DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL CANCER INSTITUTE
121st NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
February 20-21, 2002

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

NATIONAL CANCER ADVISORY BOARD
BETHESDA, MARYLAND
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The National Cancer Advisory Board (NCAB) convened for its 121st regular meeting on Wednesday, February 20, 2002, in Conference Room 10 of Building 31, National Institutes of Health (NIH), Bethesda, MD. The meeting was open to the public on Wednesday, February 20, 2002, from 8:45 a.m. to 4:00 p.m. The meeting was closed to the public from 4:15 p.m. until adjournment at 5:00 p.m. The meeting was reopened to the public on Thursday, February 21, 2002, at 8:30 a.m. until adjournment at 12:00 noon. Dr. Phillip A. Sharp, Institute Professor, Center for Cancer Research, Massachusetts Institute of Technology, and Chair of the NCAB, presided during both the open and closed sessions on February 20. Dr. Ivor Royston, Managing Member, Forward Ventures, presided during the open session on February 21.

NCAB Members

Dr. Phillip A. Sharp (Chairperson)
Dr. Richard J. Boxer
Mr. Stephen C. Duffy
Dr. Ralph S. Freedman
Dr. James H. French
Dr. Elmer E. Huerta
Dr. Howard K. Koh
Dr. Frederick P. Li
Dr. Susan M. Love
Dr. Sandra Millon-Underwood
Dr. Arthur W. Nienhuis
Dr. Larry Norton
Dr. Amelie G. Ramirez
Dr. Ivor Royston
Ms. Ellen L. Stovall

President's Cancer Panel

Dr. Harold Freeman (Chairperson)
Ms. Frances Visco

Alternate Ex Officio NCAB Members

Dr. Steven K. Akiyama, NIEHS
Dr. T. G. Patel, VHA
Dr. Peter Kirchner, DOE
Ms. Yvonne Thompson Maddox, NICHD
Dr. Hugh W. McKinnon, EPA
Dr. John M. Powers, DOD, OASD, HA
Dr. Anita Schill, NIOSH

Members, Executive Committee, National Cancer Institute, NIH

Dr. Alan Rabson, Deputy Director, National Cancer Institute

Dr. Robert Wittes, Deputy Director for Extramural Science; Director, Division of Cancer Treatment and Diagnosis

Dr. Dinah Singer, Director, Division of Cancer Biology

Dr. Joseph Fraumeni, Director, Division of Cancer Epidemiology and Genetics

Dr. Peter Greenwald, Director, Division of Cancer Prevention

Dr. Marvin Kalt, Director, Division of Extramural Activities

Dr. Barbara Rimer, Director, Division of Cancer Control and Population Sciences

Dr. Carl Barrett, Director, Center for Cancer Research

Dr. Joseph Harford, Associate Director for Special Projects

Ms. Sandy Koeneman, Executive Secretary, NCI Executive Committee

Liaison Representatives

Dr. John Currie, American Association for Cancer Education, Inc.

Ms. Barbara Duffy, Association of American Cancer Institutes

Dr. Margaret Foti, American Association for Cancer Research

Dr. Edward P. Gelmann, American Society of Clinical Oncology, Inc.

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

Dr. Stanley Zinberg, The American College of Obstetricians and Gynecologists

Ms. Barbara LeStage, NCI, Director's Consumer Liaison Group

Mr. George Dahlman, The Leukemia and Lymphoma Society

Dr. Carl M. Mansfield, American Society of Therapeutic Radiology and Oncology

Ms. Alexine Jackson, International Cancer Council

Ms. Kristin Simonson, American Society of Therapeutic Radiology and Oncology

Ms. Mary Mitchell, The American College of Obstetricians and Gynecologists

Mr. William J. Haskins, Association of American Cancer Institutes

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DAY ONE—WEDNESDAY, FEBRUARY 20, 2002

I. INTRODUCTION, WELCOME, AND ACCEPTANCE OF MINUTES—DR. PHILLIP SHARP

Dr. Sharp welcomed Board members, representatives of liaison organizations, and members of the public, and he invited the public to submit to Dr. Marvin Kalt, Director, Division of Extramural Activities, and Executive Secretary, NCAB, in writing and within 10 days, comments regarding items discussed during the meeting. Dr. Sharp also reviewed the confidentiality and conflict-of-interest practices required of Board members in their deliberations.

A motion was requested and made to approve the minutes of the December 2001 NCAB Meeting. The motion was seconded and the minutes unanimously approved by the Board.

II. APPROVAL OF FUTURE MEETING DATES THROUGH 2004—DR. PHILLIP SHARP

Dr. Sharp called Board members' attention to future meeting dates listed in the Agenda, pointing out that the dates for 2004 were being listed for the first time. He asked Board members to review these dates and contact Dr. Kalt as soon as possible to discuss any potential conflicts.

III. INTRODUCTION OF DIRECTOR, NCI—DR. ALAN RABSON

Dr. Alan Rabson, Deputy Director, NCI, reviewed the *curriculum vitae* of the new National Cancer Institute (NCI) Director, Dr. Andrew von Eschenbach, noting that he was born in Philadelphia, attended St. Joseph's College, and received an M.D. degree from Georgetown University. In 1976, he went to work at The University of Texas M. D. Anderson Cancer Center in Houston, where he was Director of the Genitourinary Cancer Center and Director of the Prostate Cancer Research Program. Dr. Rabson noted that although he had met Dr. von Eschenbach only recently, he had known him for years as the best referral resource in Texas for patients with prostate and bladder cancer. Dr. Rabson added that Dr. von Eschenbach has a broad understanding of cancer research from molecular biology to cell biology, to clinical oncology. He cited several important papers coauthored by Dr. von Eschenbach on genitourinary cancer, with focuses ranging from molecular biology to early detection, to treatment. Dr. Rabson noted that the NCI had been captivated by Dr. von Eschenbach's warmth and friendliness, as well as by his decisiveness and ability to get to the bottom of a problem.

IV. NCI DIRECTOR'S REPORT—DR. ANDREW VON ESCHENBACH

Dr. von Eschenbach expressed his gratitude to the NCI staff, and in particular to the Division Directors, for the warmth with which they have welcomed him, and for the effort they have put into bringing him up to date on the many activities the Institute is involved in. He referred to a series of briefings in which key leaders of the NCI have been bringing him information on a one-on-one basis, focusing not only on describing their programs, but also on key issues affecting future plans.

Dr. von Eschenbach reported that he had been able to attend, as a guest, the recent Intramural Retreat, and he was impressed with both the scientific content of the Intramural Research Program and the personnel and their interactions. He said that he looked forward to being part of and paying a great deal of attention to this program, explaining that one of his conditions on accepting the Directorship was that he would be able to continue to practice medicine. Dr. von Eschenbach added that he will not

continue to perform surgery, but he will be involved in early detection, diagnosis, and consultation in prostate cancer, as well as in investigational protocol development.

Recognizing the importance of the foundation in basic science built by Dr. Klausner and those who came before him, Dr. von Eschenbach expressed his determination to build upon that foundation and nuture the "discovery engine," while complementing it with increased efforts to translate knowledge into detection, treatment, and prevention interventions that will directly benefit people with cancer. He cited recent events—such as the development of Gleevec as a therapeutic agent and Dr. Lance Liotta's work on detection of ovarian cancer through computer analysis of a constellation of proteins in a drop of blood—as examples of ways in which the Institute and the cancer community can capitalize on advances in basic science.

The second focus of his Directorship, Dr. von Eschenbach continued, will be to engage in and encourage effective collaboration with the larger community. Noting that his second condition on accepting the NCI Directorship was that he would be able to continue his participation in the National Dialogue on Cancer, Dr. von Eschenbach stressed his belief that an important part of his role as Director will be to expend a great deal of energy in networking, interacting, and cooperating with many other components of the national effort against cancer, not only within the Federal Government, but also at the state level and with nongovernmental organizations, such as survivor groups.

As an example of his immersion in the work of the NCI, Dr. von Eschenbach mentioned recent events related to mammography screening. The Executive Committee quickly came together, he said, to discuss reemerging controversies over mammography as portrayed in the press. A rapid telephone poll of various experts involved in this issue was quickly conducted, and a deliberative process among NCI staff and consultants soon produced a consensus that the information available was not sufficient to warrant a major change in the NCI's recommendations regarding mammography. Dr. von Eschenbach thanked Drs. Peter Greenwald and Barbara Rimer for their leadership on this issue, noting that they were scheduled the following day to brief the Secretary of the Department of Health and Human Services (HHS) prior to his press conference on mammography screening, during which he was expected to base the Departmental position on input from the NCI and the Preventive Services Task Force. Dr. von Eschenbach said he has also asked the Institute of Medicine (IOM) to continue its periodic updates of the body of knowledge on the early detection of breast cancer. The NCI, he added, will not reconvene its own panels on the issue, but will continue investigating new strategies for early detection.

Dr. von Eschenbach reported that soon upon his arrival, he began the process of making courtesy visits to Capitol Hill. At his first meeting, he said, Senator Feinstein presented him with her outline draft of legislation that would revise the National Cancer Act. She understood that he was not able, as NCI Director, to participate in drafting legislation, but she was reassured that the NCI would provide appropriate technical support. Dr. von Eschenbach noted that members of the NCAB are likely to be called upon in their other capacities to comment upon or contribute to the development of this very important legislation.

Dr. von Eschenbach said that another significant portion of his first few weeks as NCI Director has been focused on preparations for House and Senate budget hearings. He noted that further discussion of the President's 2003 budget was scheduled for later in the day.

In addition to the issues already mentioned, Dr. von Eschenbach stated that he has been looking at the organization of the NCI and beginning to consider the relationship between the Office of the Director

and the Executive Committee and other NCI components. He said that he expects to be paying particular attention to communications, noting that issues exist regarding the missions of the Office of Communications and the Press Office that affect the ability of the NCI to respond to the media on emerging issues like mammography. Dr. von Eschenbach has asked a small group of advisors to provide insight and guidance regarding opportunities and challenges in supporting the Office of Communications and making it a more effective organization.

Another issue that is critically important to translational research and that will be receiving a great deal of attention, Dr. von Eschenbach stated, is that of Centers, SPOREs, and training. This is an area that has undergone significant change in the recent past. Budgetary issues related to Centers, SPOREs, and training will be a very high priority in the near future.

Dr. von Eschenbach reviewed some organizational changes occurring at the Departmental level that will affect the NCI. HHS Secretary Thompson is looking at many functions that exist at the Institute level that may be consolidated at the Departmental level. Some relate to facilities, some to public relations, and others to personnel management. Thus, Dr. von Eschenbach stressed, changes currently under development at the macro level will affect the NCI, and he will be paying a great deal of attention to these changes.

Another issue facing the NCI is determining the best use of advisory committees and the most effective integration of the Director's office with the NCAB. Dr. von Eschenbach suggested that the NCAB serves, in a corporate model, as the "Board of Directors" for the NCI, and he stated his belief that he will need to be in ongoing communication with the Board, rather than simply on a periodic basis. His spirit of leadership, he said, is based on lessons learned in 25 years as a surgeon at M. D. Anderson. No individual, no matter how talented, can bring to the care of a patient everything required; the best treatment, Dr. von Eschenbach stressed, is multidisciplinary. Another lesson he learned is that one cannot solve a problem one does not fundamentally understand. These lessons, he said, represent the collaborative, multidisciplinary approach he wants to bring to his role as Director of the NCI.

Questions and Answers

Dr. Norton, Director, Medical Breast Oncology, Evelyn H. Lauder Breast Center, Memorial Sloan-Kettering Cancer Center, mentioned that Dr. Klausner had organized large, informal advisory bodies on disease-specific topics to review the state of the art and to guide the NCI. He asked whether Dr. von Eschenbach's comments about reviewing the role of advisory groups extended to those groups as well. Dr. von Eschenbach replied that he has not crystallized in his own mind yet what the most effective use of advisory groups might be. He said he looks forward to the opportunity to bring additional expertise within his office—including individuals on sabbatical—as well as working with ad hoc advisory groups convened on specific topics that might not have a permanent existence. In terms of large standing committees, such as the Board of Scientific Advisors (BSA), Board of Scientific Counselors (BSC), the NCAB, and the Program Review Groups (PRGs), Dr. von Eschenbach said that it is important for him to look at these groups to determine whether the NCI is getting the most effective use of their time, energy, and talents. He noted that he would address this issue at the next NCAB meeting and provide an update on advisory groups.

Dr. Sandra Millon-Underwood, Professor, University of Wisconsin–Milwaukee School of Nursing, expressed her hope that significant support will continue to be provided for the new Center to Reduce Cancer Health Disparities (CRCHD). She asked Dr. von Eschenbach to comment on his vision

related to supporting initiatives to reduce disparities. Dr. von Eschenbach stated that strengthening this program is one of his first and most important priorities. He said that he has assured Dr. Harold Freeman, Director, CRCHD, that the program has his total and complete support.

Dr. Amelie Ramirez, Deputy Director, Chronic Disease Prevention and Control Research Center, Baylor College of Medicine, asked for a comment on where the NCI is going in terms of training future researchers—including behavioral scientists and clinicians—especially in the area of developing more researchers who represent special populations. Dr. von Eschenbach agreed that it is shortsighted to develop research opportunities without also ensuring a workforce to implement them. He added that this is a comprehensive problem, encompassing not only basic scientists and physician researchers, but also nurses, social workers, and others involved in cancer research and care. Dr. von Eschenbach stressed the importance of addressing this issue in partnership with those outside the Institute, beginning at the high-school level to develop interest in cancer-related careers. This question, Dr. von Eschenbach continued, speaks to the broader issue of the limits of what can be done within the NCI. In preparing the Bypass Budget, he said, the Institute needs to pay special attention to what it must do because no one else can do it—compared with things that must be done in collaboration and cooperation with others and things for which other organizations must take the lead role.

Dr. Royston asked whether Dr. von Eschenbach intends to maintain the accelerated executive review mechanism to consider, at the request of investigators, applications that score above the payline. Dr. von Eschenbach replied that he has seen nothing so far that would indicate a need to change that procedure.

Dr. Howard Koh, Commissioner, Massachusetts Department of Public Health, asked for specific comments related to prevention as a research priority. Dr. von Eschenbach said that he sees two important complementary components of prevention. The first is the evolution of prevention based on our biologic understanding of cancer, and the second is the behavioral component. He added that the NCI's contribution to prevention will involve partnerships with other organizations, particularly the American Cancer Society (ACS), which is making an enormous investment in cancer control and prevention.

Dr. Elmer Huerta, Director, Cancer Risk Assessment and Screening Center, Washington Cancer Institute, Washington Hospital Center, noted that one of the most frustrating aspects of working to reduce the impact of cancer on underserved populations is the issue of access to care. Questions related to lack of insurance coverage and other problems that affect access to care are not seen as research questions and, therefore, are not part of the NCI's mission. Dr. Huerta asked Dr. von Eschenbach to comment on how he envisions NCI's role in collaborative efforts to encourage changes in policies that affect access to care in light of the fact that the Institute is a Federal agency and thus not allowed to lobby the Congress. Dr. von Eschenbach stated that this is a very complex question that does not have a simple answer. Although he agreed with the statement that the priority of the NCI is research, Dr. von Eschenbach acknowledged that there are other dimensions to the Institute's mission, and one way to achieve goals that go beyond research is through collaboration. He cited as one example of an area for potential collaboration, the possibility of working with the states in developing their cancer plans as part of the National Dialogue on Cancer. It is expected that all 50 states will have cancer plans in place by 2003. Many states are looking for a partnership with the NCI and its Cancer Centers to help them integrate scientific discovery with the delivery of cancer care. Dr. von Eschenbach expressed his hope that the Executive Committee of the NCI will be able to find a way for the Institute to make a contribution to this effort.

Dr. Sharp mentioned that he had recently chaired a session in which international leaders in the fields of basic science, translation science, clinical science, and prevention discussed the frontiers of cancer research. A consensus was reached that the greatest anticipated advances will be in the area of the interface between genomics and proteomics. He added that recent technological advances are changing the way people think about cancer, and that equally important impacts are likely to be made in engineering, chemistry, information science, and other disciplines.

Dr. Sharp asked Dr. von Eschenbach if he had any final remarks. Dr. von Eschenbach said that there are likely to be many opportunities to increase the understanding of cancer coming from areas not traditionally associated with the cancer research community. He stressed the importance of making effective use of the other Institutes on the NIH campus and said he looks forward to collaborative relationships with those Institutes.

V. UPDATE FROM THE OFFICE OF POLICY ANALYSIS AND RESPONSE— MS. DOROTHY FOELLMER

Ms. Dorothy A. Foellmer, Director, Office of Policy Analysis and Response, NCI, reported that Dr. von Eschenbach has already met with a number of Members of Congress: Senators Feinstein, Stevens, Hutchinson, Kennedy, Specter, and Harkin; and Representatives Myrick, Regula, Caps-Price, and Cunningham. Additional meetings are scheduled. These face-to-face courtesy visits give the NCI Director the opportunity to let Members of Congress know he is looking forward to working with them.

Hearings on the NCI Budget. The President's budget for FY 2003 calls for an appropriation of $23.3B for NIH and $4.2B for NCI. NCI representatives will participate in appropriations hearings scheduled in the House on March 14, and in the Senate on April 11. A joint hearing with the Senate Authorizing Appropriations Committees that have jurisdiction over NCI on mammography is scheduled for February 28. Ms. Foellmer went on to highlight specific diseases and research areas of interest to Members of Congress.

Best Pharmaceuticals for Children Act. This legislation, which was signed into law on January 4, provides for a 6-month extension of market exclusivity to drug companies that will test their products on children. If the holder of the exclusivity protection declines to pursue research on the drug, the NIH Foundation may award funds to allow the research to continue; the HHS Secretary is authorized to directly award contracts if an agent does not have market exclusivity or patent protection.

Other provisions include procedures to ensure proper pediatric labeling. The bill also calls for the establishment of the FDA Office of Pediatric Therapeutics and a new Pediatric Pharmacology Advisory Committee. NIH is directed to publish a list of drugs for which pediatric studies are needed and to establish mechanisms for reporting and tracking adverse events for pediatric drugs.

Several reports are mandated by the Act: The IOM will prepare a report on pediatric study practices; the General Accounting Office (GAO) is required to report on the enrollment of ethnic and racial minorities; and the FDA will report on patient access to new therapeutics and on the pediatric exclusivity program.

According to Ms. Foellmer, NCI's largest role would be participation on the Pediatric Subcommittee of FDA's Oncology Drugs Advisory Committee (ODAC). The legislation requires the participation of two NCI pediatric oncologists as well as representatives from NCI-supported

organizations. NCI is directed to expand, intensify, and coordinate the development of preclinical models for the evaluation of pediatric cancer therapies. Other responsibilities required by the Act include participating in the preparation of the list of drugs to be published by NIH and in awarding contracts for studies of drugs with no market exclusivity.

NIH is assembling a coordinating committee to plan the implementation of this Act, with the National Institute of Child Health and Human Development as the lead and the NCI, the National Institute of Mental Health, the NIH Foundation, and the FDA also participating.

Questions and Answers

Dr. Ralph S. Freedman, Professor, Department of Gynecologic Oncology, University of Texas M.D. Anderson Cancer Center, asked whether this Act might facilitate keeping in the pipeline drugs that companies might otherwise withdraw. Ms. Foellmer replied that the list of drugs for which pediatric studies are needed may address this issue. Ms. Ellen Stovall, President and CEO, National Coalition for Cancer Survivorship, noted that the Act initiates a process for greater cooperation and coordination between the NCI and the FDA.

VI. RECOGNITION OF THE NCAB CLASS OF 2002—DR. ANDREW VON ESCHENBACH

Dr. von Eschenbach noted that the departure of members of the NCAB represents not only a loss to the cancer community, but a personal loss of the opportunity to work with them; he added that these members are not retiring so much as being transitioned to a different role in which their contributions to the NCI will be less formal. Dr. von Eschenbach awarded plaques recognizing the contributions of the following NCAB members whose terms end in 2002: Dr. Richard Boxer; Dr. Howard Koh; Dr. Frederick Li; Dr. Sandra Millon-Underwood; Dr. Ivor Royston; Ms. Ellen Stovall; and Dr. Phillip Sharp. Each departing member made brief remarks of thanks to the NCI. Dr. von Eschenbach then took the opportunity to acknowledge the retirement of Dr. Robert Wittes, who is leaving the NCI to join the staff at Memorial Sloan-Kettering Cancer Center. Dr. Wittes said that the NCI is not an easy place to leave and characterized it as a unique and singular institution.

VII. UPDATE ON EXTRAMURAL STATISTICS AND POLICIES—DR. MARVIN KALT

Trends in Submission of R01 Applications to NCI. Dr. Kalt drew Board members' attention to the growth in the number of grant applications from about 1,500 to 1,700 per round for the last two rounds. If this volume continues, there will be an increase of 600 applications requiring 126 additional awards and an increase of $35M in competing dollars to maintain the payline at the 21st percentile. In addition to putting stress on the NCI budget, the large volume of applications will require an increased workload for NCI staff for receiving, referring, tracking, and managing the applications, and it will require three additional study sections from the Center for Scientific Review (CSR) to manage the applications as well.

Dr. Kalt observed that CSR is already midway though a process of restructuring and redefining boundaries for its study sections. The Oncologic Sciences Internal Review Group Cluster is the next group of study sections to be posted on NCI's Web site for comment. A description of the proposed restructuring plan will be included, and a comment period of 90 days will start March 1, 2002. Dr. Kalt encouraged Board members to inform their colleagues that the restructuring initiative is available for comment.

The Kurzon Case. Dr. Kalt explained that the Kurzon lawsuit began with an individual's filing of a Freedom of Information Act (FOIA) request for the names of unsuccessful applicants for grants from the National Institute of Mental Health (NIMH). NIH had always denied such requests on the grounds that it was an invasion of privacy. In July 2001, the U.S. District Court for New Hampshire ruled against the Government, but stipulated that the only information that can be released is the names of applicants—the applications themselves and summary statements are still protected by the Privacy Act. Dr. Kalt pointed out that the ruling might also apply to situations such as requests for names of people nominated for, but not appointed to the NCAB. He asked members to provide Dr. Wendy Baldwin, Deputy Director for Extramural Research, with their opinions on whether they felt the ruling might be a material invasion of personal privacy.

NIH Data-Sharing Policy. As of October 1, 2002, NIH will implement a new policy regarding the obligation of researchers to share data. Dr. Kalt suggested that this requirement has many positive aspects: it will ensure rapid dissemination of information to interested parties; it will help address Congressional concerns about the release of data; and it will avoid duplication of effort. Moreover, costs incurred by data sharing are allowable grant costs. Several different means of releasing data can be used, such as publication, the World Wide Web, and data-sharing archives. Peer review of data-sharing plans will be subject to community standards and "culturally specific" to disciplines—for example, a molecular biologist's plan will be judged by other molecular biologists. Investigators will be expected to include in their proposals a timeframe for data sharing.

The policy allows for exemptions in certain cases—for instance, small studies where it is impossible to shield the identities of participants or studies involving proprietary information such as applications from biotechnology companies. Other privacy issues may also allow exemptions.

Dr. Kalt stated that the data-sharing policy is mandatory, but its implementation will involve experimenting with different strategies to determine which ones work best for a particular type of scientific research. If a data-sharing plan is rated unacceptable by a study section, the priority score should not be affected. The matter can be resolved through negotiation with Program Directors.

Questions and Answers

Dr. Sharp asked whether the growth in the number of applications represented an increase in the number of applicants or an increase in the number of applications from existing grantees. Dr. Kalt responded that there was an increase in the number of applicants as well as of applications.

Dr. Sharp asked if the data-sharing policy applied to all data collected under the support of an NIH grant, regardless of whether these data were published or unpublished, or whether the investigator deemed the data reliable. Dr. Kalt replied that the investigator could select subsets of final—not raw—data to disclose if some data were proprietary or would violate privacy. He suggested that the data-sharing plans emphasize methods of collating and displaying the data, as well as selecting the subsets of information to be shared. Dr. Kalt referred the Board to the NIH Web site where grants policy guidance and the history of this requirement can be found.

Dr. Norton expressed concern about a potential negative effect of the new policy on collaboration between public and private sectors and on the peer-review process. Data shared via a Web site, for example, could circumvent the traditional scrutiny that ensures the quality of the information. Dr. Kalt

suggested that the Board invite a representative from the Office of Extramural Research to discuss this at the next meeting.

Dr. Freedman asked about data sharing in the case of large Phase III clinical trials where data must remain confidential until the trials are complete or until the Data Monitoring Committee decides to release the data. Dr. Kalt replied that data sharing will not change in such situations, and he emphasized that the way data-sharing plans will be evaluated is specific to the type of research.

Dr. Hugh McKinnon, Associate Director for Health, National Risk Management Laboratory, U.S. Environmental Protection Agency, asked Dr. Kalt to explain how this data-sharing policy is related to a Federal Government-wide requirement. Dr. Kalt referred to legislation that calls for any scientific study (and its underlying data) that a Federal agency cites in making a Federal rule or regulation to be subject to FOIA, along with any federally supported research.

Finally, Dr. Kalt introduced Claire Benfer, DEA's new Conference Management Officer, to the Board.

VIII. ANNUAL DELEGATION OF AUTHORITIES—DR. MARVIN KALT

Dr. Kalt reminded the Board that NCI functions under the provisions of the Public Health Service Act, which calls for an annual review of those provisions that represent a compact between the NCAB and the NCI. This agreement is renewed each year to permit NCI staff to carry out the Institute's mission. Delegation A allows the NCI Director to acquire the services of not more than 151 special experts or consultants. Delegation B allows the NCI Director to appoint one or more advisory committees composed of private citizens and officials of federal, state, and local governments to advise the Director. These committees include groups like the BSA and other working groups.

The "Statement of Understanding of Operating Principles in Extramural Awards" is a series of operational principles that permit NCI staff to review applications and make awards. It specifies exceptions that do not require NCAB approval—such as applications requesting direct costs of $50,000 or less—and it permits expedited concurrence for R01 and R02 grants that fall within the established payline and raise no concerns that would represent an administrative bar to award, such as compliance with rules concerning the treatment of human subjects. Electronically expedited concurrence with these applications is carried out by a subcommittee of the Board that includes the Chair, the Head of the Subcommittee on Special Actions, and two other members. A final operating principle deals with delegation of administrative adjustments regarding terms and conditions of award that NCI can negotiate with potential grantees. These include cost adjustments, administrative supplements, restorations of time and amount, changes within the existing scope of research, and F and A cost adjustments.

Motion: A motion was made to approve the Delegations of Authority as presented by Dr. Kalt. The motion was seconded and unanimously approved.

IX. NEW BUSINESS I—DR. PHILLIP SHARP

There was no new business conducted at this time.

X. UPDATE FROM THE AMERICAN ASSOCIATION FOR CANCER RESEARCH— DR. WAUN KI HONG

Dr. Waun Ki Hong, Professor and Chairman of the Department of Thoracic Head and Neck Medical Oncology at the University of Texas M.D. Anderson Cancer Center, and President of the American Association for Cancer Research (AACR), provided an update from the AACR.

Dr. Hong stated that the mission of the AACR is to prevent and cure cancer through research, education, communication, and collaboration. He estimated that the cost of cancer in the United States was $157B in 2001, and that more than a million new cancer cases will be diagnosed in 2002. In the United States, the lifetime risk for developing cancer is over 40 percent for men and 30 percent for women. Given these numbers, Dr. Hong affirmed AACR's commitment to research. He stated that the goal of the AACR is to foster research in cancer and biomedical science; educate the public about cancer and train new investigators in the field of cancer research; promote and communicate new research findings; advocate for cancer research funding; and establish partnerships to advance cancer research.

Dr. Hong expressed excitement about the potential for genomics to revolutionize cancer treatment. He then described a new facet of cancer research: molecular target therapy. Molecular targets are small molecules that inhibit key pathways in tumor growth; they have shown promising results in early clinical trials. In October 2001, the AACR held a conference, entitled *Molecular Targets Cancer Therapeutics Discovery and Biological Clinical Application,* to further explore this new group of therapeutic agents.

Dr. Hong described the AACR's interest in cancer prevention research. He emphasized the need to approach cancer as a chronic disease and intervene during early stages rather than wait to treat it in its later stages. He cited intraepithelial neoplasia as a model for early intervention with a molecularly targeted agent. The AACR established the Intraepithelial Neoplasia Task Force, which included more than 25 experts involved in addressing important issues related to the treatment and prevention of this cancer. Recommendations from this task force were published in the February 2002 issue of *Clinical Cancer Research*. To underscore AACR's commitment to cancer prevention, Dr. Hong announced plans for an October 2002 conference that will focus on cancer prevention. Finally, Dr. Hong reviewed several initiatives that have been instituted to ensure scientific excellence and balance within the AACR. These include a scientific retreat in 2002 and the establishment of standing committees, task forces, think tanks, and scientific working groups in several different research areas.

Dr. Hong discussed the education component of the AACR and emphasized its role in both the professional development of women and minorities and the increased dialogue between cancer researchers and the public. Examples of these initiatives are scientific awards and lectureships, including the creation of two $200,000 Landon prizes for basic and translational research; research professorships; scholar awards for investigators in training; career development awards; and research fellowships. Dr. Hong then reviewed the AACR public education program, which comprises several interesting initiatives. One of those mentioned by Dr. Hong is the Scientist-Survivor Program, in which a scientist interacts directly with cancer advocates and survivors. He explained how this program has been successful in building consensus among all members of the cancer research community. Other programs include the AACR Public Forum, Ask-the-Experts Sessions, and the Science Policy and Legislative Affairs Committee.

Next, Dr. Hong addressed the role of communication in the AACR. The AACR offers five scientific journals, including the newest one, *Molecular Cancer Therapeutics*. Dr. Hong mentioned the upcoming AACR conference in April 2002 in San Francisco. He expects more than 14,000 attendees from all over the world. In addition to the annual meeting, the AACR holds special conferences regarding cutting-edge science.

Dr. Hong summarized AACR's participation in a range of collaborations. He believes that the AACR should serve as a catalyst for discovery and innovation in cancer research by promoting multidisciplinary efforts and communication among all members of the cancer research community, the government, industry, academia, the philanthropic community, the general public, cancer survivors, and advocates. Dr. Hong illustrated this commitment to collaboration with a compilation of all the organizations around the world that are partners with the AACR. He described how the NCI and AACR have a unique collaborative relationship, as evidenced by the Joint Molecular Targets meeting and the scholarships these two organizations have arranged together. Workshops in conjunction with the NCI and the American Society for Clinical Oncology (ASCO) have also been held.

Dr. Hong concluded his presentation by stating that the ultimate goal of the AACR is to eliminate cancer as a significant health threat. To accomplish this goal, Dr. Hong proposed several approaches: (1) eliminating tobacco use; (2) encouraging modification of unhealthy behaviors; (3) developing molecular therapeutics; (4) increasing screening and early detection; (5) developing predictive risk models; (6) focusing on targeted chemoprevention; and (7) understanding gene-gene and gene-environment interactions.

Dr. Sharp thanked Dr. Hong and Margaret Foti, the CEO of AACR, for the contributions they have both made to the AACR.

Questions and Answers

Dr. Norton as President of ASCO, thanked Dr. Hong for his leadership and for developing collaborations between AACR and ASCO and said he looked forward to future partnerships with the AACR.

Dr. Sharp commented on AACR's commitment to international collaborations in cancer research and suggested that NCI and the entire NIH should consider investing more in international grant support for cancer and other health-related issues.

Dr. von Eschenbach appreciated Dr. Hong's reference to President Bush's commitment to cancer research. He clarified that the cancer research budget the President will present to Congress specifies $5.5B, of which $4.7B would be for NCI. He also stated that it was important for the NCI to collaborate with other organizations that have a broader cancer research agenda.

Dr. Huerta asked about Dr. Hong's vision for chemoprevention and whether it included the establishment of risk-assessment clinics along with traditional cancer treatment clinics. Dr. Hong thought that the paradigm was shifting towards screening, early detection, and prevention. He stated that physician education and research were the keys to understanding the potential of chemoprevention, especially in a disease like intraepithelial neoplasia, in which the disease takes 10 to 20 years to develop.

XI. GYNECOLOGIC CANCERS PROGRESS REVIEW GROUP REPORT— DRS. TED TRIMBLE, WILLIAM HOSKINS, AND NICOLE URBAN

Dr. Ted Trimble, Executive Director of the Gynecologic Cancers PRG and Head of the Surgery Section at the NCI Clinical Investigations Branch, introduced the Co-Chairs of the Group: Dr. Nicole Urban, Full Member, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center; and Dr. William Hoskins, Director, Anderson Cancer Institute, Memorial Health University Medical Center. Dr. Urban described the burden that gynecologic cancers represent, with more than 80,000 cancer cases and 26,000 cancer deaths in the United States every year.

Cervical cancer is well controlled in developed countries because its precursor lesion is known; an effective screening test—the Pap test—is widely available; and screening is widely disseminated. Dr. Urban noted that cervical cancer offers an extraordinary opportunity to develop vaccines because of the role the human papillomavirus (HPV) plays in the etiology and pathogenesis of this disease.

Of the two types of endometrial cancer, the hormone-dependent type is well controlled. The hormone-independent type is aggressive and not well understood; it is similar to ovarian cancer.

Ovarian cancer is sometimes known as the "silent killer." The disease tends to be advanced at the time of diagnosis because it is usually very aggressive and has no symptoms. Serum markers represent one possibility for early detection, and the recent work in proteomics that distinguishes cancerous from noncancerous blood serum among women being tested for ovarian cancer offers great promise.

PRG Process. Dr. Urban described how the format of the Gynecologic Cancers PRG differed in some respects from other PRGs. Because the PRG was reviewing three types of tumors, members wanted to make sure that each tumor type was appropriately addressed. Each PRG member had the opportunity to participate in three breakout sessions: two scientific sessions and one devoted to a specific tumor type. The breakout groups were asked to identify the gaps in knowledge and barriers to progress, and to recommend an action plan and the resources needed to carry it out. According to Dr. Urban, some clear priorities emerged—one mentioned so frequently that it was categorized as the "essential priority." Three "high-impact" priorities and six scientific priorities were also identified.

Virtual Shared Specimen Resource. The "essential priority" was to develop and make available to the gynecologic cancer research community a Virtual Shared Specimen Resource (VSSR). Dr. Urban maintained that translational research may be impossible without access to high-quality fresh-frozen tissue and fluids obtained at critical points in the disease process, associated with high-quality clinical and follow-up data, and processed and stored in evolving ways. "Virtual" means that the information describing the specimens is managed by a single coordinating center but that the specimens themselves reside at the institutions where they were collected. Features of the VSSR include specific scientific goals, a coordinating center, and an advisory committee to ensure efficiency, equity, quality, and inventory control in specimen collection, management, and distribution. Dr. Urban asserted that the time is right for pursuing this initiative, and it can build on the efforts of other NCI initiatives, such as the Human Genome Project, SPORE, the Early Detection Research Network (EDRN), the Tissue Procurement Network, and the Common Data Elements team. Dr. Urban called on NCI to provide resources for developing a VSSR, establish an advisory committee to oversee the progress of the resource, invite multiple institutions to collaborate in the development and use of the VSSR, and set up a commission to facilitate resolution of privacy issues.

High-Impact Scientific Priorities. Dr. Urban stated that identification of markers of risk, early detection, and targets for treatment was the first high-impact priority. The VSSR is designed to support this effort. In addition, emerging technologies should be developed to identify precursor lesions, markers of risk, markers for early detection, molecular disease classifications, prognostic indicators, and targets for prevention and treatment. The new technologies involving proteomics in detecting ovarian cancer should be further exploited.

The PRG's second high-impact priority is the development of effective HPV vaccines for cervical cancer. Although in the developed world cervical cancer is an infrequent cause of death, it is the second most common cause of cancer death in women worldwide. Moreover, the cost of evaluating and treating abnormal Pap smears in the United States exceeds $6B annually. To date, neither an effective prophylactic nor a therapeutic vaccine has been developed, most likely because a framework for comprehensive clinical evaluation of vaccines is lacking; clinical trials are hampered by fragmentation of efforts; and few partnerships exist among scientists, industry, and government. The role of mucosal and humoral immunity, the impact of endogenous (hormones) and exogenous (other pathogens and smoking) factors on the risk of developing cervical neoplasia, more efficacious vaccine strategies, and immunologic biomarkers that might be used to clinically evaluate vaccines are the key issues to be addressed, according to Dr. Hoskins. Recommended actions include encouraging studies to improve basic understanding of mucosal immunity, developing understanding of the initiation of effective mucosal immunity, and determining why some individuals develop chronic HPV infection and others do not. Dr. Hoskins listed resources needed to advance the development of HPV vaccines: (1) core laboratories for viral and immunologic evaluation of specimens; (2) worldwide network for clinical trials; (3) expanded cadre of individuals with interest and expertise in HPV immunology; (4) partnerships among scientists, industry, and government; and (5) integration of research efforts worldwide.

The third high-impact priority involved the conduct of research with the aims of understanding and improving quality of life and reducing or eliminating treatment disparities among patients with gynecologic cancer. Because cure rates for gynecologic cancers are good compared with many cancers, there are a large number of gynecologic cancer survivors. The treatment for these cancers can result in significant changes for women in hormonal function, sexual function, sense of self-worth, and social adjustment; however, research into these quality-of-life issues has been very limited. Recommended actions for reducing health disparities included performing large observational cohort studies of patients with gynecologic cancer to: investigate the impact of targeted interventions; identify the influences of modifiable risk factors; discover options for eliminating disparities in the delivery of high-quality health care; and design interventions to correct disparities. According to Dr. Hoskins, the PRG felt that resources required to make an impact on quality of life and health disparities could be found through the Cancer Care Outcomes Research and Surveillance Consortiums (CanCORS), Clinical Trials Cooperative Groups, and Cancer Centers, as well as individual investigators. Collaborations among investigators who have expertise not only in gynecologic oncology, but also in epidemiology, health services research, health communications, and psychology should be promoted.

Scientific Opportunities. The PRG identified six scientific opportunities: (1) characterization of hormonal, immunologic, and epithelial-stromal interactions that result in the development of gynecologic cancers; (2) development of imaging techniques to evaluate tumor biology, molecular signatures, and therapeutic response; (3) development of relevant preclinical models for gynecologic cancers; (4) identification of strategies to overcome resistance to chemotherapy and radiotherapy; (5) development of individualized and optimized radiation therapy techniques in conjunction with other treatment modalities; and (6) encouragement of increased participation in clinical trials in gynecologic cancers.

Dr. Hoskins concluded the presentation by stating that the PRG believes that implementing these priorities is essential for significant contributions to the control of gynecologic cancer over the next 5 years. He thanked all who had participated in the PRG process.

Questions and Answers

Dr. Frederick Li, Chief, Division of Cancer Epidemiology and Control, Dana-Farber Cancer Institute, pointed out that the interface between the patient and the health care system is frequently conducted through neighborhood health centers and city hospitals, and abnormal Pap smears do not always receive appropriate follow-up. He reminded the Board that Dr. Freeman, as Chair of the President's Cancer Panel, has led efforts to develop a Patient Navigator model, and he asked the presenters how this model fits in with their plan. Dr. Hoskins replied that funding for communities that suffer health disparities is essential to achieving significant success in reducing the disparities.

Dr. Freedman observed that cervical cancer is one tumor that offers a definite target. The impetus for developing vaccines is likely to come from industry, and he wondered whether NCI could facilitate interactions among gynecology groups, the FDA, and private industry in bringing these vaccines to clinical trials. Dr. Trimble described some work on vaccines being carried out by NCI's Intramural Research Program, including a vaccine that will enter a Phase III clinical trial in Costa Rica later in 2002. A number of investigators have received funding from the Rapid Access to Intervention Development (RAID) program of NCI's Developmental Therapeutics Program (DTP) for HPV vaccines. Dr. Trimble noted that NCI is hoping to intensify its efforts to reach out to industry and individual scientists because laboratory studies suggest that various vaccine combinations of naked DNA and other structures seem to be more potent than individual vaccines.

XII. LUNG CANCER PROGRESS REVIEW GROUP REPORT—DRS. MARGARET SPITZ AND JACK RUCKDESCHEL

Dr. Margaret Spitz, Professor and Chair, Department of Epidemiology, University of Texas, M.D. Anderson Cancer Center, enumerated the public health problems that lung cancer represents. Statistics from the ACS estimate that there will be 169,000 new cases of lung cancer and 154,900 lung cancer deaths in 2002. Eighty-five percent of patients diagnosed with the disease will die of it. More patients die from lung cancer than from the next five most common cancers combined. The impact of therapy has been at best modest, and scientists do not yet understand the mechanism of the resistance to therapy.

The scientific problems facing investigators include a lack of knowledge of the cellular and molecular events underlying lung carcinogenesis; the need to explore the complex interplay between smoking and genetic and molecular factors, as well as other biologic responses; and the need for an answer to the question of why so many *former* smokers develop cancer. Moreover, there is no effective chemopreventive agent against lung carcinogenesis.

Lung cancer also represents a social problem. A "blame the victim" mentality has pervaded society and deprived patients with lung cancer of the social support routinely given to patients with other malignancies. In addition, "therapeutic nihilism" is rampant in clinical settings. The health care system is not set up to promote multidisciplinary care of patients with lung cancer. Relative to its public health impact, lung cancer research is underfunded.

Organization of the PRG. Dr. Spitz explained that a total of 110 participants attended the PRG roundtable meeting in April 2001. Participants were divided into three working group clusters, each cluster representing a range of scientific specialties: (1) biology, etiology, and chemoprevention; (2) prognosis and staging, quality of care, and therapy; and (3) detection and diagnosis, and tobacco control. This structure was designed to promote cross-fertilization of ideas and to facilitate in-depth discussions.

Recommendations. Dr. Jack Ruckdeschel, Center Director, H. Lee Moffitt Cancer Center and Research Institute, University of South Florida, listed NCI infrastructure initiatives currently underway that should be continued, enhanced, and expanded to lung cancer, where necessary. These initiatives include: bioinformatics, animal models, molecular profiling, special populations and population disparities, tissue and data repositories, drug development, clinical trials infrastructure, and the Centers of Excellence, particularly in communications.

Overarching Recommendation. Dr. Ruckdeschel observed that there is nearly complete dispersion of lung cancer clinicians and translational scientists across multiple clinical cooperative groups and scientific endeavors. The main reason for this is that there are fewer than 300 general thoracic surgeons working part-time in the area of lung cancer. There are even fewer pulmonologists who specialize in lung cancer, and surgeons and pulmonologists represent the entry point into the health care system for patients with lung cancer. Dr. Ruckdeschel indicated that for these reasons, the PRG's first recommendation is for the establishment of cross-disciplinary lung cancer consortia. The consortia could incorporate an infrastructure for treatment, prevention, and screening and could be linked to SPORE institutions. The consortia would facilitate cross-disciplinary studies along a biology/behavior/exposure continuum, as well as facilitate population-based studies.

Early Detection. One initiative led by NCI is a large-scale assessment of spiral computed tomography (SCT) as a means of early detection. SCT has the potential to make an enormous impact on cancer mortality—greater than identification of molecular targets, for example. Therefore, the PRG recommended that NCI continue to take a strong leadership role. In addition, since fully powered randomized clinical trials are expensive to run, collaboration with international groups should be sought.

Tobacco Control. Tobacco control transcends the clinical and scientific boundaries of lung cancer. Thus, one recommendation was to establish and empower a Tobacco PRG or a Tobacco Research Implementation Group. There was a consensus that the greatest challenge to tobacco control is the need to understand the biology and treatment of nicotine addiction. More research is needed on biobehavioral aspects of nicotine addiction and novel pharmacologic treatments. Dr. Ruckdeschel also explained that "harm-reduction" approaches, part of the PRG's tobacco control recommendations, referred to the new round of so-called safer cigarettes being marketed by the tobacco companies. Research on the previous generation of "reduced harm" cigarettes showed that reduced levels of tar and nicotine did not result in fewer cases of cancer, heart disease, or pulmonary disease. The PRG noted the importance of immediately beginning to study the effects of harm-reduction approaches.

Biology. The Biology Group agreed that there is a need to better understand the relationship between injury, inflammation, and infection and the influence of these factors on the genesis of lung cancer. A concerted multidisciplinary approach is needed to elucidate steps that drive cell renewal and overall cell fate.

Etiology. The Etiology Group noted that there is no validated risk-assessment model incorporating biomarkers of susceptibility for pulmonary carcinogenesis. A recommendation to meet this need is to explore etiology and low- and high-penetrance susceptibility genes in subgroups, such as former smokers and people who never smoked; people with obstructive airway disease and a strong tendency to develop lung cancer; and various histologic subtypes.

Chemoprevention. The Chemoprevention Group concluded that there is no successful proof-of-principle trial of an effective agent and no clear definition of the appropriate high-risk target population, and there are no validated surrogate endpoints. The recommendation was to conduct smaller, targeted biomarker-integrated mechanistic studies with selective agents, looking at combinations, novel delivery, and diagnostic imaging approaches to this problem.

Dr. Ruckdeschel explained that an issue discussed by nearly all subgroups was inadequate interdisciplinary training. There is a serious imbalance between training programs in cardiac surgery and general thoracic surgery, he said. Training programs for pulmonologists are also imbalanced, with their emphasis on critical care. There is a need to expand early and mid-career training programs in lung cancer care and research. Regarding outcomes, there is a need to further develop and implement models of care delivery.

Dr. Ruckdeschel concluded his presentation by stating that the United States faces further decades of the lung cancer epidemic—even if smoking were completely eradicated—because the number of former smokers is about equal to the number of current smokers—about 45 million each. Progress in mitigating the devastating effects of lung cancer will not take place without a concerted multidisciplinary approach and elucidation of the biology of the disease to advance diagnostic, preventive, and therapeutic approaches.

Questions and Answers

Dr. Koh pointed out that states like Massachusetts have cigarette consumption rates that are declining faster than the national average. This has been accomplished through aggressive antitobacco programs, including a media campaign that has been evaluated longitudinally. He suggested that such prevention and control efforts be part of the PRG's recommendations. He added that he was interested in the suggestion that NCI work more closely with the National Institute on Drug Abuse (NIDA) since NIDA defines substance abuse as including alcohol, tobacco, and other drugs. Dr. Koh also noted that since the traumatic events of September 11, cigarette use in Massachusetts has increased, reversing a trend of many years. Dr. Spitz agreed that an investigation into the states' broad-ranging policies was warranted to determine the most effective programs in reducing rates of smoking. She also observed that nicotine addiction has close genetic similarities to other high-risk behaviors such as alcohol abuse, other substance abuse, and even overeating.

Dr. Frederick Li wanted to know whether the PRG had decided that training more surgeons is more cost-effective than training more educators to prevent smoking in children and youth and encourage smokers to quit. Dr. Ruckdeschel responded that the need for surgeons is great because of the large numbers of both current and former smokers. To spend another 20 years without being able to detect lung cancer at an early stage, treat the disease early, and stage it properly is unacceptable, according to the PRG.

Dr. Susan Love, Adjunct Professor, Department of Surgery, University of California School of Medicine, suggested that lower reimbursement rates for pulmonary surgery might be the reason for many surgeons to choose cardiac surgery. Dr. Ruckdeschel added that the excitement of operating on a human heart might also tend to attract more surgeons.

Dr. Huerta informed the Board that he also served on the Board of the American Legacy Foundation, which was created with funds from the settlement with tobacco companies. He reported that the Lorillard Tobacco Company had sued the Foundation for violating the provisions of the Master Settlement Agreement between the states and the tobacco companies concerning "vilifying" companies or individuals. Dr. Huerta noted that the PRG report appeared to focus on biology, but that, perhaps, discussions of nicotine addiction should also include a statement regarding the behavior of the tobacco industry. Dr. Spitz agreed and directed Dr. Huerta's attention to a statement regarding the financial disadvantage antismoking groups have compared to the tobacco companies and the millions of dollars they spend on advertising.

CLOSED SESSION

REVIEW OF APPEALS, INTRAMURAL SITE VISITS, TENURE APPOINTMENTS, PERSONNEL, AND PROPRIETARY ISSUES

This portion of the meeting was closed to the public in accordance with the provisions set forth in Sections 552b(c)(4) and 552b(c)(6), Title 5 U.S. Code and 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. appendix 2).

Dr. Sharp reminded Board members that the material furnished for review and discussion during the closed portion of the meeting is considered privileged information.

He stated that advisors and consultants serving as members of chartered advisory committees may not participate in situations wherein any violation of conflict of interest laws and regulations might occur. He indicated that responsible NCI staff would ensure that each Board member would not perform duties or render advice that might have a direct and predictable effect on the interest of any organization or institution in which he/she had a financial interest. In particular, Board members were informed that they could not participate in the evaluation of grant applications or projects for Federal funding, in which, to the member's knowledge, any of the following had a financial interest: the committee member; his/her spouse; an individual with whom the member has a close personal relationship; a dependent child, parent, partner (including close professional associates) or with an organization with whom the member or other parties named is seeking employment or serving as an officer, director, trustee, general partner, agent, attorney, consultant or contractor.

Members were instructed to exit the room if they deemed their participation in the deliberation of any matter before the Board to be a real conflict or would represent the appearance of a conflict. Members were asked to sign a conflict of interest/confidentiality certification to this effect.

During the closed session of the meeting, a total of 1,203 grant applications were reviewed requesting support of $369,921,115. Funding for those 1,203 applications was recommended at a level of $302,897,324.

The closed session adjourned at 5:00 p.m.

DAY TWO—THURSDAY, FEBRUARY 21, 2002

XIII. EXTRAMURAL CLINICAL AND PEDIATRIC LOAN REPAYMENT PROGRAMS—DR. CAROLYN STRETE AND MR. MARC HOROWITZ

Dr. Carolyn Strete, Chief of the Cancer Training Branch, Office of the Deputy Director for Extramural Sciences, NCI, and Mr. Marc Horowitz, Director, Office of Loan Repayment and Scholarship, NIH, presented two new initiatives to attract and retain clinical and pediatric investigators. The terms of these programs include the repayment of up to $35,000 of the principal and interest of eligible educational loans for each year of research service; the payment of an additional 39 percent of the loan repayment amount towards the Federal tax liability; and a contractual agreement whereby awardees agree to engage in clinical or pediatric research for a minimum of 2 years.

Mr. Horowitz described the history of Loan Repayment Programs (LRPs) at the NIH. The first LRP was established in FY1989 and was designed to attract investigators working in AIDS-related research. Several other LRPs were implemented in the 1990s, including a clinical research LRP for individuals from disadvantaged backgrounds, a general research LRP, and a contraception and infertility research LRP. In FY2001, two additional extramural LRPs were authorized by Congress; these programs included 28 awards for a health disparities research LRP, and 18 awards for an extramural clinical research LRP for individuals from disadvantaged backgrounds. Mr. Horowitz then introduced the two LRPs for FY2002: an LRP regarding clinical researchers, and a pediatric research LRP.

Mr. Horowitz explained the eligibility requirements for the clinical and pediatric LRPs. First, the individuals must be engaged in qualifying research as NIH employees or grantees. They must be United States citizens, permanent residents, or nationals, and hold a doctorate-level degree (i.e., Ph.D., M.D., M.D./Ph.D., D.O., D.D.S., D.V.M., D.M.D., D.P.M., D.C., N.D., Pharm.D., or equivalent). Finally, the individuals must have educational debt equal to or exceeding 20 percent of their annual income. In addition, the research conducted by these individuals must be consistent with Federal regulations governing research supported by Federal funds. Mr. Horowitz reiterated that the individuals must commit to 2 years of research service and may apply to only one LRP. He then listed all the eligible funding mechanisms for prospective applicants, such as the Postdoctoral National Research Service Award (T32 and F32); individual or institutional research career development awards (K01, K07, K08, K12, K22, K23, and K25); first-time receipt of NIH grant support as a Principal Investigator (R01, R03, R21, and U01); or first-time Director of subprojects on a multicomponent grant (P and U series). He noted that the eligible grants list would be expanded by FY2003.

Mr. Horowitz reviewed the LRP expenditures in FY2001 and the estimated budget for FY2002, for which approximately $35M has been proposed. This amount includes $28M for the clinical research and pediatric LRPs. Mr. Horowitz described the application process for the LRPs, noting that applications will be filed electronically and are due on February 29, 2002. He indicated that, based on the activity noted on the LRP application Web site, there was a high level of interest for these LRPs.

Dr. Strete then presented information regarding the application review process. She explained that the goal of this process is to assess the long-term scientific potential of each candidate, not the research proposed by the individual. A Special Emphasis Panel (SEP) will review the applications, followed by a second-level review by the NCI Executive Committee. Applications will be scored using the usual NIH scoring system, and a summary of the review will be provided to each applicant. Dr. Strete then outlined the review criteria and noted that they were not weighted. The applications comprise a personal statement,

including a discussion of career goals, research, and academic plans; a description of the current research being conducted in the laboratory; a description of the proposed research project, including the role of the applicant; three recommendation letters addressing the applicant's potential for success in research; and a research training plan, if applicable.

Dr. Strete presented the hierarchy for selecting the awardees. She recognized that the priority scores were important, but she named other factors that also merit consideration, such as the proximity of an applicant to career independence. The next line of consideration, Dr. Strete maintained, would be postdoctoral fellows and career awardees focusing on patient-oriented research, cancer prevention, cancer control, population science, or basic science that is directly relevant to cancer prevention. Dr. Strete stated that the next levels of consideration would be postdoctoral fellows in the T32 training program and the degree to which the applicants' career goals demonstrate a commitment to study human cancer. Dr. Strete concluded her presentation by requesting feedback from Board members regarding the application review process.

Questions and Answers

Dr. Royston asked about the likely success rate and the number of applications expected for these LRPs. Dr. Strete replied that about 40 individuals will receive funds, since the average grant will be $100,000, and there is $4.1M available for these programs. She also indicated that about 200 applications are expected.

Dr. Millon-Underwood wondered whether recent Ph.D. graduates could be successful in obtaining these awards, because the system is set up in a way such that these individuals would have to write their own R01 or P01 application. Dr. Strete agreed that new postdoctoral fellows would not be as competitive in the clinical research area as more established fellows.

Dr. Norton inquired whether there is a mechanism to try to improve the number of researchers who are members of minority groups. Dr. Strete responded that minorities are eligible for these awards, but there is no formal system within the current LRPs to encourage minority participation. Mr. Horowitz further addressed the question by citing Federal regulations that prevent the inclusion of specific statements in the LRPs indicating that a funding or application priority could be provided to individuals who hold underrepresented minority status. He pointed out that the National Center for Minority Health and Health Disparities has one LRP in which 50 percent of the contracts must be awarded to individuals who are members of health disparities populations. Mr. Horowitz also highlighted the extramural clinical research LRP for individuals from disadvantaged backgrounds funded by the National Center for Minority Health and Health Disparities that can target individuals who are members of underrepresented minority groups.

Dr. Freedman indicated that the likelihood of a fellow coming directly from the clinical program and being named the Principal Investigator on a P01 grant was quite low. He suggested that the review committee could better assess this fellow's potential for moving towards independence if the individual were designated as a Co-Investigator, and if the individual's role in the research project were better defined.

Dr. Richard Pazdur, Director, Division of Oncology Drug Products, FDA, asked which individuals, in terms of the number of years post training, are being targeted for the new LRPs. He expressed concern about the preparedness of new fellows to compete with those who have already

received some type of grant, as well as the idea that recent graduates could have a greater need to repay student loans than those in a later career stage. Dr. Strete responded that she had not considered the number of years following formal training as a criterion for awarding applicants. Rather, the LRPs consider individuals at a time in their careers when they have received their first grant awards and are, therefore, committed to the research process.

Dr. Strete asked Mr. Horowitz whether there was a way to infer the number of years of postdoctoral training an applicant has received from reviewing the application. Mr. Horowitz stated that while that information is not directly asked on the application, it should be possible to extract it from the applicant's *curriculum vitae*. He emphasized that the NIH is making a commitment to identify individuals who wish to pursue research early in their careers but may be hindered by financial considerations. He concluded with a reminder that funding criteria are established by each Institute, and not by the NIH as a whole.

Dr. Pazdur asked for information regarding the median time period from the completion of training to grant award for grantees of other LRPs. Mr. Horowitz stated that the majority of individuals funded in the intramural programs are equivalent to fellows. An exception is the General Research Loan Repayment Program, which by statute has a funding priority for individuals who are more senior in their careers. Historically, the NCI has received 45 to 50 percent of the intramural LRP contracts, and most of the individuals awarded these contracts have been fellows in the fellowship programs.

XIV. SUBCOMMITTEE REPORTS/NEW BUSINESS II

Ms. Ellen Stovall, Chair, Subcommittee on Planning and Budget, summarized the discussion held at the previous day's meeting of the Subcommittee and noted that Dr. von Eschenbach was present to share his vision regarding the Bypass Budget. She complimented John Hartinger on his presentation of NCI's budget. Ms. Stovall stated that, because of time constraints, the agenda item focusing on understanding the planning process was not discussed at the meeting but that Board members are interested in determining how the success of the planning process will be measured on a regular basis.

A motion was made to approve the minutes of the February 20, 2002, meeting of the NCAB Subcommittee on Planning and Budget. The motion was seconded and unanimously approved.

Dr. Norton, Chair, reported on the Subcommittee on Clinical Investigations meeting held the day before. He explained that there were two presentations: one by Dr. Jeffrey Abrams regarding the Cancer Therapy Evaluation Program (CTEP) pilot projects, and the other by Dr. Margaret Holmes regarding the implementation of NIH policies on Data and Safety Monitoring of Clinical Trials. During his review, Dr. Norton described the new system devised by CTEP to allow broader input into the design of clinical trials and provide a broader reach of these trials into the community. For this purpose, State-of-the-Science meetings were held on clinical research covering many malignancies, and Concept Evaluation Panels were established. Dr. Norton added that there was discussion on the Clinical Trials Support Unit (CTSU), which was designed to streamline the clinical trials process. He reported that the Subcommittee felt it was too early to evaluate the performance of the CTSU but that a report to the Subcommittee would be appropriate within a year. In addition, Dr. Norton recounted the Subcommittee's discussion regarding the status of the Centralized Institutional Review Board (CIRB) and how its operation was still at an early stage. He reported that the Subcommittee would like to assess the CIRB's performance next year.

Dr. Norton then outlined the second part of the Subcommittee meeting, in which Dr. Holmes reviewed the implementation of new NIH policies on Data and Safety Monitoring of Clinical Trials. These efforts were aimed at the Phase I and II trials levels. He thought that an important point in the discussion was that there was no monitoring mechanism in place for the Data and Safety Monitoring Boards, and that this function should be added to the process.

A motion was made to approve the minutes of the February 20, 2002, meeting of the NCAB Subcommittee on Clinical Investigations. The motion was seconded and unanimously approved.

Dr. Royston opened the floor for new business. Ms. Stovall introduced, for the Board's discussion and comment, a resolution drafted by several members of the Subcommittee on Planning and Budget expressing concern over the consolidation of certain administrative functions within the NIH being planned by HHS and the potential loss of autonomy by the NCI. Dr. Arthur W. Nienhuis, Director, St. Jude Children's Research Hospital, thought the wording of the resolution was too vague and suggested alternative wording for one of the sections. Dr. Freeman shared concerns about how to formally define the National Cancer Program, because NCAB members have no historic definition of the Program. He also stated that the powers of the NCI Director have been modified since the 1971 Cancer Act, and if the resolution refers to the powers of the NCI Director, it is essential to understand the specifics of the Director's powers.

After much discussion, Dr. Norton proposed delaying the motion to approve the resolution. He expressed concern that, given the vague language of the current resolution, the message could be misinterpreted. He maintained that he would appreciate some time to review and discuss the implications of the resolution. Ms. Stovall expressed concern about delaying the passage of the resolution and proposed, instead, drafting a letter to the HHS Secretary. Dr. Norton reiterated the importance of reviewing the key issues in the resolution. Dr. Royston suggested that Ms. Stovall and Drs. Norton and Nienhuis form a subcommittee to revise the resolution. Dr. Kalt will then organize a Board conference call. Dr. Royston stressed that these actions should take no longer than one week.

XV. PALLIATIVE CARE FOLLOW-UP—DR. ROBERT WITTES

Dr. Robert Wittes, Deputy Director for Extramural Science, NCI, reminded Board members that following a presentation on palliative care from the Institute of Medicine at the December 2001 NCAB meeting, NCI staff proposed a meeting of representatives from other groups with an interest in palliative care and end-of-life issues. This meeting, *Partners in Palliative Care Research*, was held February 6-7, 2002, and involved 16 groups, including Government agencies, professional societies, funding agencies, and funded research organizations. Dr. Wittes reported that the discussion was wide-ranging and included such issues as training and credentialing of subspecialties in medicine, nursing, and social work, and many other topics. He also stated that meeting participants agreed that a widely advertised NCI program announcement would be constructive. NCI staff have not determined the focus of such a program announcement, but they came to the conclusion that by working with other Institutes, they could best highlight the current weaknesses in the NIH research portfolio. Institutes that have had initiatives in palliative care include the National Institute on Aging and the National Institute of Nursing Research. NCI staff plan to have a draft of the program announcement ready for the State-of-the-Science meeting, to be held in the summer of 2002, and let the results of that meeting shape the program announcement's final form. The end product, according to Dr. Wittes, will be a broad-based initiative that will place NIH in a strong position to increase funding for these widely needed areas.

In response to recommendations made by both the IOM report and participants at the February meeting, NCI plans to establish a position in the Office of the Director for a coordinator who would bring together activities of the various divisions and offices involved in palliative care and serve as a single entry point for inquiries on the Institute's initiatives. Dr. Wittes noted that a number of NCI programs dealing with palliative care and end-of-life issues are already underway, and he pointed to quality-of-care initiatives in the Division of Cancer Control and Population Sciences (DCCPS) as examples. Moreover, some 17 clinical trials on palliative care are underway under the sponsorship of the Community Clinical Oncology Programs (CCOPs).

Dr. Wittes indicated that information dissemination efforts received the greatest attention at the meeting. There was general consensus that organizations involved in information dissemination should work more closely together, making the information more easily accessible by means of improved gateways on the Web. Other suggestions included better targeting of this information to particular groups.

Dr. Wittes stated that NCI staff raised the issue of creating "Programs of Excellence in Palliative Care," but despite great interest on the part of meeting participants, there was no consensus regarding the implementation of such programs. He cited a range of ideas from conducting basic science programs to sharing the best interventions in palliative care to ensure their availability to all.

Dr. Wittes concluded his presentation by stating that a barrier to palliative and end-of-life care is differential reimbursement rates. The NCI will need to determine whether it has the budget to support an enhanced clinical trials effort. He expressed interest in conducting demonstration projects in conjunction with Centers for Medicare and Medicaid Services (CMS, formerly Health Care Financing Administration [HCFA]) to try to circumvent this barrier.

Questions and Answers

Dr. Freedman asked for a definition of palliative care: whether it is applied to patients with symptomatic disease for whom all reasonable therapy has failed, or whether it is applied to patients who have failed their first line of therapy and are going to die of their disease. Dr. Wittes responded that he and his colleagues use the term to cover a continuum of symptom reduction from the time of diagnosis until death. He stated that patients at the end of life represent the underserved part of the research portfolio.

Dr. Love pointed out that knowledge of symptom relief is generally applied largely to patients at the end of life, and that knowledge should also be applied to patients who are newly diagnosed or in their initial treatment. Symptom management should be integrated into the whole continuum of patient care.

XVI. MINI-SYMPOSIUM ON CANCER SURVIVORSHIP

INTRODUCTION—DR. BARBARA RIMER

Dr. Barbara Rimer, Director, DCCPS, NCI, introduced the session on cancer survivorship. She noted that, together, the 8.5 million cancer survivors form a very heterogeneous group. It was the size of the survivor population and the challenges and opportunities associated with survivorship that led Dr. Klausner to establish the Office of Cancer Survivorship within the NCI. Dr. Julia Rowland has been the Director of the Office for 2H years. Dr. Rimer introduced Dr. Rowland as the first survivorship researchers to speak in this mini-symposium, followed by Dr. Ganz, Dr. Ahles, Dr. Antoni, and

Ms. Stovall. Dr. Rimer communicated the need for feedback from the NCAB in developing the next level of the Office of Cancer Survivorship agenda.

CANCER SURVIVORSHIP: MOVING BEYOND CURE—DR. JULIA ROWLAND

Dr. Julia Rowland, Director, Office of Cancer Survivorship, DCCPS, NCI, thanked the Board for the opportunity to speak and welcomed Dr. von Eschenbach to his first NCAB meeting. She cited an 8.9 million figure for the number of cancer survivors in this country—a figure derived from the Connecticut Surveillance, Epidemiology, and End Results (SEER) registry that goes back over 50 years. She stated that more detailed information about the survivorship population will be available when data from the nine SEER registries are applied. Unfortunately, these nine registries go back only 20 years; however, the data from the other sites will provide information on geographical differences.

Dr. Rowland reminded NCAB members that cancer is a disease associated with aging. The vast majority of cancer survivors are 65 or older. She provided additional facts about cancer survivors. The three largest constituency groups within the survivorship population are those who diagnosed with breast, prostate, and colorectal cancers. Of adults diagnosed with cancer, 62 percent will be alive in 5 years; for all children under 15 years old diagnosed with cancer, the 5-year survival rate is 77 percent. Importantly, 80 percent of cancer survivors receive treatment in the community rather than at comprehensive cancer centers. This latter fact contributes to the challenge of following individuals over the years to collect information and provide follow-up care. Dr. Rowland emphasized that for most people, cancer is a chronic illness.

Dr. Rowland presented survival rate trends for cancer patients since 1960. Most impressive is the increase in 5-year survival rates—from 4 to 85 percent—in children under 15 years of age. Improvement in survival trends has also been observed in young adults ages 20 to 40, although adult survival trends are not as remarkable. Moreover, it has now been recognized that improvements in survival rates are not shared equally by all members of society. In particular, the African-American and Native American populations do not benefit from medical advances in the treatment of cancer in the same ways as other members of society.

Another change in health care is its mode of delivery. With shorter hospital stays, the burden of patient care falls increasingly on the family. Dr. Rowland noted that the American Cancer Society estimated in 1996 that three of every four families will have at least one family member diagnosed with cancer. Moreover, a quarter of adults with cancer have a child 18 years old or younger living at home. The effect of cancer on these children and the way they deal with their own health care has not been studied.

The Office of Survivorship was established in 1996 to assess the unique needs of individuals surviving cancer over long periods of time. A major thrust of the office is to support research on the physical, psychosocial, and economic sequelae of cancer diagnosis and treatment among survivors. Ultimate goals of the Office are to prevent adverse disease- and treatment-related outcomes, provide a knowledge base for optimal follow-up care and surveillance of survivors, and optimize health after cancer treatment.

Dr. Rowland described the areas of research embraced by the Office of Cancer Survivorship. First and foremost is descriptive and analytic epidemiologic research on the diverse late effects that occur in the population of cancer survivors. The second area is development of interventions to address problems

experienced by cancer survivors. Five other areas include family issues; economic outcomes and patterns of care; development of instruments, especially for posttreatment evaluation; groups neglected by cancer site, culture and income, geography, and age; and training and education.

Dr. Rowland characterized the FY2001 grants portfolio that supports research on cancer survivorship—particularly those grants focused on posttreatment survivors living with chronic illness. The breakout analysis was categorized by NIH Institute, cancer site, and grant focus. Of 142 grants, the majority were funded by the NCI, and the disease most likely to be studied is breast cancer. Intervention-type studies predominate. Fourteen percent of the grants focus on health disparities related to ethnicity or culture, and 11 percent of the grants support research on cancer survivors aged 55 and older, despite the large percentage this age group represents of the overall cancer survivor population.

To move cancer survivorship beyond a cure, Dr. Rowland outlined her plan for the Office of Cancer Survivorship. She indicated that the approach needs to be interdisciplinary. Attention should be directed to under-studied populations and to evolving questions. Finally, there should be recognition that survivorship begins at the time of diagnosis. Dr. Rowland emphasized the involvement of newly diagnosed patients in defining the road ahead.

Questions and Answers

In response to a specific question, Dr. Rowland acknowledged that there are funded grants addressing the issues of stress in the families of cancer survivors. In particular, a P30 supplement to the Cancer Centers has been generated to invite researchers to focus on this area. Intervention research that seeks to minimize the primary occurrence of cancer could be particularly effective in families of cancer survivors.

Dr. Koh observed that cancer survivors act as powerful advocates for survivorship research. By channeling their pain into something productive, they often increase quality of life for themselves and others. Dr. Rowland underscored the importance of advocacy groups for the Office of Cancer Survivorship, and she challenged survivors to be engaged in the advocacy process from the outset. A book will soon be available through the NCI called *Giving Back*. This publication helps individuals diagnosed with cancer get involved in advocacy.

UNDERSTANDING THE LATE EFFECTS OF CANCER TREATMENT: A MEDICAL ONCOLOGIST'S PERSPECTIVE—DR. PATRICIA GANZ

Dr. Patricia Ganz, Director, Division of Cancer Prevention and Control Research, Jonsson Comprehensive Cancer Center, University of California at Los Angeles, recalled the environment in which she trained as a medical oncologist in 1976. Women with radical mastectomies had to deal with arm dysfunction and severe edema. It was also during a time when cisplatin was first being tested in phase II trials and in fact was able to cure young men with testicular cancer, and cyclophosphamide/methotrexate/5-fluorouracil (CMF) was used effectively to treat stage 2 breast cancer. Because she felt cancer would be cured in her lifetime, Dr. Ganz's interest in survivorship research was sparked, and it developed into a career she has pursued with enthusiasm.

Dr. Ganz outlined her talk as a review of the late physical, psychological, and social effects of cancer treatment; a look at some of the existential and spiritual issues that cancer survivors face; and a

series of case examples to highlight both clinical and research issues in this field. As a conclusion to her talk, she stated she would make recommendations for future work.

To begin her presentation, Dr. Ganz commented on the sources of data for cancer survivorship research. Although there are an increasing number of adult cancer survivors, systematic research is limited. The most frequently studied group is women with breast cancer, and both younger and older women have made themselves available to discuss their experiences. This is in contrast to other cancer sites, where older cancer survivors do not participate in research at the same level as younger individuals. As Dr. Ganz pointed out, it will be important to distinguish with further study the disease- and treatment-related issues from those issues related to both a person's individual experience and aging.

Dr. Ganz also expressed disappointment about the limited ability to link survivors' outcomes with treatments used in the cooperative clinical trials programs. She emphasized the unique opportunity presented by clinical trials for the examination of the late effects of rigorously tested treatments and said that she was encouraged by the successes of pediatric cancer groups in getting information from research on children's cancers represented in these databases.

On the topic of physical and medical late effects, Dr. Ganz provided a long list, at the top of which was body changes/scars. She observed that this top item may be dealt with silently by the cancer survivors, yet it presents very difficult challenges for them. Other effects of cancer include fatigue, cognitive dysfunction, cardiorespiratory symptoms, immunological dysfunction, sexual and urinary problems, and infertility. On this last topic, Dr. Ganz questioned whether women are universally counseled before receiving a course of alkylating-agent therapy that they may become amenorrheic or go through early menopause. Many of these changes in physical functioning are related to the effects of the treatment—not of the cancer itself or any other underlying disorder. There is a critical need for prevention and intervention of the negative effects of cancer treatment.

A particularly important late medical effect of surviving cancer is the threat of getting a second cancer. Examples of this include survivors who develop cancer in a paired organ, as in breast cancer, or in the remaining colon in someone surviving colorectal cancer. Moreover, survivors may develop chemotherapy-related or radiation-induced cancers. A substantial number of new cancers each year are second cancers. Dr. Ganz identified the need for strategies to prevent these second cancers.

A second category of late effects experienced by cancer survivors is in the realm of psychological outcomes. These effects range from feelings of gratitude and good fortune to vulnerability and inability to make future plans. A loss of fertility in young cancer survivors presents a particularly painful reality. The late psychological effects experienced by cancer survivors influence late social effects. Some survivors feel altruistic; others feel alienated and isolated. Interaction with peers can be a very positive social routine. However, a negative effect may be divorce, and socioeconomic stress may also play an influential role in marital status. Clearly, individuals who have a cancer diagnosis struggle with issues such as the maintenance of health insurance and employment, when to return to work, and how to handle the financial impact of the disease.

Dr. Ganz also spoke about existential and spiritual effects experienced by cancer survivors. These were summarized as an appreciation of life, a new orientation to time and the future, changed values and goals, concerns about death and dying, and a sense of purpose.

Dr. Ganz used case examples to illustrate the late effects of cancer treatment in several individuals. Cancer survivors deal with myriad medical, psychological, social, and spiritual issues. These are the issues relevant to survivorship research. She then addressed the lack of a sound strategy for monitoring and studying cancer survivors for late effects. Dr. Ganz stated that, ideally, oncology specialists should have a prolonged involvement with survivors; however, she recognized the current overload of patients handled by these physicians for acute treatment. She also maintained that the primary care physician is not trained to deal with the late effects of cancer treatment. Therefore, most of the responsibility for adequate care after treatment falls on the survivors themselves. They should keep their own records in case they move and should be knowledgeable about their own treatments. Dr. Ganz suggested developing specialized clinics for evaluating and treating individuals who have a cancer history.

Importantly, cancer survivors need to acknowledge their own need for long-term follow-up care. Information should be provided about cancer treatment and its late effects. In addition, survivors should be encouraged to participate in research studies, when available. Dr. Ganz urged increased systematic research on the prevalence of late-occurring problems related to cancer treatment. She noted that cooperative groups and cancer registries could be used for this purpose. Finally, Dr. Ganz supported the establishment of survivor clinics and registries and hoped that funds could be provided to the clinics for medical and psychosocial evaluations of cancer survivors.

Questions and Answers

Dr. Freedman seconded Dr. Ganz's proposal of specialized clinics for cancer survivors. He felt this would need multidisciplinary interactions and could be an opportunity for NCI to cross or surmount Institute barriers (to facilitate this effort). Dr. Love agreed and noted that long-term consequences of cancer treatments such as bone-marrow treatments were simply unknown. A specialized clinic would provide an arena for such questions to be researched and answered.

NEUROPSYCHOLOGICAL IMPACT OF SYSTEMIC CHEMOTHERAPY— DR. TIM AHLES

Dr. Tim Ahles, Head of the Center for Psycho-Oncology Research, Dartmouth-Hitchcock Medical Center, thanked the Office of Cancer Survivorship for funding much of the work done at his Center. He reported that cancer survivors helped direct research on the cognitive effects of systemic chemotherapy by calling attention to problems they felt they had with memory, concentration, and learning or mentally manipulating new material. These cognitive deficits in the cancer population appear to be fairly prevalent and have a negative impact on performance in school and at work as well as on the general quality of life. These claims by cancer survivors are now being confirmed in the research setting.

Dr. Ahles asserted that the tools for clinically studying these neuropsychologic issues are in place. These tools will aid not only in measuring cognitive functioning, but also in elucidating the underlying mechanisms by which chemotherapy produces cognitive deficits. An important goal is to develop strategies to either prevent or significantly reduce the impact of therapy on cognitive function.

Initially, long-term survivors of childhood leukemia caught researchers' attention by exhibiting poor outcomes on standard IQ and neuropsychological tests, behavioral problems, and difficulties performing in the workforce. As the problem became better defined and understood, clinicians modified

treatment regimens and were able to significantly reduce the negative cognitive impact on children. Attention is now being drawn to adult cognitive deficiencies.

Dr. Ahles indicated that his research has focused on cognitive problems resulting from bone-marrow transplantation and high-dose chemotherapy. He cited research from the Netherlands that documented the negative effects of high-dose chemotherapy on cognitive function in women with breast cancer. Moreover, this study indicated that women treated with standard-dose chemotherapy also experienced cognitive impairment when compared with women treated with local therapy.

Dr. Ahles described his recent studies of long-term survivors of breast cancer and lymphomas; these studies controlled for age, education, depression, anxiety, and fatigue. His data indicate an effect of standard-dose chemotherapy on all forms of cognitive functioning that were assessed, including verbal ability/learning/memory, ability to learn new information, psychomotor functioning (manipulation of two or more sets of information), and short-term memory.

Dr. Ahles remarked on the variety of domains in which cognitive deficiencies were noted. Cancer survivors who experience these mental weaknesses relate that these long-term effects have had an important impact on a variety of areas in their lives; however, it may be that a subgroup of cancer survivors is maximally affected. Other survivors feel that their cognitive abilities have returned to pretreatment levels. Dr. Ahles then discussed the need to perform longitudinal studies in adults, assessing both pre- and posttreatment levels of cognitive abilities in cancer survivors. Studies at Dartmouth are planned with this design and incorporate as controls both healthy adults and cancer survivors treated with local therapy.

Dr. Ahles commented on the lack of knowledge about the mechanism by which chemotherapy produces cognitive changes. The standard of care is treatment with a combination of agents, so isolating the drug(s) responsible for cognitive impairment is impossible. Mechanisms proposed for inducing damage in the brain include vascular injury, direct brain injury, white matter demyelinization, immunologic reactions, and proinflammatory cytokine induction. Dr. Ahles remarked that mechanistic studies will rely primarily on imaging techniques. Structural magnetic resonance imaging (MRI), MRI spectroscopy (MRS), and diffusion tensor imaging are all useful tools, but a particularly exciting development is functional MRI (fMRI). This noninvasive, repeatable method permits direct observation of brain activity during neurocognitive assessment. A small pilot study indicates that these approaches are suitable for measuring chemotherapy-induced cognitive changes. A grant proposal has been submitted.

Dr. Ahles added that already-established animal models of memory and learning will help define the structure and function of the area of the brain that might be affected by chemotherapy. Importantly, chemotherapy agents can be given singly or in different combinations in the animal models. The research teams at Dartmouth and the University of Colorado have submitted a joint proposal to evaluate animal models for their ability to replicate cognitive deficits seen in cancer survivors.

Research on the mechanism of cognitive deficiencies in cancer survivors will also examine, separately, interactions of chemotherapy agents with hormonal levels and the influences of genetic components, such as the presence of a particular apolipoprotein E allele.

Dr. Ahles concluded his presentation by mentioning interventions to improve neuropsychologic functioning in cancer survivors. Chemotherapy regimens can be changed; there are a variety of

pharmacologic interventions to be evaluated; and cognitive rehabilitation approaches can be tested. The tools are in place. The studies need to begin.

STRESS MANAGEMENT: EFFECTS ON QUALITY OF LIFE, PHYSIOLOGICAL FUNCTIONING, AND HEALTH IN CANCER SURVIVORS—DR. MICHAEL ANTONI

Dr. Michael Antoni, Professor, Department of Psychology, University of Miami, explained that research on the effects of stress management on psychoneuroimmunologic (PNI) outcomes began during the 1990s with patients infected with HIV. It showed that psychosocial factors, including stress, are associated with immune measures such as T lymphocytes, lymphocyte proliferative responses, and natural killer (NK) cell function. According to Dr. Antoni, however, a major question remains: Do the ways in which people respond to stressors (coping strategies, social support) relate to changes in immune function? If so, can patients be taught techniques to manage stress more effectively, leading to improvements in quality of life, immune response, and ultimately physical health outcomes?

One of the most commonly cited explanations for stress-immune associations has to do with the endocrine system. Dr. Antoni summarized research findings that stress activates the hypothalamic-pituitary-adrenocortical (HPAC) axis, and sex hormones, like estrogen, and stress hormones, like cortisol, contribute directly to tumor growth. Moreover, HPAC-related cortisol and other hormones related to the sympathetic nervous system suppress T lymphocytes and NK cell cytotoxicity (NKCC).

Dr. Antoni noted that his research is focused on optimizing health outcomes and increasing survival. He posed three questions: (1) Do psychosocial interventions have the ability to reduce cancer initiation and promotion in patients whose cancers have already begun? (2) Can such interventions prevent complications after treatment—e.g., immunosuppression, infectious disease, and side effects? and (3) Can the progression of cancer be slowed, thus lengthening disease-free survival?

No research has been done to show that psychosocial interventions can affect the promotion of cancer in people in whom the carcinogenic process has already started. Dr. Antoni suggested populations that could be studied to examine this question: people with HIV where there is a backdrop of immunosuppression, women with human papillomavirus (HPV)-associated cervical cancer, people with Epstein-Barr virus (EBV)-associated lymphoma or human herpesvirus (HHV)-associated sarcoma, men with elevated prostate-specific antigen (PSA) levels, and women who have tested positive for *BRCA* genes.

Administering stress-reducing interventions just before treatment may strengthen the immune system, thus yielding two benefits: it could halt the spread of cancer cells as a result of a surgical procedure, and it could reduce the risk of infectious disease.

At least seven studies have tested the effects of psychosocial interventions on survival of patients with cancer and found beneficial effects; four studies have, however, found opposite results. Dr. Antoni stated that these studies vary widely in terms of their follow-up periods, the disease stages of the patients involved, and the types of cancer studied. Because of these variations, he recommended that more attention be paid to stage-specific and disease-specific outcomes in intervention studies.

Dr. Antoni's research involves a cognitive behavioral stress management (CBSM) intervention that combines relaxation, cognitive restructuring, coping skills, and interpersonal skills training to change the way patients deal with breast cancer. If stress has both psychological and physiological effects, the

stress management intervention could have effects on patients' physical health, their sense of self-efficacy, their responses to social support, and so forth. Dr. Antoni described a trial his team carried out for the NCI with women who had undergone surgery for breast cancer 2 to 8 weeks prior to the trial. The intervention was a 10-week version of CBSM that was compared against a 1-day seminar in stress management, and they were followed at 3 months, 6 months, and 1 year.

Subjects who took part in the 10-week stress management intervention tended to show lower levels of clinical depression than the 1-day seminar group and higher scores on "benefit finding"—that is, positive growth that comes through the cancer experience such as acceptance of situations one cannot change, development of closer family ties, and a achievement of a greater sense of meaning. Benefit finding was also associated with reductions in cortisol levels and increases in lymphocyte proliferation.

A second NCI trial tests the effects of the 10-week CBSM program over a longer period of time and is looking at two immune measures: NKCC and lymphokine-activated killer (LAK) activity. Interim analysis reveals that subjects in the 10-week intervention group showed an increase in NK functioning and LAK activity compared with the 1-day seminar group, and this finding was also associated with an increase in benefit finding.

Dr. Antoni's team is also following a group of women who have not developed cancer, but who have early signs of changes—i.e., human papillomavirus (HPV) infection. They hope to determine whether psychological factors in their interventions can predict the development of cervical cancer. Their findings so far indicate that: (1) women who are more pessimistic tend to have poorer NK cell functioning; (2) women with greater negative life stresses have a greater likelihood of developing cervical intraepithelial neoplasia or herpesvirus outbreaks that are accompanied by a drop in NK cells; and (3) women who were more socially isolated showed poorer NK cell functioning and lower T-cytotoxic/suppressor cell counts.

Center for Psycho-Oncology Research. Dr. Antoni stated that the Center for Psycho-Oncology Research is conducting research based on the findings from the HIV studies done several years ago, as well as on recent studies of psychosocial interventions among women with breast cancer. The intervention is "Cognitive-Behavioral Stress Management (CSBM)," and it is designed to modify psychological parameters to bring about changes in quality of life, health behaviors, immune status, stress and reproductive hormones, and disease outcomes. Groups under study include women with HIV and HPV at risk for cervical neoplasia, women who had chemotherapy or adjuvant therapy for breast cancer 3 months before the CSBM intervention, and men who have recently undergone surgery for prostate cancer.

The researchers plan to analyze data from these studies using a common set of psychosocial and biological assessments, including measures of endocrine and immune system functioning, and to make comparisons across the different populations. Dr. Antoni described the project as multidisciplinary, involving physicians, immunologists, endocrinologists, statisticians, and psychologists. Health indicators that the researchers hope to measure include immune indicators, clinical indicators, and neuroendocrine parameters, including stress hormones and sex hormones.

In total, this Center involves four major randomized trials, five core laboratories, and a pilot project research program. All of these projects may help develop predictors of long-term survival and quality of life. Dr. Antoni concluded his presentation by expressing hope that his team will be productive in terms of generating data about psychosocial interventions.

Questions and Answers

Dr. Royston asked whether studies of cervical cancer progression were performed only on HIV-positive women. Dr. Antoni responded that at the present time, the studies are limited to HIV-positive women because the development of cervical cancer is faster among HIV populations.

Dr. Norton noted that sharing this information with the general medical practice community, as well as with specialists, is important because general practitioners will likely see an increasing number of cancer survivors in their practices. Dr. Rowland pointed out that the Office of Cancer Survivorship has a Web site, www.survivorship.cancer.gov, where research results will be posted. The NCI also plans to hold series of biennial meetings on survivorship sponsored jointly with the ACS. The first meeting will be held June 2-4, 2002.

Dr. Huerta suggested that the research be translated into a tool for primary care physicians, clinics, and other care providers. He noted that the National Coalition for Cancer Survivorship (NCCS) has a set of tapes that could serve as a model.

Dr. Love agreed, saying that offering speakers opportunities to give presentations at meetings of primary care and internal medicine physicians would be another effective way to reach those groups. Dr. Rowland responded that the NCI has been working with the American Association of Family Practitioners, which has selected cancer as its topic of interest for its education mission. She noted that the NCI is revising a book entitled *Facing Forward,* produced in collaboration with the NCCS, that focuses on the posttreatment phase.

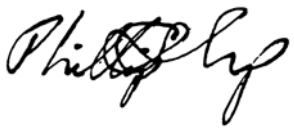
Ms. Stovall reported that the IOM, under the aegis of the National Cancer Policy Board, is preparing a study on survivorship, involving adult survivors of both pediatric and adult cancers.

Ms. Stovall was scheduled to report on "Cancer Survivorship from the Survivor-Advocate's Perspective," but she agreed to postpone her session due to lack of time.

XVII. SUMMARY AND ADJOURNMENT—DR. IVOR ROYSTON

Dr. Royston thanked the speakers, and Dr. von Eschenbach echoed his thanks, saying that the meeting reminded him of the great strength within the NCI and the many challenges facing the Institute. Dr. Royston reminded Board members that they could send any additional ideas about agenda items for future meetings to Dr. Kalt. Finally, he thanked the class of 2002 for contributions to the NCAB.

There being no further business, the 121st meeting of the National Cancer Advisory Board was adjourned at 12:00 p.m. on Thursday, February 21, 2002.



June 11, 2002

Date

Phillip Sharp, Chairperson

June 11, 2002

Date

Marvin R. Kalt, Executive Secretary