Miller asserted that the hospice movement is an attempt to correct these problems. Hospice patients are able to remain with their families to increase their level of comfort. Community hospice stands as a symbol of the commitment of doctors to their patients throughout their illnesses and serves as a center for training in palliative care.

Dr. Levy began by providing a definition of hospice care that was established by the National Hospice Organization's standards of 1987, which was the provision of palliative and supportive services regarding physical, psychological, social, and spiritual issues for dying persons and their families either at home or in hospitals. Hospice care involves the use of a medically directed, interdisciplinary team working to provide a patient with as comfortable a death as possible and then to support the family after death. Dr. Levy noted that this definition involves family as not just part of the therapy, but also as part of the focus of care.

Hospice care began in the United States as an antiestablishment movement in response to the growing number of unmet needs of dying patients. The first hospice, the Hospice of Connecticut, started in 1974.

Dr. Miller noted that the NCI did fund three programs to examine the feasibility of hospice care. These studies, however, did not explore efficacy or outcome, but only cost, and examined an expensive model. Medicare chose to fund hospice care not because it was viewed as the right care, but because it would save money by keeping patients at home. This view was reflected in the research conducted—research topics focused on cost efficiency, not efficacy of treatment, and, as hospice care was not done in hospitals because it would have been more expensive, research was very difficult to conduct.

The National Hospice Organization, which was formed in 1978, represents over 1,600 hospice programs and cares for nearly 200,000 patients each year, of which 85 percent are people with cancer. Each day, a typical hospice handles about 22 patients who have been diagnosed as terminally ill—individuals for whom curative therapies are no longer effective, appropriate, or desired and whose prognosis is approximately 3 to 6 months.

The Academy of Hospice Physicians was formed in 1989 and represents over 1,000 physicians who work in hospice care, 25 percent of whom are oncologists. Only 3 percent of the members conduct hospice care as a full-time job and 40 percent are volunteers. These statistics indicate the difficulty encountered in obtaining a sufficient number of hospice workers, without considering development or expansion of research in the field.

Dr. Levy highlighted events leading to the current focus on hospice care. Half a million people die each year of cancer. Despite the advances in early detection, combined modality, and dose intensity that are helping to cure many patients, a large proportion of patients have not benefited from these developments. Congress has requested reports detailing expenditures on cancer and updates on efforts in psychosocial support, pain management, and rehabilitation. Initiative 119, which would have legalized euthanasia, was narrowly defeated by a 54 to 46 vote and the California State Death with Dignity Act received enough signatures to be on the ballot this November. The Patient Self-Determination Act mandated that all patients be asked whether they have living wills.

Dr. Levy continued with a discussion of the major obstacles to hospice and palliative care. He indicated that one of the major problems facing palliative care is that many patients are referred too late. Another obstacle to pain control is that there is not enough research-based information regarding aggressive symptom control to allow documentation or improvement of treatments. Some physicians are resistant to prescribing pain medicine for fear of addiction and tolerance. Other physicians have never been taught to consider the benefits and risks of therapy or the life enhancement that is possible through hospice care. Dr. Levy commented that limited availability of hospice care and funding is also a problem.

Dr. Levy suggested that palliative care must be made into a specialization to become a priority. Dr. Levy asserted that issues of education, research, and accountability regarding pain

control need to be examined. He added that issuing an RFA on cancer education programs related to palliative care would be helpful.

Dr. Levy summarized recent activities addressing palliative care. He commented that he and a group of physicians convened a meeting with the Office of Cancer Communications to examine future directions for pain control treatment among patients and their families. Last March, the American Society of Clinical Oncologists (ASCO) formed an ad hoc committee on cancer pain. A policy statement was developed that the Board accepted, which stated that cancer patients have a right to pain control and oncologists have a responsibility to control it. He stated that a cancer pain curriculum will be presented to the Board this month for approval, which he hopes will be incorporated into all oncologist training programs.

Dr. Levy mentioned that since he began working in palliative care he had tallied the number of abstracts at the American Society of Clinical Oncologists each year in relation to the number that address supportive care. This past year there were 1,471 abstracts and only 139 were related to supportive care. Of these, 65 percent dealt with supportive cancer therapy, infection, nausea, vomiting, bone marrow transplants, and biologic response modifiers; 15 percent discussed pain; and 2 percent involved hospice care. He stated that the resistance to pain proposals does not come from bias at ASCO, but from the lack of funds for research for pain control.

Dr. Levy reported the findings of a survey he conducted to determine whether various cancer centers had pain management teams. He discovered that many had pain teams and that 16 centers had pain clinics. Dr. Levy also learned that only nine centers had hospice or palliative care teams and that only one had a unit for this purpose. He asserted that the sciences of leukemia and bone marrow transplant were advanced by placing special focus on them and creating units devoted to their study. Funds must be allocated to palliative and hospice care programs to allow palliative care to follow the lead of these sciences.

Dr. Levy concluded by stating that palliative care must become a part of comprehensive care, which was judged to be the flagship of state-of-the-art technology. He reiterated that increased access to care and increased funding of research and technology transfer are the primary needs of palliative care programs. These programs help patients to not just die with cancer, but to live with cancer.

Ms. Mayer then opened up the floor for NCI staff to offer comments, as they were not formally included in the presentation. Dr. Leslie Ford took the floor. She remarked that she had no formal comments, but complimented all of the morning's speakers on enlightening presentations. She spoke about the Community Oncology and Rehabilitation Branch. She remarked that they consider rehabilitation research to be very serious, and described the two major avenues through which research is implemented. She mentioned the Community Clinical Oncology Program (CCOPs) as the mechanism for conducting the tamoxifen chemoprevention trial. CCOPs are comprised of community physicians who spend their time with patients who have cancer. A large portfolio of clinical trials exist through which Cooperative Groups examine pain management and techniques for pain management, including PCAs, patches, and long-acting or sustained-release medications.

She said the other major avenue is through the investigator-initiated R01/P01 applications and the RFAs. She said they have a large, but not totally comprehensive, R01 and P01 portfolio funding a number of the investigators mentioned by Dr. Ferrell. She mentioned that their Board of Scientific Counselors are examining psychosocial intervention and programs of psychosocial interventions and evaluating their efficacy.

Dr. Cairoli updated the Board on the status of the RFA that emerged from the workshop on cancer pain. He stated that awards would be made by July 1 for the initiative regarding educational programs for health professionals, cancer patients, and their families in terms of state-of-the-art technology for cancer pain management, psychosocial issues, and rehabilitation problems. Of the 30 applications that were submitted from a wide range of organizations, approximately 12 will be funded.

Dr. Cairoli also announced that the guidelines for the Cancer Education Program are being revised. Palliation training and education will not only be included within the standards, but will be highlighted as part of the new guidelines.

Dr. Bettinghaus said the results that Dr. Spiegel attained are fascinating. He asked Dr. Spiegel whether he has considered an alternative explanation for the finding—that the year delay in splitting among the groups was due to the strength of the intervention. Dr. Bettinghaus hypothesized that had the intervention been delivered in intense amounts at the beginning of metastatic disease development, the condition would have improved dramatically.

Dr. Spiegel agreed with Dr. Bettinghaus' idea. He remarked that it is logical to assume that an intervention would be more effective on a smaller tumor burden. Dr. Spiegel added that he hopes to be able to perform the same intervention on women with primary disease or, possibly, on women at risk for breast cancer.

Dr. Durant commented that he had listened to the chief actuary from the Health Care Financing Administration (HCFA) talk about the cost of health care and an actuarial study he had conducted of the cost/benefit analysis of hospice. The results of that analysis did not provide evidence of a large cost benefit due to hospice care. He asked Dr. Levy to comment on these findings.

Dr. Levy replied that initial studies indicated that home hospice was cheaper. These studies were successful in getting many patients care in their homes. Currently, a great deal of health care is being moved into the home. As the science of palliative care has advanced, some more expensive treatments are being funded by hospice programs; therefore, hospice care has become more expensive. More recent studies, however, have shown that the real advantage of hospice care is the quality of life these patients achieve. Dr. Levy said that it is also important to consider how many other aspects of health care have been asked to prove that they are cheaper instead of more effective.

Dr. Broder expressed concern regarding the need to develop programs that clearly communicate to cancer patients that it is not their fault that they have developed the disease. He commented that doctors have an obligation to avoid blaming patients for having cancer; for example, if they develop lung cancer after years of smoking. He said that members of cancer survivorship organizations have approached him and requested that he issue a statement to this effect.

Dr. Bragg asked whether there is a shortage of staff for acute care of cancer patients, especially due to burnout. In addition, he inquired what is being done to address staffing needs in terms of training and recruitment.

Ms. Mayer responded that the ONS has conducted surveys to examine staffing levels. She mentioned that oncology patients do require a higher nurse-to-patient ratio than most medical or surgery patients. Ms. Mayer emphasized that a master's study that she conducted revealed that working with cancer patients did not cause burnout, but the frustrations of working within a hospital system did. In fact, Ms. Mayer said, working with cancer patients was one of the factors that balanced out the negative forces.

Ms. Mayer indicated that the symposium surfaced a great many worthwhile topics, but that time constraints need to considered. Dr. Calabresi asked the Board whether they would like to continue the discussion or postpone it until after the committee reports were delivered.

Dr. Jako said that he would like to make a short comment on the symposium from his surgical perspective. Dr. Jako reiterated the importance of Dr. Broder's statement in regard to avoiding blaming patients for their disease: doctors must care for patients no matter what their past actions. Dr. Jako stated that living with cancer and living after cancer treatment have a great impact on the quality of life of the cancer patient.

Surgical treatment can have extreme disabling effects, he said. Standard thoracotomy incisions are 10 to 14 inches long to allow standard instruments to be used within the chest and proper lighting of the chest cavity. However, these incisions are responsible for a great deal of postoperative pain and respiratory dysfunction. Thirty years ago, Dr. Jako developed a minimally invasive endoscopic procedure for the larynx. During subsequent years he was able to adapt this technology for application in thoracic surgery, especially lung surgery. He designed a special indirect endoscope, referred to as the surgical endoscope, or Jakoscope, which allows the surgeon to see all parts of the chest cavity, lungs, mediastinum, and esophagus. Lobectomies for lung cancer can now be performed through a 2- to 3-inch incision. This procedure reduces cost, pain, disability, and respiratory dysfunction associated with the older procedure and, consequently, increases the quality of life experienced by the patient. Dr. Jako said that until more effective medical treatments can be discovered, surgical treatments must continue to become progressively less invasive.

Dr. Calabresi thanked Dr. Jako. Dr. Temin complimented the speakers from the symposium and highlighted some of the issues raised by the presentations, including the large potential role of palliation and bereavement counseling in cancer treatment.

Dr. Calabresi thanked Ms. Mayer and the speakers for the presentation. He reiterated the statistic that Ms. Mayer opened the symposium with, indicating that more than half of the patients now are living with cancer, with little hope of cure.

XI. PROTON BEAM THERAPY EVALUATION UPDATE—DR. LESTER PETERS

Dr. Calabresi announced that the Board had requested a periodic evaluation on efforts related to proton beam therapy. He stated that Dr. Chabner would introduce Dr. Lester Peters from the M.D. Anderson Cancer Center in Texas, who would present the update.

Dr. Chabner explained that several years ago the Board was asked to examine the possibility of supporting further particle facilities for the treatment of cancer. About 15 years ago, the Board initiated a program that was responsible for the construction and support of four facilities to support neutron therapy. Studies of this therapy continued to assess the effectiveness of the treatment. Some time later, one of the NCI's grantees requested that they consider supporting the construction of a facility for proton therapy. The NCI Board decided that as these facilities are highly expensive, long-term investments, it would not be wise to start the production of a new facility until the review of the neutron program was completed. Subsequent to this decision, Congress passed a line item supporting the design of new proton facilities in the United States. The NCAB asked the NCI to conduct an assessment, which would involve extramural expertise, of the potential value of such facilities to guide funding decisions. A panel was formed, which included Dwight Kaufman, Deputy Director of the Division of Cancer Treatment, as the organizer of the effort and Dr. Peters as the chairperson. Dr. Peters is the head of the Radiotherapy Department at M.D. Anderson. He presented the results of the panel's deliberations regarding the proton therapy facility.

Dr. Peters reiterated that the report he would present emerged from a direct request by NCAB to assess the status of proton beam therapy, largely as a result of the Congressional appropriation of funds to study planning for construction of additional facilities. Dr. Peters indicated that the basic topics he would cover included the rationale, current status, future prospects, and economic implications of proton beam therapy. He stated that the full report is contained within the Board members' notebooks. He requested that Board members read the summary and recommendations of the report, which was the output of the committee.

Dr. Peters then introduced the members of the panel, a well-credentialed, multidisciplinary group, none of whom had any vested interest in proton beam therapy. Names that appeared with an asterisk indicated a member of the Board of Scientific Counselors of the Division of Cancer Treatment. In addition to Dr. Peters and Dr. Kaufman, members of the panel included: Dr. J. Fischer, Chairman of Radiation Oncology at the Yale-New Haven Hospital and Medical Center; Dr. S. Fuks, Chairman of Radiation Oncology at the Memorial Sloan-Kettering Cancer Center; Dr. W. Hryniuk, Medical Oncologist and Director of the Comprehensive Cancer Center at the University of California at San Diego; Dr. G. MacLeod, Professor of Health Services Administration at the Graduate School of Public Health at the University of Pittsburgh; Dr. J. Purdy, Chief of Medical Physics at the Mallinckrodt Institute of Radiology at St. Louis, Washington University; Dr. G. Steele, Chairman of Surgery at the Deaconess Hospital in Boston; and Dr. R. Withers, Head of Experimental Radiotherapy at the University of California at Los Angeles. Dr. Peters thanked Dr. Kaufman for his organizing role and the staff of the Radiation Research Program at DCT for their help with the panel's work.

Dr. Peters explained that as he had encountered difficulty in assembling the panel members in immediate response to the directive, he decided to give each member a written assignment along with aspects of the report that they would be asked to develop in prototypical form. This initial step was followed by a data collection stage that was conducted by each member in response to a particular assignment. On April 21, hearings involving interested parties were conducted. The panel then entered a session of consensus development, which led to the production of the report. Dr. Peters noted that the report is divided into seven sections, which he briefly presented.

Dr. Peters described proton beam therapy as the "quintessential method of achieving conformal therapy in radiation oncology." The term "conformal therapy" is defined as the delivery of radiation to a volume that corresponds precisely and exactly with the target volume. Dr. Peters remarked that while proton beam therapy is the ideal method of producing conformal therapy, there are other possible methods. He added that although the technology is extremely complex, the biologic rationale is simple.

Dr. Peters presented the rationale by saying that if conformal therapy was achieved with better dose localization, then morbidity resulting from damage to critical normal structures would be automatically reduced as they would be excluded from the radiation dose volume. In addition, if dose localization is improved, then dose escalation can be achieved, which directly relates to tumor control. Dr. Peters commented that estimates of improvement in tumor control and reductions of normal tissue morbidity are contained within the report.

The next section of the report discusses the established utility of proton beam therapy. Dr. Peters pointed out that although 12,000 patients worldwide have been exposed to proton beam therapy, the majority of these people were treated for nonmalignant conditions in facilities that were not hospital based. Oncologic assessment of proton beam therapy, therefore, has not been extensive. Dr. Peters stated that there are two oncologic situations in which there is preliminary evidence of the therapeutic superiority of proton beam therapy: in ocular melanomas and in skull base or paraspinal tumors. In both cases, the tumors are close to critical normal structures, the optic nerve and the spinal cord and brain stem, respectively. The evidence indicates that with proton therapy it is possible to achieve dose localization with sufficient

precision that these tumors can be cured in a high proportion of cases without causing serious morbidity in nearby critical tissues.

Dr. Peters continued by explaining that these are extremely rare tumors; therefore, the panel estimated that only one or two facilities would be needed nationwide. He concluded that based solely on this evidence, there is not a need for a proliferation of proton beam facilities.

The next section, Dr. Peters explained, details the potential greater role for conformal therapy as a general approach to radiation oncologic research. The estimated number of cancer patients who die yearly from uncontrolled local or regional disease is between 80,000 and 160,000. Consequently, better treatment of local and regional disease could prevent a large number of cancer deaths. Dr. Peters acknowledged that radiation therapy would not control every local or regional cancer growth, but that these data indicate the enormity of the problem of uncontrolled local growth. He added that sometimes local control is naively dismissed as a problem, causing doctors and researchers to overlook a large potential source of patients who potentially could be cured.

Dr. Peters reported that the panel examined the types of cancer that would be amenable to better local/regional control by radiotherapy. This analysis led to the estimation that up to 130,000 patients a year could potentially benefit from dose escalation, which is 30 percent of all patients currently being treated curatively by radiotherapy. He indicated that to treat this number of patients with protons, approximately 500 machines would be needed, which could only be justified if substantial therapeutic gain could be demonstrated.

Dr. Peters stated that the panel believed that alternative approaches for conformal therapy need to be considered. He said that although proton beam therapy is the ideal method for achieving conformal therapy, linear accelerators can attain a close approximation, when treatment is planned and executed using a process called three-dimensional conformal radiotherapy (3-D CRT).

The panel, therefore, undertook a cost comparison analysis between proton beam therapy and 3-D CRT. The capital cost of a proton facility is approximately 10 times more than a conventional facility equipped for 3-D CRT. The operational costs for a proton facility were estimated to be approximately 20 to 30 percent higher, mainly due to staffing differences and the higher utility costs. Dr. Peters emphasized that the aggregate cost per patient of proton beam therapy, however, is only two to three times higher than 3-D CRT treatment, primarily because the procedures needed to plan and execute the treatment are essentially identical with the two approaches. In addition, the amortization of a proton facility could be extended over a much greater period of time than a conventional facility, as cyclotrons have a longer working life.

Dr. Peters stressed that it is wrong to think of these therapies only in terms of initial investment. He asserted that in comparison to competing treatment options, current state-of-the-art radiotherapy is really inexpensive. A typical linear accelerator costs about $1.4 million. Although this is a substantial figure, when one considers that this machine has a working life in excess of 10 years and can potentially treat over 2,500 patients during this time, the capital cost per patient treated is approximately $500. Dr. Peters compared this figure to the costs incurred for drug therapy or surgical treatment of cancer and concluded that radiotherapy is a bargain.

Dr. Peters continued his analysis of proton beam therapy with a discussion of the cost to the NCI. Of the $35 million that the NCI has expended on this technology thus far, $25 million was awarded to peer-reviewed research. The other $10 million was appropriated by Congress. Dr. Peters stated that the panel decided that the NCI should support this technology only through peer-reviewed research, which includes clinical trials of conformal therapy. The committee did not think that the NCI should be committed to the capital cost of these facilities. Dr. Peters noted

that last Friday an RFA was published for research that explores the effect of dose escalation in treatment of prostate cancer.

Dr. Peters indicated that Dr. MacLeod, the panel's health economist, wrote the cost analysis section of the report, which presents three possible perspectives on these comparative analyses. The standard cost/benefit analysis assesses the benefits only in monetary terms. The cost minimization analysis attempts to identify the least expensive method of achieving a goal. The method that Dr. MacLeod recommended is called the cost/utility analysis, which incorporates the societal benefit of the intervention in the denominator of the equation. The societal benefit is measured in terms of quality adjusted life years, which Dr. Peters remarked is consistent with the ideals expressed during the mini-symposium. In addition, a patient who is cured saves the health care system a great deal of money.

Dr. Peters summarized the recommendations from the panel. One, the NCI should endorse the funding of two state-of-the-art, hospital-based proton therapy facilities to treat patients for whom a *prima facia* case exists, and to perform peer-reviewed research examining the value of proton beam therapy for other tumor types. Two, the NCI should actively support research exploring all aspects of improving radiation dose distribution using any modality. Three, the NCI should sponsor comparative studies of the impact of improved dose distribution and/or dose escalation on local tumor control, survival, and treatment-related morbidity. The final recommendation is that if prospective trials support the case for a large number of additional facilities, the NCI should undertake a cost/utility analysis of proton beam therapy.

Dr. Calabresi thanked Dr. Peters for his excellent presentation and called for questions and comments. Dr. Bragg stated that there are numerous international proton therapy facilities available and suggested that the experiences of these efforts could be networked with those in the United States. Dr. Peters agreed with Dr. Bragg's suggestion and added that he strongly endorses international collaboration.

Dr. Durant inquired about the results of the neutron trials. Dr. Chabner responded that a review of the status of these trials is scheduled to occur at the next Board meeting. Dr. Peters commented that as neutron and proton therapies have very different rationales, he feels simultaneous discussion of the two would be confusing.

Dr. Salmon questioned the meaning of the terminology in the report stating that the NCI should endorse the funding for construction of facilities. He asked whether the panel intended to recommend that the NCI invest its own dollars in the production of these facilities. Dr. Peters replied that the words were carefully chosen. The panel concluded that the NCI should not provide the funds for constructing these facilities; however, if they were built, the facilities would provide an opportunity for beneficial research in dose conformation, which the NCI should support. Dr. Salmon asked whether that should be stated more clearly in the report. Dr. Peters indicated that the panel worded the recommendation in this manner to allow for further Congressional appropriations. Dr. Peters clarified that the panel did not recommend that the NCI pay the capital costs for new proton facilities.

Dr. Salmon asked if randomized clinical trials would be conducted on the dose escalation studies once they were completed. Dr. Peters replied that the dose escalation studies should definitely be subjected to randomized clinical trials.

Dr. Calabresi asked Dr. Peters to compare gamma knife versus proton beam therapy for lesions in the brain. Dr. Peters summarized that the gamma knife could be used for only a few types of well-circumscribed intracranial lesions. Although proton beam therapy could be used for these lesions, it is not as cost-effective as the gamma knife or stereotaxic linear accelerator

therapy which can achieve similar results. However, proton therapy is more versatile than the gamma knife and may have wider application in the treatment of intracranial tumors.

Dr. Chabner noted that a functional proton beam facility exists at Loma Linda, which the DOE funded; therefore, the report actually recommends that the NCI support the funding of a facility to be located on the east coast (as the other facility is on the west coast). Dr. Salmon suggested that the first recommendation needs to include the following statement: "In making this proposal, we do not directly recommend the NCI fund the construction of capital facilities." Dr. Chabner clarified that Congress would fund this facility through specific line item designation, it would not expect the NCI to divert money from, for example, the grant pool to support construction. Congress would indicate that they wanted the NCI to build a proton facility and allocate appropriate funding into the NCI's construction line.

Dr. Peters pointed out that the report is worded to convey the idea that two research facilities are needed to do the necessary proton beam therapy studies, and that if Loma Linda does not undertake the appropriate studies, then a second new facility would need to be constructed.

Dr. Calabresi thanked Dr. Peters. The meeting was adjourned at 12:18 p.m.

XII. SUBCOMMITTEE REPORTS

Aging and Cancer Subcommittee

Dr. Calabresi announced that at the Subcommittee's second meeting the previous day, Debbie Mayer agreed to replace him as Chairperson.

Dr. Calabresi commented that the link between aging and cancer is an important one, as the majority of people with cancer are elderly. He added that as the proportion of elderly people continues to grow over the next few decades, this correlation will become even more significant.

Dr. Calabresi stated that the next Subcommittee agenda item was a presentation from Mr. John Burklow from the Office of Cancer Communications. He discussed his recent activities to coordinate NCI efforts relating cancer and aging with those of other federal agencies. Mr. Burklow said that the topic of breast cancer was designated as a major focus of education, especially for primary care physicians. He explained that primary care providers tend to under-refer elderly patients for cancer screening tests such as mammograms and Pap smears, despite the fact that many people in these age groups have stopped being routinely examined by a gynecologist. Mr. Burklow also described the established mechanisms for communication between NCI and other agencies such as the National Institute on Aging and the Centers for Disease Control. He detailed efforts to disseminate public health information concerning cancer and aging to the mass media. Dr. Calabresi added that Ms. Mayer noted that information distribution efforts should target professional organizations to induce the incorporation of special issues for the elderly within the curriculum of training programs.

During a discussion of interactions with the American Cancer Society, Dr. Lawrence remarked that the ACS often serves as a source of public information, while the NCI and the physician's data query (PDQ) database are viewed as information providers for physicians. The importance of clarifying information regarding screening and treatment for prostate cancer was highlighted by the Subcommittee. Dr. Calabresi stated that new tests, such as PSA and ultrasound, have caused a great deal of confusion. Dr. Greenwald suggested that an interim forum to provide guidance to patients and health care providers would be appropriate. He acknowledged that a definitive consensus conference would not be proper at this point, as the field of prostate screening and treatment is advancing too quickly. Dr. Calabresi and Dr.

Lawrence agreed that the NCI and ACS should collaborate to develop consistent advice and then disseminate the unavoidably incomplete information that exists.

Dr. Calabresi reported that the meeting concluded with an announcement of an upcoming conference on cancer to be held in Argentina in the fall. Dr. Calabresi also announced that he is working with Dr. Knight Steele, Director of the Geriatrics Program for the World Health Organization, to organize an international conference regarding cancer and aging. Sites that have been considered for the conference are several cities in Europe; Washington, DC; and New York.

Dr. Lawrence commented that he and Dr. Greenwald recently discussed the possibility of forming a subcommittee to develop a common educational statement regarding prostate cancer. He emphasized that they will pursue this idea.

The report for the Aging and Cancer Subcommittee was voted on and accepted. The next report, from the AIDS Subcommittee, was announced.

AIDS Subcommittee

Dr. Temin reported that the AIDS Subcommittee discussed two topics. The first subject was the announcement by Dr. Yarchoan that use of dideoxycytidine (ddC), a dideoxynucleoside reverse transcriptase inhibitor for HIV, in conjunction with AZT, was approved by the FDA AIDS Advisory Committee during the April 1992 meeting. Dr. Temin commented that this drug was developed by NCI scientists, including Dr. Broder, and was the third drug approved by the FDA to be used to treat people with AIDS. Data regarding the drug were mainly generated through NCI clinical trials.

The other topic involved the increased occurrence of aggressive B-cell non-Hodgkin's lymphomas (NHL) which arise late in the progression of AIDS. Dr. Temin explained that people with AIDS are beginning to live longer as a result of treatment with AZT—and soon ddC and ddI—and, consequently, have a greater chance of developing NHL.

Responses to this increased incidence of NHL have included the development of an RFA regarding the disease and increased funding of research encompassing a wide spectrum of approaches to curing NHL. In addition, an internal intramural AIDS lymphoma working group was formed in July to address this problem. Elucidation of two risk factors—elevations in serum IL-6 levels and a CD count below 50 per cubic millimeter—has led to two new strategies for treating NHL. One of these strategies is currently in clinical trials.

Dr. Bohr discussed the potential relationship between aberrations in the DNA repair process and predisposition to NHL. Dr. Grever reported that efforts to develop agents to selectively target lymphomas have surfaced several new compounds that are different from those previously tested. Dr. Temin summarized the discussion by stating that the ability to define and detect the factors and mechanisms that predispose a person to develop lymphomas in a setting of HIV infection may lead to the development of strategies to effectively treat or even prevent the emergence of AIDS lymphoma.

Dr. Salmon asked Dr. Temin whether there is any evidence that HIV was in the NHL and had thereby directly incited the formation of the lymphoma. Dr. Temin responded that this was not the case and that the virus contributes to the general milieu by inducing a prolonged immune depression, but probably does not directly cause the lymphoma.

The report was voted on and approved. Dr. Calabresi then announced that Dr. Salmon replaced Dr. Durant as Chairperson of the Cancer Centers Subcommittee.

Cancer Centers Subcommittee

Dr. Salmon reported that there were two primary issues discussed during this Subcommittee meeting. The first topic involved the general policies the NCI should follow when a change in a center director or principal investigator was scheduled to occur.

The Subcommittee made a motion that institutions should have a clear plan for identifying interim leadership, which would be considered during the peer review process when the core grant was reevaluated. The Subcommittee also expressed a need to develop a set of consistent guidelines regarding the handling of grants and their renewal process when a principal investigator leaves. Dr. Salmon stated that members of the cancer centers subcommittee also considered the adoption of a motion regarding the background of a center director of either a clinical or comprehensive cancer center. Members asserted that if the center director did not have a clinical research background and was not actively involved in the care of patients, then the center should be required to appoint a deputy director or prominent senior leader with these credentials. Further discussion resulted in the determination that peer review was a sufficient mechanism for addressing this issue; however, there was some dissension surrounding this decision.

Dr. Salmon mentioned that a brief discussion was held concerning the draft guidelines for recognition as a comprehensive cancer center. The group decided on a few word changes and then agreed that the standards are satisfactory to be presented at the NCI's June meeting with the center directors.

Dr. Salmon concluded his report by commenting that the Subcommittee thanks Dr. Durant for his excellent leadership. Dr. Lawrence moved to accept the report. Dr. Chan commented that he would like the Subcommittee to examine the incorporation of hospice care or a pain control element within the cancer centers at their next meeting. Dr. Salmon responded that this topic will be addressed at the next meeting and that, in fact, he has requested that Dr. Kimes bring data he has compiled in regard to existence of these elements in various cancer centers to the next meeting. The report was then voted on and approved.

Environmental Carcinogenesis

Dr. Becker stated that the May 5, 1992, meeting primarily focused on low-frequency electromagnetic fields (EMFs). He explained that these are low-range magnetic fields that are created by a 60-cycle alternating current. A large number of articles has appeared in the lay press questioning whether these fields are responsible for outbreaks or clusters of cancer, especially leukemia in children.

Dr. Adamson opened the meeting by noting that the NCI has initiated a large collaborative study of the effects of EMFs. Dr. Martha Linet was appointed the NCI Principal Investigator of the study, which is a case control involving 2,000 leukemic patients and an equal number of appropriate control subjects. Dr. Becker stated that the study requires measuring of the low magnetic exposures to children not only within the home but also in external environments. Dosimeters, which measure the amount of exposure, were designed that a baby or small child could wear for an entire day. He remarked that the study does take into account other conditions that may contribute to the development of leukemia, such as radon and pesticide exposure. Dr. Becker indicated that the study results will not be available until approximately April of 1995.

Dr. Becker reported that the next speaker was Dr. Stanley Sussman, Program Manager of the Electric and Magnetic Fields Health Study Program of a group called the Electric Power Research Institute (EPRI). EPRI represents a cooperative effort of 700 utilities to examine

aspects of energy generation and its effects. This organization researches the effects of magnetic and electrical fields directly and by conducting literature reviews of related studies. Dr. Becker concluded, based on what was revealed thus far, that there is a slight link between leukemic risk and measured electrical fields, but not magnetic fields.

Dr. Richard Griesemer was the final speaker at the Environmental Carcinogenesis Subcommittee meeting the previous evening. Dr. Griesemer, of the National Toxicology Program, is involved in efforts to establish animal models for studies of EMF effects. Dr. Becker explained that EMFs have primarily affected cells in ways that are reversible when the fields are removed. Nothing definite has surfaced involving EMF effects on animals' cells. Dr. Becker announced that he believes an RFP will be issued by the toxicology group for researchers who have a method for studying exposed animals.

Dr. Becker stressed that no genetic effects have ever been discovered as an expression of exposure to these fields. Dr. Becker hypothesized that this is a result of the fact that low EMFs are nonionizing. Dr. Becker stated that household exposure from hair dryers, black-and-white televisions, and electric blankets are likely the most common sources of EMFs, not power lines.

Information and Cancer Control in the Year 2000 Subcommittee

Dr. Walter Lawrence delivered the report from the Subcommittee in place of Marlene Malek. He reported that there is one action item from the meeting. During the Subcommittee meeting, Susan Hubbard detailed a problem that has arisen concerning licensing the use of the PDQ system to outside private vendors. A potential licensee has requested a PDQ license for use in making reimbursement decisions. Staff at NCI and on the editorial board of PDQ have reiterated that it is inappropriate to use the treatment recommendations in PDQ to make reimbursement decisions because the list of treatment options is far from exhaustive.

The situation was presented to Dr. Broder, who stated that he wanted the Subcommittee to explore the possibility of modifying the database license. The Subcommittee developed a policy regarding the licensing of the PDQ database by outside vendors (Attachment A of the Subcommittee Report). Dr. Lawrence noted that the license agreement should state clearly that this database is intended for educational use only and is not an exhaustive list of all acceptable treatments. In addition, the policy states that if the information is used for reimbursement decisions, it will constitute a breach of contract. He mentioned that legal counsel reviewed the changes to the license agreement. He added that the Subcommittee decided they would like the entire Board to vote on this matter. Therefore, he indicated that when members vote on his report they will also be voting on the action item.

Dr. Lawrence highlighted the remaining proceedings of the meeting. Paul Van Nevel showed a short public service announcement (PSA) and a longer PSA on the National Basketball Association (NBA) wives' program for developing breast cancer awareness. Dr. Lawrence commented that Mrs. Pollin deserves to be complimented for her work on the NBA wives' project.

Dr. Lawrence indicated that the final topic discussed by the Subcommittee was the first two regional summit meetings. Ms. Malek presented reports on the success of these summits. The summits are cosponsored by NCI and the Komen Foundation and are conducted under grants to comprehensive cancer centers. Ms. Malek stated that the local American Cancer Society chapters are also involved in these projects.

Dr. Lawrence reported that Ms. Malek replaced Erwin Bettinghaus as Chairperson of the Subcommittee. Dr. Calabresi called for a motion to approve the report or for comments. Ms. Mayer inquired whether the license agreement is enforceable. Dr. Lawrence responded that it is

not enforceable, but stated that the Subcommittee feels that a clear statement absolving the PDQ and the NCI from accountability for private vendors' actions is necessary.

The report was approved with the Attachment. The Board's approval of the Subcommittee report also endorsed the Subcommittee's concept approval, by mail ballot, of a 5-year continuation of the support contract for the Office of the Director, NCI.

Minority Health Research and Training

Mrs. Zora Brown replaced Dr. Salmon as Chairperson of this Subcommittee. Mrs. Brown reported that the meeting began with an information item on the NCI Training Workshop for Native Americans. An initial problem was identifying key leaders involved in Native American outreach and which groups should be targeted for training efforts. Members of the Subcommittee suggested various agencies that would be able to help identify individuals who have expertise concerning Native American cancer needs and issues. Mrs. Brown indicated that Dr. Su Yang presented a description of the workshop scheduled for August 31 and had already contacted appropriate agencies and participants. Dr. Becker motioned that the Subcommittee supported the initial conference in August and that the NCI should consider an interagency cooperative agreement to work on the Native American cancer problem.

Mrs. Brown stated that Dr. Lemuel Evans described the Minority Health Professional Training Initiative, which included several RFAs that were later changed to program announcements. The possibility of changing the PAs back to RFAs was discussed, and a resolution was passed stating that this conversion would provide a better mechanism for these training grants.

Mrs. Brown indicated that plans for Phase II of the Minority Health Professional Training Initiative and an outline of needed improvements of medical oncology departments within minority schools of medicine were developed. In the future, the Subcommittee will consider mechanisms for communicating with these schools, identifying their particular shortcomings, and making suggestions for training minority health professionals to strengthen the departments.

Mrs. Pollin suggested that the Subcommittee consider utilizing the Science Enrichment Program, which is aimed at high school-level minority students. She noted that it possibly could be expanded to include undergraduate, graduate, and doctoral candidates.

Mrs. Brown indicated that she and Dr. Evans will meet to develop recommendations for improving the Minority Health Initiative at the NCI and that they will present these suggestions at the next meeting.

Mrs. Brown reported that Dr. Cairoli presented a brief description of the Minority Individual Predoctoral Fellowship Program at the NCI. Mrs. Brown commented that this program must also be evaluated in terms of specific measures of success and failure. Mrs. Brown mentioned that she is expecting a list of NCI outreach programs targeted at racial/ethnic minority group members.

Mrs. Bynum clarified that the Science Enrichment Program is in a preselection phase, but that it would be reasonable to discuss expanding it. Dr. Salmon commented that very few funds have been awarded to the Health Minority Professional Training Initiative. He stated that if funds are not specifically identified for this program through up-front commitments to applications received in response to RFAs, instead of general intent money for a PA, then even fewer monies will reach these programs. Mrs. Bynum added that the cancer education line, under which this program falls, was not allocated an increase in funds this year.

Dr. Chan asked what is the specific date for the Research Training Conference for Native Americans. Mrs. Brown replied that it is scheduled to occur on August 31, at the Bethesda Hyatt.

Dr. Bragg expressed concern regarding the lack of programs that target cancer prevention and treatment in rural areas. Dr. Broder responded that several prevention and early diagnosis programs focus on rural areas, including an Appalachian Initiative and the P-20 planning grants to develop cancer centers in States that are currently underserved. Dr. Greenwald added that the surveillance system under SEER compiles data on rural areas and that some initiatives within the CCOP cover these areas. Dr. Adamson commented that several inhouse studies have been initiated in these regions as a result of the development of cancer maps, which have indicated high rates of cancer in certain rural areas. Possible environmental factors that increase the risk of cancer are being explored in these regions.

The report of this Subcommittee was voted on and approved. Dr. Calabresi then introduced Dr. Erwin Bettinghaus, who replaced Dr. Fisher as Chairperson of the Planning and Budget Subcommittee, to present the report of that committee.

Planning and Budget

Dr. Bettinghaus reminded members of an issue raised during the January NCAB meeting which involved the Outstanding Investigator Grant and MERIT Award mechanisms. Steve Hazen prepared data on these instruments for the Subcommittee, which showed that 13.4 percent of the total FY 1991 RPG budget was directed to OIGs and MERIT Awards, as opposed to an NIH award rate of 5.9 percent. Dr. Bettinghaus noted that most other ICDs only use the MERIT Award. Dr. Bettinghaus stated that the Subcommittee discussed the matter for an extensive period of time, during which they heard a report from the Outstanding Investigator Grant Working Group. The Subcommittee decided unanimously to recommend to the Board that the OIG mechanism be discontinued.

Dr. Bettinghaus indicated that the motion made by the Subcommittee to eliminate the OIG, in addition to the guidelines for implementation of the recommendation, is included in the documents distributed to Board members. He stated that a vote to accept the report of the Subcommittee would be interpreted as an approval of the motion to discontinue the OIG. Dr. Bettinghaus mentioned that there was further discussion of Dr. Temin's question pertaining to an eventual increase in MERIT Awards. Upon consideration of the matter, the Subcommittee decided not to recommend an expansion of MERIT Awards until the effects of the elimination of the OIG mechanism were elucidated.

Dr. Bettinghaus reported that the second major issue considered by the Planning and Budget Subcommittee concerned the amount of research funding directed to individual researchers. Dr. Bettinghaus reminded members that this subject was also raised at the previous NCAB meeting, where it was decided that data should be compiled for the Subcommittee to examine. Based on those data, the group recommended that the NCI look closely at applications where a single investigator's total funding in direct costs would be over $500,000 and study total research support to determine whether research dollars were concentrated in a few labs. Dr. Bettinghaus emphasized that the results of the investigation could indicate that there is not an inappropriate concentration of funds, in which case the efforts would be discontinued.

Dr. Bettinghaus informed members that the fiscal year 1994 bypass budget, which will be considered at length at a future meeting, was briefly discussed. Dr. Bettinghaus concluded his report by announcing that the NIH strategic plan is under review. An all-extramural public task force meeting is scheduled to convene on June 23 to 25 to discuss the matter, with 200 participants from across the nation attending. He added that on July 15 and 16, Dr. Healy will

host a retreat, which ICD directors and some task force representatives will participate in, to further refine the draft plan.

Dr. Temin summarized that after June 1 no further Type 2 applications will be accepted as a result of the unanimous motion to eliminate the OIG mechanism. Mrs. Bynum commented that some staff have indicated that they believe that 1 additional year should be allowed for submission of competing continuation applications for Type 2 awards. She also clarified that the Outstanding Investigator Grant Working Group did not specifically recommend the discontinuation of the OIG, but that it had presented three alternatives to the Subcommittee, who chose to support this option. In response to a request for an explanation of the rationale for extending the deadline an additional year, Mr. Hazen indicated that the extension would allow time for those individuals who had received their initial award in 1987 to reapply. Mrs. Bynum pointed out that the announcement of the discontinuation of this mechanism would be made only 2 weeks before the phasing out was scheduled to occur. Some researchers may have decided to reapply next year and, therefore, would have essentially no time to prepare their application before the deadline. Other investigators were aware that this matter was being considered and waited to begin their applications until a final decision regarding the OIG was reached by the NCI. Dr. Durant suggested that the motion could state that Type 2 applications for current OIG grantees in their sixth year would be accepted. This wording was accepted by those involved in the discussion.

Dr. Broder stated that he interprets the intent of the advisory board as being to discontinue the OIG program and to ensure that those who are already supported by it are provided with a "back out" process. Dr. Broder maintained that if this recommendation is issued, the OIG program will be eliminated. He requested, however, that the Institute be given flexibility to deal with researchers currently in the program, so that individual cases can be considered.

Dr. Temin continued the discussion of the rationale of the discontinuation of the OIG mechanism. He explained that the group determined that the OIG and MERIT grants were supporting essentially the same criteria, and that it is unnecessary to have one instrument for outstanding investigators and a separate mechanism for outstanding projects. Those investigators who have outstanding projects will receive MERIT support. The combination of the two types of grants is consuming too large a proportion of the RPG.

Dr. Becker asked whether the Subcommittee has discussed a limit on MERIT Awards. Dr. Bettinghaus replied that the Subcommittee declined to set a level of MERIT funding until they observe the effects of the elimination of the OIG. Dr. Becker asked what would happen if some applications that would have originally been within the OIG mechanism were rereviewed and judged to be meritorious. The resultant funding level for MERIT Awards could potentially surge to 15 percent of the RPG, which was the percentage devoted to the combination of the two mechanisms. Mrs. Bynum replied that the peer review study section does not make decisions regarding merit, it only makes recommendations; therefore, it cannot simply convert an application from an OIG to a MERIT Award without approval of the Board.

Dr. Salmon observed that MERIT Awards and Outstanding Investigator Grants are different in that the OIG supports researchers who have a proven track record of accomplishments, whereas the MERIT Awards can fund a new researcher with an outstanding idea. Mrs. Bynum remarked that this distinction is preserved within the second bullet under general precepts, which requires a continued focus on past accomplishments. Dr. Temin added that a recommendation has been made that the OIG Working Group consider a proposal for a new award fostering innovative research, which requires that the investigator have a proven record of accomplishment or training as an eligibility requirement. The Subcommittee will discuss this subject at its next meeting. Mrs. Bynum noted that Dr. Healy has indicated that she

would like to institute an NIH-wide award for high-risk and innovative research. She suggested that this proposal should not be considered until it becomes clear whether NIH intends to create this grant mechanism.

Dr. Becker initiated a discussion regarding the recommendation that the NCI review its external support. Dr. Becker expressed concern that this examination of external funding may prompt staff review. Dr. Temin and Dr. Bettinghaus assured Dr. Becker that this is not the intent of the proposal. Dr. Becker asked whether a similar review process is conducted for intramural support of investigators. Dr. Adamson responded that since about 1980, the NCI has displayed its budgets for the laboratory as a whole, and over the last 5 or 6 years, project by project.

Dr. Calabresi reminded Board members that the vote to accept the report would be viewed as approval of all the recommendations of the Subcommittee, including the elimination of the OIG program. Dr. Salmon briefly returned to the discussion of the research support review by commenting that budget figures should be confirmed by principal investigators. The vote was held and the report was passed unanimously.

Dr. Broder remarked that he approved of the purpose of this recommendation if it is intended to reduce overlap and redundancy in grant mechanisms. He stressed that he does not support attempts to place a limit on the amount of funds that a particular investigator can receive. He added that the peer review system is an effective method for determining the worth of an investigation, it does not need to have limits placed on its authority. Dr. Broder recognized that others do not support his position and said that he respects their viewpoint.

Dr. Bettinghaus stated that in the lay press various articles have charged that research money is awarded to very few people. He commented that he does not believe that the facts will support this assertion, but that it must be investigated.

Women's Health and Cancer

Dr. Calabresi introduced Brenda Johnson, who replaced Mrs. Pollin as Chairperson of the Women's Health and Cancer Subcommittee. Ms. Johnson commented that although she will miss Mrs. Pollin, she is extremely pleased to be given the opportunity to chair the Subcommittee. Ms. Johnson added that as she is in her fifth year of recovery from colon cancer, she believes that she can provide a layperson's perspective to women's health and cancer.

Ms. Johnson announced that two presentations were delivered during the meeting the day before. Dr. Adamson presented an update on the PHS Task Force on Breast Implants, and Dr. Giusti reported on the health effects of DES exposure.

Ms. Johnson remarked that as many of the members of this Subcommittee are new members of the NCAB, a great deal of time was devoted to consideration of future directions.

Ms. Johnson stated that Dr. Adamson pointed out that Dr. Broder is extremely interested in breast cancer research. She added that the Subcommittee is very grateful for this attitude and the support of the Board, especially in light of the recent attention focused on the effects of breast implants.

Dr. Becker commented that with the recent onslaught of multimillion dollar lawsuits, if there is to be research to develop new implants, it might be necessary for the government to

consider underwriting the liability for implants for breast reconstruction, but not for augmentation. With five of the seven companies that manufacture breast implants leaving the business, no company will venture to explore new types of implants without a guarantee that they will not lose everything they have to lawsuits.

Rosemary Locke, a member of Y-ME who attended the meeting, suggested that a study of hormone replacement therapy in women who have had breast cancer be initiated. This recommendation is under consideration.

Dr. Bragg requested that the Subcommittee compile data on cancer incidence by site for males and females, the proportional NCI investment in research, and information regarding the representation of women among NCI-funded clinical trials. Ms. Johnson stated that they hope to have that information for the next meeting.

Dr. Calabresi called for a vote on the report. It was approved unanimously. He said that he wants the record to indicate that the Board thanks all past chairpersons of the subcommittees for their work and welcomes future chairpersons.

XIII. NEW BUSINESS

Dr. Salmon stated that he had two related motions to present. The first proposal involves evaluation of translational research P01 grants by the NCAB. This grant mechanism has received wide support and is considered to be important. Current policies on P01s, however, make it difficult for investigations that have translational research elements to compete successfully against basic research P01s without translational research elements. The NCI initiated the use of interactive R01s, which support basic research, to address issues of grant size, cost containment, and total number of grants that need to be awarded. One suggestion is to focus the P01 to include a subset of what it currently funds.

Dr. Salmon continued his explanation of the rationale for the proposal by explaining that there is a fixed priority score attached to each application. A cutoff point for funding is determined by the en bloc vote of the NCAB. Additional funding is achieved by exception by NCI staff. P01s present a unique challenge in that there is no standing study section or arrangement beyond the individual site visit team to rank the order of merit of the awards. Once P01s are voted on en bloc, there is no automatic, established mechanism that informs the NCAB of funding judgments that affect P01s they felt were worthy of support.

Dr. Salmon indicated that the proposal would require the NCI to review, during the closed session of each NCAB meeting, the funding status of translational research P01s that were approved in the en bloc action at the previous meeting. A condition of this proposal is that only those P01s that were in the excellent range would be discussed. Dr. Salmon noted that the NCI staff would be allowed to determine what the range was. This design would allow time for the NCAB to take remedial action if they felt it was necessary. A copy of the summary statement and the NCI statement regarding the funding status of each grant would be included in the packet for the meeting.

After the motion was seconded, Dr. Calabresi called for comments or questions on the motion before the vote was held.

Dr. Broder remarked that the NCI has no objection to providing feedback on the status of various P01s. He suggested that presenting this information at the immediate meeting after an action may be too short a period of time to make a realistic judgment of the funding status of a particular P01. He explained that there are peculiarities in the budget process, which can be

unique to a fiscal year. Some years there is no real budget and other years contain considerable budgetary challenges. Dr. Broder recommended that this feedback process be held at the end of each fiscal year or the beginning of the next fiscal year. This schedule would allow the Board the opportunity to advise the NCI if they had acted inappropriately regarding a P01 and provide ample time for remedial action. Dr. Broder urged Board members to give the program staff as much flexibility to deal with fiscal realities as possible in this matter.

Dr. Salmon agreed to the change suggested by Dr. Broder—that the review of funding status of various P01s be within the range of time in which action could still be taken, which is 1 year. Dr. Broder replied that there is no perfect system for this process, damage to some P01s may be irreversible, but if the Board advises the NCI that a grievous error was made, then it is possible for the Institute to act on this recommendation. Dr. Salmon indicated that the NCAB has a meeting near the close of the fiscal year, during which this update on funding status could occur. Dr. Salmon stated that this is an acceptable change to his motion.

After a period of discussion, the Board decided that P01s that are judged to be within the outstanding category, instead of those that are excellent, will be reviewed. Dr. Salmon pointed out that the numbers which define a P01 as outstanding or excellent can change, but the description will still be appropriate. The motion was passed as such.

Dr. Salmon presented his second motion. He proposed that the P01 grant mechanism be limited primarily to translational research. Dr. Salmon defined translational research as research that transfers findings from the laboratory to the clinic or field, which involves extensive interaction in both directions. The new focus of the P01 mechanism would be published within the NCI's guidelines for program projects.

Dr. Adamson remarked that he believes this topic requires further discussion. He asserted that there are many individual basic research grantees that have common goals and coordinate their efforts under the P01 mechanism. In addition, both epidemiologic research, which is not a directly translatable technology, and grantees that use the SEER database to elucidate environmental risk factors for areas that experience clusters of certain types of cancer, utilize this grant mechanism. These types of research endeavors would no longer be able to use the P01 mechanism. Dr. Salmon commented that he believes they will fit within the new definition of the P01. Dr. Adamson replied that they are not translational, because they can only be basic studies concerning etiology of cancers. Dr. Salmon asserted that they are field studies. Dr. Bettinghaus added that the P01 mechanism is often used by institutions conducting three or four similar basic behavioral research studies, which can utilize the same questionnaire to maximize efficiency. This grant mechanism coordinates their efforts in a highly cost-efficient manner. This research is not translational and would be much more costly if the efforts were funded by an R01 mechanism.

Dr. Adamson suggested that this motion be tabled so that it may be discussed at a subcommittee meeting, which would allow time to compile data on the number of P01s that currently fund technology transfer, basic research, and other types of research. Dr. Temin moved to refer this proposal to the Planning and Budget Subcommittee. The motion to table was voted on and approved. Dr. Broder indicated that discussion of the tabled motion will be an agenda item at the next NCAB meeting.

Mrs. Bynum suggested that the P01 Working Group, which included staff from all divisions of the Institute, should be reconvened to develop the recommendations for the Board on this matter. Dr. Broder said that he will ask the program staff to provide a summary of how other NIH Institutes deal with the challenges of the P01 mechanism. He indicated that there are a full range of methods for dealing with the P01 that are utilized, including not using this mechanism and placing a limit on the funding allocated to it. He requested that members of the

Planning and Budget Subcommittee gather opinions from numerous NCI staff members to be able to accurately portray their wishes during the meeting.

Dr. Calabresi announced the next item of new business. He moved to empanel a new subcommittee entitled "Subcommittee on Interaction with Voluntary Organizations." The purpose of this group would be to explore, improve, and advance interactions and collaborations with voluntary organizations that have a primary interest in promoting the advances in prevention, diagnosis, and therapy of cancer, as well as basic and clinical research in cancer. The Subcommittee would primarily address issues related to research directions, emphasis, support, and evaluation with a focus on prevention, detection, rehabilitation, and recovery. The motion was passed unanimously.

Dr. Calabresi asked Dr. Lawrence to chair this committee, since he was very active in its planning. He requested that anyone who would like to serve on this committee communicate this interest to either Mrs. Bynum or himself by the fall.

Dr. Calabresi reopened the discussion on the morning's mini-symposium as the next item of new business. He asked Ms. Mayer to summarize recommendations from the symposium.

Ms. Mayer indicated that she had six points to make regarding the morning's events. She stated that she agrees with Dr. Broder's suggestion that the morning's proceedings be developed into a monograph. Ms. Mayer also said that she will try to obtain the rehabilitation film for the September NCAB meeting. Her third point involved appointing a cancer representative to the advisory board of the National Center for Rehabilitation Research to ensure that oncology interests are suitably addressed as they appear in their agenda. Dr. Broder recommended that the NCAB negotiate to have one of its members serve in an *ex officio* manner on the advisory board. Dr. Calabresi suggested that Ms. Mayer should be the representative. She thanked Dr. Calabresi.

The next point Ms. Mayer discussed concerned the opportunity for the Subcommittee on Cancer Centers to reply to the question of whether the pain and palliative care elements are addressed as requirements for either clinical or comprehensive cancer centers. Dr. Salmon stated that the committee first needs the results of Dr. Kimes' survey. He added that developing a summary of the center directors' impressions of the survey, which could be gathered at their June meeting, would also be helpful.

Ms. Mayer remarked that methods for handling the issues that Dr. Mellette raised concerning the tamoxifen trial need to be explored. Dr. Salmon stated that further research is needed to determine whether it is appropriate to use topical estrogen to counteract local side effects of the use of tamoxifen and in what doses the hormone nullifies tamoxifen's effects. Ms. Mayer indicated that issues concerning quality of life also surrounded this trial. Dr. Greenwald commented that there is a process involving the National Surgical Adjuvant Breast and Bowel Program (NSABP) that allows substudies as part of a clinical trial. Dr. Salmon replied that he is not proposing that pharmacology studies of the use of estrogen in combination with tamoxifen be conducted within that trial. Dr. Broder suggested that Leslie Ford be asked to address this issue.

The final point that Ms. Mayer raised involved examining opportunities for training or educational activities. Mrs. Bynum indicated that an RFA was recently published to set up training programs. Ms. Mayer asked whether there are any broader initiatives. Mrs. Bynum said that she is not aware of any.

Ms. Mayer thanked the Board for their support of the symposium. She challenged everyone to continue to consider the issues raised during the session in terms of their own institutions.

Dr. Calabresi then opened the meeting for discussion and welcomed reflections on the issues raised during the symposium, as time for questions and comments had been limited in the morning.

Dr. Temin stated that if the statistics that 85 percent of cancer patients could have their pain relieved and that 80 percent do not receive palliative care are accurate, then 65 percent are suffering from unnecessary pain. He characterized this condition as "scandalous," but qualified his statement by adding that this is only true if the numbers are correct. Dr. Becker and Dr. Bettinghaus voiced their agreement with Dr. Temin. Dr. Broder replied that the NCI is in a difficult position regarding these data, as many possible actions to remedy the situation would require that they tell private physicians how to conduct their practices. He agreed that a knowledge base regarding the existence of palliative care must be developed. In addition, he suggested that asking the NCI's comprehensive cancer centers to assume a leadership role in the community in palliative care would be an effective means for inducing widespread incorporation of pain control elements in cancer patients' regimens. He added that the centers must not only set an example by including palliative care within their repertoire, but they should institute programs for increasing the awareness about and training in palliative care among health care practitioners in their communities. Dr. Broder stated that he will support the inclusion of a palliative care element in the requirements for eligibility as a comprehensive care center. He indicated that he hopes the Cancer Centers Subcommittee will address this topic at their next meeting and explore whether there is a consensus to expand the definition of "comprehensive" to include pain control.

Dr. Calabresi emphasized that the importance of pain control needs to be stressed not only within the oncology community, but among internists and family practitioners and other primary care providers who also deal with cancer patients. Dr. Calabresi commented that this issue must be raised with the deans of medical schools to induce the inclusion of pain control in the curricula of the students. He also noted that residency programs should incorporate training in palliative care.

Dr. Salmon remarked that his center has coordinated several conferences for the practicing community on pain management and that they have received widespread support. He also pointed out that 90 percent of the comprehensive centers do have pain teams as indicated by Dr. Levy's data, and, while few of them own hospices, it must be remembered that just as many do not own hospitals.

Dr. Chan prepared a statement for the Board to consider on this issue. It stated: "... it seems that the pain control research has not been receiving adequate attention as cancer chemotherapy, though pain is an inherent symptom with most cancer. As part of the effort to improve the quality of life and to relieve suffering of patients given therapy, I would suggest that NCI would look into the possibility of increasing support on pain control research, especially in the pharmacologic and pharmacokinetic areas and also to increase support of education to heighten the public awareness of this problem."

Dr. Calabresi asserted that much research already exists. What is needed is for that knowledge to be applied. He stated he believes the emphasis should be on pain control education. Dr. Salmon supported Dr. Calabresi's position. Dr. Calabresi indicated that if Dr. Chan's statement reflects this modification, then it will be acceptable to him.

Dr. Lawrence stated that he believes that there is more activity within the cancer centers regarding pain management than what it seemed from the symposium presentations. He suggested that perhaps more information on what is currently being done needs to be compiled, before recommendations on what should be done are made. After this information has been gathered, if necessary, the Subcommittee can add a statement about pain control in the outline of requirements for comprehensive centers.

Dr. Becker supported this recommendation. He reiterated the importance of gathering information on the current status of palliative care in the cancer centers.

Dr. Salmon recommended that professional societies be utilized to raise awareness of pain management. He added that the WHO published a short monograph on the three stages of cancer pain and its management. This monograph, however, was received by few physicians.

Dr. Calabresi said that if Catherine Foley and some of the morning's speakers organized a symposium, he would introduce it at the American College of Physicians' next meeting. As some 60,000 physicians belong to this society, such an announcement would reach a majority of primary care physicians. Ms. Mayer stated that all the recommendations merit implementation. Dr. Salmon observed that some medical house staffs may be nervous about the use of narcotic analgesics.

Dr. Broder commented that he believes that nurses and nurse-practitioners deliver a large percentage of the care discussed during the symposium. It is the nurses who are largely responsible for detecting uncontrolled pain and for making recommendations about specific therapeutic options for patients; therefore, these groups must be targeted by education and training efforts. Dr. Broder suggested that many of these recommendations could be informally implemented. He added that the R25 mechanism, which is a special kind of education grant, could be explored to see whether it could be used for curriculum grants to medical schools or other innovative options that address the need for pain education.

Dr. Calabresi remarked that he believes that Dr. Broder's idea is extremely meritorious. He added that Dr. Salmon's suggestion that the Cancer Centers Subcommittee discuss this issue and gather further information should also be followed.

Mrs. Bynum commented that Mr. Van Nevel's office informed her that the Office of Cancer Communication's meeting in March with pain management experts had surfaced similar information, which pinpointed dissemination as the problem. OCC is developing an action response to that group's recommendation.

Dr. Salmon maintained that in regards to Dr. Spiegel's presentation, not all forms of stress are bad. For certain cancers, being a Type A personality gives one a better chance for a positive outcome than does possessing a Type B personality.

Dr. Calabresi and Ms. Mayer agreed that no formal motion was necessary for any of the recommendations.

XIV. ADJOURNMENT—DR. PAUL CALABRESI

There being no further business, the 82nd National Cancer Advisory Board was adjourned at 3:22 p.m., May 6, 1992.

Sept. 17, 1992
Date

Paul Calabresi, M.D.
Dr. Paul Calabresi, Chairman