

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL CANCER INSTITUTE
125th NATIONAL CANCER ADVISORY BOARD**

**Summary of Meeting
February 11–12, 2003**

**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 125th regular meeting on Tuesday, February 11, 2003, in Conference Room 10 of Building 31, National Institutes of Health (NIH), Bethesda, MD. The meeting was open to the public on Tuesday, February 11, 2003, from 8:30 a.m. to 4:25 p.m. The meeting was closed to the public from 4:25 p.m. until adjournment at 5:40 p.m. The meeting was reopened to the public on Wednesday, February 12, 2003, from 8:30 a.m. until adjournment at 10:50 a.m. NCAB Chair Dr. John E. Niederhuber, Professor, University of Wisconsin Comprehensive Cancer Center and Assistant Dean for Oncology, University of Wisconsin School of Medicine, presided during both the open and closed sessions.

NCAB Members

Dr. John E. Niederhuber (Chairperson)
Dr. Samir Abu-Ghazaleh
Dr. James O. Armitage
Dr. Moon S. Chen, Jr.
Dr. Kenneth H. Cowan
Dr. Jean B. deKernion
Mr. Stephen C. Duffy
Dr. Ralph S. Freedman
Dr. Elmer E. Huerta
Dr. Susan M. Love
Dr. Arthur W. Nienhuis
Dr. Larry Norton
Ms. Maryls Popma
Dr. Franklyn G. Prendergast
Ms. Lydia G. Ryan
(Dr. Eric S. Lander – Consultant)

President's Cancer Panel

Dr. LaSalle D. Leffall, Jr. (Chairperson)

Alternate Ex Officio NCAB Members

Dr. Steven K. Akiyama, NIEHS
Ms. Raye-Ann Dorn, VA
Dr. Ann Farrell, FDA
Dr. Peter Kirchner, DOE
Dr. Hugh McKinnon, EPA
Dr. John Powers, DOD

Members, Executive Committee, National Cancer Institute, NIH

Dr. Andrew von Eschenbach, Director, National Cancer Institute
Dr. Alan Rabson, Deputy Director, National Cancer Institute
Dr. Anna Barker, Deputy Director, Strategic Scientific Initiatives
Dr. J. Carl Barrett, Director, Center for Cancer Research
Ms. Nelvis Castro, Deputy Director, Office of Communications
Dr. Robert Croyle, Acting Director, Division of Cancer Control and Population Sciences
Dr. Ellen Feigal, Acting Director, Division of Cancer Treatment and Diagnosis
Dr. Joseph Fraumeni, Director, Division of Cancer, Epidemiology and Genetics
Dr. Harold P. Freeman, Director, Center to Reduce Cancer Health Disparities
Dr. Peter Greenwald, Director, Division of Cancer Prevention
Mr. John Hartinger, Acting Deputy Director for Management, Office of the Director
Dr. Marvin Kalt, Director, Division of Extramural Activities
Ms. Sandy Koeneman, Executive Secretary, Office of the Director
Dr. Dinah Singer, Director, Division of Cancer Biology

Liaison Representatives

Dr. Clare O'Connor, National Science Foundation
Dr. Robert W. Frelick, Association of Community Cancer Centers
Ms. Barbara K. LeStage, National Cancer Institute, Director's Consumer Liaison Group
Ms. Judy Lundgren, Oncology Nursing Society
Ms. Nancy O'Reilly, The American College of Obstetricians and Gynecologists
Ms. Mary F. Mitchell, American Society of Therapeutic Radiology and Oncology
Ms. Roshundd Drummond, American Society of Therapeutic Radiology and Oncology
Ms. Barbara Stewart, Association of American Cancer Institutes
Ms. Julie Taylor, American Society of Clinical Oncology
Ms. Pamela Wilcox, American College of Radiology

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DAY ONE—TUESDAY, FEBRUARY 11, 2003

**I. INTRODUCTION, WELCOME, AND APPROVAL OF MINUTES—
DR. JOHN E. NIEDERHUBER**

Dr. Niederhuber began by asking for a moment of silence to think of cancer patients and those who have passed away from cancer. He welcomed Board members; representatives of liaison organizations; members of the President's Cancer Panel (PCP); Dr. Marvin Kalt, Director, Division of Extramural Activities (DEA), National Cancer Institute (NCI), and Executive Secretary, NCAB; other NCI staff; and members of the public. Dr. Niederhuber also welcomed Dr. Eric Lander, Director of the Whitehead Institute/Massachusetts Institute of Technology (MIT) Center for Genome Research, who was recently nominated for Board membership. He invited the public to submit to Dr. Kalt, in writing and within 10 days, comments regarding items discussed during the meeting.

Dr. Niederhuber reviewed the confidentiality and conflict-of-interest practices required of Board members in their deliberations.

Motion. A motion was requested and made to approve the minutes of the December 2002 NCAB meeting. The motion was seconded, and the minutes were unanimously approved by the Board.

**II. FUTURE MEETING DATES CONFIRMED THROUGH 2005—
DR. JOHN E. NIEDERHUBER**

Dr. Niederhuber called Board members' attention to future meeting dates listed in the Agenda; dates have been confirmed through 2005.

**III. NCI DIRECTOR'S REPORT—DR. ANDREW von ESCHENBACH AND MR. JOHN
HARTINGER**

Dr. von Eschenbach noted that this meeting marked his first anniversary as Director of the NCI. He said he would spend most of his allotted time bringing the Board up to date on budgetary issues and the Institute's strategic planning efforts. He stressed the fact that, in spite of other challenges, the President and his administration remain committed to the war on cancer. Dr. von Eschenbach mentioned his recent trip to Ireland to help launch the All Ireland Clinical Trials Network, noting that the NCI has for several years been supporting efforts to bring Northern Ireland and the Republic of Ireland together in a common effort against cancer.

Staff Changes

Dr. von Eschenbach reviewed staffing changes at the NCI. Dr. Anna Barker, who recently joined the Institute as Deputy Director for Strategic Scientific Initiatives, has brought Greg Downing into her office as Director of the Office for Technology and Industrial Relations. Cathy Zoon, formerly of the Food and Drug Administration (FDA), has joined as Principal Deputy Director of the Center for Cancer Research (CCR). John Hartinger has resumed his role of Chief Financial Officer, and Janice Mullaney has stepped in as Acting Deputy Director for Management. Dr. von Eschenbach also announced that Dr. Margaret Kripke, Executive Vice President and Chief Academic Officer at the M. D. Anderson Cancer Center and former president of the American Association for Cancer Research (AACR), has been selected to serve on the President's Cancer Panel.

NCI Planning Activities

A large portion of his first year as NCI Director, Dr. von Eschenbach stated, has been dedicated to bringing together Division Directors and other senior leadership to address strategic planning, building on and expanding the portfolio of initiatives described in the Bypass Budget. Several retreats have been held focusing on team building and developing a long-range strategic planning process. A key factor in this process is the broadening of the cancer-related enterprise that was initiated over the past several decades.

The NCI has accepted a “challenge goal” of eliminating suffering and death due to cancer by 2015. Dr. von Eschenbach pointed out that this does not mean eliminating cancer, but represents a commitment to work collaboratively to eliminate the burden of cancer. To accomplish this, long-range strategic planning is being directed at the “three *Ds*”: discovery, development, and delivery. Within the discovery portfolio, the NCI’s long-range objective is to define all of the relevant mechanisms responsible for the initiation and progression of cancer in the cell, in the individual, and in populations. Based on this knowledge, interventions to predict, detect, diagnose, treat, and prevent disease will be developed and delivered as state-of-the-art care to all who need it. In the context of clinical trials, the delivery process itself will produce new knowledge. All of these activities will be designed to ensure that all populations benefit and health disparities are eliminated.

This process, Dr. von Eschenbach continued, is a “road mapping” exercise to put into place short-, intermediate-, and long-term objectives and initiatives. A financial plan for resource acquisition and allocation will be superimposed on that map. Because this must be done in the context of accountability, milestones and measurable outcomes will be constructed to evaluate incremental success on the road to achieving long-range goals. In the coming months, Dr. von Eschenbach reported, the NCI will focus intensely on its intramural program; many opportunities will be presented by the planned opening of the new NIH Clinical Center, and new activities and facilities are being planned for the Frederick, Maryland, campus.

Dr. von Eschenbach added that it is also important to remember that this process does not go forward in isolation; the NCI has a responsibility to provide leadership and add value to the efforts of the broader community. Planning input from that community will be invited through a variety of activities. Dr. Eric Lander, recently nominated to join the NCAB, has been working as a volunteer to help create a strategy for using focus groups of cancer researchers in long-range strategic planning. The NCI also plans to involve the broader community in the early stages of Bypass Budget development. These activities exist in the context of similar efforts at the NIH and Department of Health and Human Services (DHHS) levels.

Several trans-NIH and DHHS initiatives have been identified for immediate attention, including Medicaid reform, emergency preparedness, prevention, elimination of health disparities, and information technology. The NCI is affected by all of these initiatives, but two—prevention and elimination of disparities—are especially relevant. In the area of prevention, the NCI will play an important role in trans-NIH activities related to tobacco use, nutrition, physical exercise, and obesity.

The DHHS initiative on disparities—led by Claude Allen, Deputy DHHS Director—is looking to the NCI for leadership and infrastructure building. One model through which the NCI is providing leadership is the Progress Review Group (PRG) process, led by Ms. Cherie Nichols, which has been effective in moving from strategic planning to implementation strategies with measurable outcomes.

Dr. Harold Freeman, Director of the NCI Center to Reduce Cancer Health Disparities (CRCHD); Dr. LaSalle Leffall, Chair, PCP; and Dr. John Kerner of the NCI Division of Cancer Control and Population Sciences (DCCPS) have been actively involved in this initiative.

Road-mapping activities within the NIH that are relevant to the NCI, Dr. von Eschenbach continued, include plans to foster interdisciplinary science and the integration of scientific activities. NIH Director Dr. Elias Zerhouni also is exploring new pathways to discovery using emerging technologies, such as nanotechnology, as well as reengineering the clinical research enterprise. These efforts have already emerged as part of the NCI's strategic planning effort, and the CCR has begun a similar mapping process to foster interdisciplinary science and develop an integrated approach to cancer biology.

Dr. von Eschenbach added that the NCI also is partnering with other agencies and organizations to achieve its challenge goal for 2015. One example is a dialogue with the FDA to discuss streamlining regulatory processes to expedite the development of interventions based on biological discoveries.

Budget Update

Dr. von Eschenbach introduced Mr. John Hartinger, who noted that the NCI was operating under the eighth in a series of continuing resolutions based on FY 2002 funding levels, but that an omnibus bill to release funds for FY 2003 was expected soon. He explained that the FY 2003 President's budget had been amended to make small adjustments, most notably to allow the NIH to complete construction of the Porter Neuroscience Building. The NCI allocation in the amended 2003 budget is \$29M less than the proposed budget presented last year. This leaves the NCI with a 12 percent increase for FY 2003 if the budget is passed as proposed.

The President's FY 2004 budget, which was released on February 4, includes an increase of about 2 percent for the NIH. However, because the 2003 facilities allocation has been reduced from \$770M to \$80M, the NIH research budget has effectively increased by about 4.7 percent. From FY 2002 to FY 2004, Mr. Hartinger noted, the NCI budget has grown from \$4.1B to \$4.7B, or approximately a 16 percent increase over 2 years; the increase from FY 2003 to FY 2004 is about 3.5 percent. Of this increase, Research Project Grants (RPGs) account for 55 to 57 percent; research grants overall, 75 to 76 percent; Cancer Centers and Specialized Programs of Research Excellence (SPOREs), about 12 percent; the intramural program, about 8 percent; contracts, about 8 percent; and the career development program, about 1 percent.

Increases from FY 2003 to FY 2004 for individual items include 4.4 percent for RPGs; almost 5 percent for Cancer Centers and SPOREs; about 1.8 percent for intramural programs; about 2 percent for prevention and control; and about 3.5 percent for most other items. There is also a small increase in stipends for training programs. The NCI budget still has a construction line, but for 2004 that line is at zero. About \$10M has been removed from the budget due to a decrease in full-time equivalents (FTEs), and about \$22M in information technology (IT) activities has been removed. As a result of this reduction, Mr. Hartinger noted, the NCI will face a challenge in consolidating its IT operations.

Mr. Hartinger called attention to an initiative within the President's budget to support all years of some grants with funds from the FY 2004 budget.

Mr. Hartinger noted that the success rate for grants is driven by the number of applications received. Last year, about 4,600 applications were received by the NCI; this year, about 400 more are

expected, or an increase of 8 to 9 percent. The success rate for R01 grants has seen a slight decline, although the absolute number of awards is at an all time record.

An issue that will affect NCI operations, Mr. Hartinger added, is an NIH-wide requirement, in response to Office of Management and Budget (OMB) Directive A76 to identify functions that might more appropriately be performed by the private sector. The NIH has determined that as much as one-half of its staff, or up to 900 people, could be involved in activities that could be commercialized. Over the next few years, he said, the NCI will study specific areas, including administrative functions such as procurement and information technology, that could be performed by the private sector.

Dr. von Eschenbach expressed his appreciation for the work of Jim Dickens and Steve Hazen in modeling various options for the Institute as it endeavors to preserve its ability to fund investigator-initiated research.

Questions and Answers

Dr. Moon Chen, Associate Director for Cancer Prevention and Control, University of California–Davis Cancer Center, asked for an example of a trans-NIH initiative that will have an impact on the NCI budget. Dr. von Eschenbach stated that the NIH Director has placed some funds in a general category dedicated to what is called “road-mapping initiatives.” One aspect of this is the reengineering of the clinical trials infrastructure. The NCI is positioned to gain competitive access to this separate pool of dollars for clinical research.

Dr. Niederhuber suggested a public relations effort to let new investigators know that the increasing competitiveness of the grants award process is caused by increasing numbers of applications. Dr. von Eschenbach acknowledged that development of young investigators is an important part of the planning process. He noted that part of the solution is creating an infrastructure that includes sources of funding other than the R01 mechanism. Increasing emphasis on team science may reduce the perception of the R01 as the only measure of success.

Dr. Jean deKernion, Professor and Chairman, Department of Urology, University of California School of Medicine, mentioned that the P30 and P50 mechanisms serve as surrogates for the R01 because they include career development support. Dr. von Eschenbach agreed, noting that he is encouraged by the fact that the pool of applications continues to grow and the quality remains high.

IV. PRESIDENT’S CANCER PANEL REPORT—DR. LaSALLE D. LEFFALL

Dr. Leffall, Charles R. Drew Professor of Surgery, Department of Surgery, Howard University College of Medicine, Howard University Hospital, reported on activities of the PCP. On behalf of the Panel’s other members, Dr. Harold Freeman and Mr. Lance Armstrong, Dr. Leffall thanked the NCAB for the opportunity to update the Board on its December meeting, hosted jointly with the National Dialogue on Cancer (NDC), and its meetings planned for 2003.

On December 7, 2002, the Panel met in Washington, DC, to obtain feedback from working groups of the NDC regarding recommendations set forth in the Panel’s report entitled *Voices of a Broken System* and to generate discussion about how to address identified barriers to cancer care. Presentations were made by representatives of those working groups, known within the NDC as Teams. The Access to Care Team recommended expanding health insurance coverage for services such as screening and

palliative care and suggested providing incentives to physicians who enroll patients in clinical trials. The Clinical Trials Team summarized its report entitled *Barriers to Clinical Trials Participation*, which compiles findings of several surveys on the subject; this Team is collecting evidence that there should be a more equitable level of reimbursement for recruiting patients for clinical research. The NDC's State Cancer Plan Team has as its goal the implementation of data-driven comprehensive cancer control plans in each state by 2005; this Team noted that the findings in the *Voices* report are very relevant to the development of state cancer plans. The Work Force Team is studying issues related to training health professionals; this Team is working with numerous Federal agencies and private organizations to address manpower shortages in areas related to oncology. The CEO Roundtable, an arm of the NDC designed to engage corporate leadership in the fight against cancer, has created a Gold Standard Task Force to determine elements that should be included in all corporate cancer plans. At the NDC meeting, the Panel also heard from Dr. Charles Cutler, Chief Medical Officer of the American Association of Health Plans. He stated that his organization supports the recommendations contained in the *Voices* report. One of the issues being addressed by the Association is the need of patients, physicians, and health plans for quality-related information.

Dr. Leffall said that the Panel's theme for 2003 will be survivorship, which has been identified as an Extraordinary Opportunity (EO) in the NCI Bypass Budget. Meetings will explore perceptions associated with surviving cancer and the concerns faced by survivors related to care delivery, health outcomes, and quality of life. The first meeting, to be held on May 27–28 in Lisbon, Portugal, will explore survivorship in a European context; one of its objectives will be to identify service delivery models that could be adapted for use in the United States. Two meetings in September, the first in Denver, CO, and the second in Austin, TX, will focus on survivorship issues for children and young adults and similar issues among adults and the elderly. In November, the Panel plans to review its findings and develop recommendations to the President.

Dr. Leffall closed by promising to report to the NCAB in June on recommendations resulting from the PCP's meeting with the Yakama Indian Nation.

Questions and Answers

Dr. Niederhuber asked whether the Panel planned to address the research agenda on survivorship or focus on the problems of society and the patient. Dr. Leffall replied that the Panel plans to address both aspects of survivorship.

V. ANNUAL DELEGATIONS OF AUTHORITY/NEW BUSINESS I— DRS. JOHN NIEDERHUBER AND MARVIN KALT

Annual Delegations of Authority

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 an agreement 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 Board of Scientific Advisors (BSA), the Director's Consumer Liaison Group, and other advisory committees.

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 fellowship awards with stipends that may exceed \$50,000—and it permits expedited concurrence for R01 and R21 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. Finally, there is a stipulation that in emergency situations, the NCI Director and the NCAB Chair can address individual issues.

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

MERIT Award Announcements

Dr. Kalt announced two NIH Method to Extend Research in Time (MERIT) awards (also called R37 grant awards) approved by the Board at its September 2002 meeting. Dr. Diane Haywood of the Johns Hopkins University received a MERIT award for her project entitled “Regulation and Replication and Latency by EBV EBNA_s,” and Dr. Martin Privalsky of the University of California–Davis received a MERIT award for his project entitled “Mechanism of Action of the V-erbA Oncogene of AEV.” Dr. Kalt said that additional MERIT awards will be announced after the FY 2003 appropriation is finalized. He added that a previous MERIT awardee, Dr. Bruce Zetter, would be making a presentation to the NCAB the next day.

Questions and Answers

Dr. Larry Norton, Director, Medical Breast Oncology, Evelyn H. Lauder Breast Center, Memorial Sloan-Kettering Cancer Center, asked what percentage of funding is in the form of MERIT awards. Dr. Kalt replied that the average number of awardees is between 60 and 70, although with the rise in R01 applications, the number of MERIT awards also may be expected to increase. The cost of a MERIT award is usually about \$150,000 over the average cost of an R01 award. Dr. Norton stated that this is a very important way to encourage the work of senior researchers.

Dr. deKernion asked who initiates recommendations for MERIT awards. Dr. Kalt said that NCI program staff are responsible for identifying investigators with established track records over at least 7 years on the same research topic and who are in the top five percentiles of all reviewed grants. They bring these to the attention of the Executive Committee, which makes the final recommendation to be sent forward to the NCAB.

NCAB Retreat

Dr. Niederhuber reminded the Board of recent discussions of how the NCAB could provide additional assistance to the NCI to support the planning process. He reported that he had met recently with Dr. Kalt and Ms. Cherie Nichols to move forward on plans for an NCAB retreat to be held in

conjunction with the Board's June 2003 meeting. The June meeting is scheduled for June 9 through 11, with June 9 designated as a travel day; Dr. Niederhuber asked Board members to add Sunday, June 8, to their calendars as a travel day so that they can participate in the retreat on Monday.

VI. P30/P50 WORKING GROUP REPORT—DRS. ARTHUR NIENHUIS AND JOSEPH SIMONE

Dr. Nienhuis, Director, St. Jude Children's Research Hospital, stated that the P30/P50 Working Group met six times over the past 6 months to consider issues related to the future of the Cancer Centers and SPOREs programs and make recommendations to the NCI Director. He said that his part of the presentation would summarize the Director's charge to the Working Group, and that Dr. Simone, President, Simone Consulting, would summarize the group's findings and recommendations.

Both programs are dedicated to translational research: bringing laboratory findings to clinical applications and returning problems encountered in the clinic to the laboratory for exploration. Together, these programs account for about 10 percent of the NCI budget. The Working Group's charge was to deliberate on how to enhance the capacity of these programs to maximize translational research; consider ways to set priorities in the context of budget constraints; explore incentives to leverage NCI support with other partners; suggest ways for Cancer Centers and SPOREs to play a greater role in setting the NCI agenda; and suggest 5-year goals and measures of progress for these programs.

Dr. Nienhuis explained that the P30, or Cancer Center Support Grant—also known as a core grant—supports infrastructure rather than research itself. Two of the most important criteria by which Centers are evaluated are the authority of the Center Director and institutional commitment. The P30 program began in the 1960s and now features 61 basic and clinical Comprehensive Cancer Centers. A P50, or SPORE, focuses on a specific cancer site. Each project is led jointly by a clinical and a laboratory researcher, and each project has a defined translational goal with a 5-year target for achievable results. The P50 program began in the early 1990s and has grown rapidly to 44 projects with a current budget of \$93M. The fact that 41 of these projects are located within Cancer Centers is a measure of the success of the P30 program; the leadership and scientific strength of the Centers allowed them to successfully compete for the SPOREs grants.

The Working Group was asked to consider the current structure and guidelines of these programs and determine mechanisms to better coordinate their activities and expand their interface with other cancer-related entities in their communities. Another charge was to find methods to ensure that P30 and P50 budgets are flexible enough to encourage innovation and empower project directors to maximize the impact of their activities in their regions. Dr. Nienhuis acknowledged the assistance of the Group's Executive Secretaries, Drs. Marvin Kalt and Paulette Gray, in arranging for presentations from a broad spectrum of experts from the NCI, Cancer Centers, SPOREs, academic centers, state organizations, advocacy groups, the pharmaceutical industry, and private medical practices.

Dr. Simone opened his remarks on the Working Group's findings by stating that the Cancer Centers program is strong and that its infrastructure is adaptable to novel approaches. Most translational research in this country is being done in Cancer Centers. The integration of Centers and SPOREs, based on a survey of the 61 Cancer Centers, is uneven. Some guidelines limit innovation, according to many Center Directors. Innovation and flexibility are inhibited by budget constraints and specific initiatives mandated by the NCI. Centers do not receive credit in their evaluations for community outreach and coordination or for affiliations with cooperative groups. The Working Group is concerned that staff

participation in NCI cooperative groups is often considered a negative factor when Centers are evaluated. It was the consensus of the Group that the review process places an excessive claim on Center staff time.

The Working Group found that the SPORes program is extremely popular among both participants and advocates; there is active communication among grantees. It was the consensus of the Group, however, that it is too early to evaluate the effectiveness of the SPORes program. Many people feel that the dramatic growth of the program cannot be sustained in the current financial climate. As with the P30s, the review process for P50s needs adjustment. The fact that SPORes are disease-specific creates special problems for review; these are addressed in the Group's recommendations.

Dr. Simone reported that the Working Group developed three major recommendations, each of which is accompanied by specific suggestions on how to approach them. The first major recommendation is that Cancer Centers and SPORes are vital and must be sustained, even in times of tight budgets. Specific suggestions under this recommendation include:

- The P20 funding mechanism, which provides planning grants for development of Cancer Centers, should be suspended.
- The growth rate of the P50 program should be slowed to that of the R01 pool.
- The average amount of awards should be reduced.
- The NCI should find ways to share resources between P30s and P50s to achieve economies of scale and require non-Federal matching funds for the P50 program.

The second major recommendation is to make better use of Centers as entrepreneurial resources for planning innovation and dissemination. Specific suggestions include:

- Center Directors should be allowed and encouraged to participate in the NCI strategic planning process.
- Some new Requests for Applications (RFAs) for research and dissemination programs could be piloted more efficiently within Cancer Centers by taking advantage of the existing infrastructure.
- The NCI should include salary support in the P30 mechanism for physicians who see patients in the conduct of clinical trials, in light of declining reimbursement for patient care.
- Financial support for underfunded shared resources such as tissue banks should be increased.
- Efforts should be made to increase the geographic distribution of Cancer Centers. Because most institutions that meet the stringent criteria already have Centers, a new category of Centers may be needed to allow institutions with a limited area of expertise to participate in the program through associations with existing Centers.
- Cooperative efforts with state agencies, health departments, and other partners should be encouraged by providing recognition of these activities.
- The P30 mechanism should be modified to encourage establishing infrastructure and developing novel methods for disseminating new knowledge.

The third major recommendation is to make a concerted effort to improve the efficiency, effectiveness, and evaluation of Centers and SPORes. Specific suggestions include:

- An integrated national clinical research informatics system should be established.
- Review of clinical trials that have already gone through peer review should be eliminated or abbreviated.
- A central Institutional Review Board (IRB) should be established for multicenter clinical trials.

- Review of P30s should be streamlined.
- Review of P30s should consider and weigh collaborative activities with P50s.
- A planning process should be initiated to develop quantifiable metrics for determining the size of P30 awards that reflect the broad impact of Cancer Centers.
- A two-tiered system should be used to evaluate SPORes, with a parent committee to review applications across tumor sites and a panel of experts on the relevant tumor site.
- There should be a process to annually describe and quantitate the overall contributions of the P30 and P50 programs, including the attraction of non-Federal funds, the impact on training, and the effect of regional collaborations.

Dr. Simone concluded by reiterating that the Working Group felt that Cancer Centers and SPORes are vital to NCI's translational and clinical research efforts and should therefore be sustained. Changes should be made to improve efficiency and effectiveness; adjustments to new budget constraints must be made; and the NCI should remain poised to enhance these programs when the financial situation improves.

Questions and Answers

Dr. Susan Love, Adjunct Professor, Department of Surgery, University of California School of Medicine, praised the Working Group's report but pointed out that most members of the Working Group were associated with Cancer Centers. She called attention to the appearance of a conflict of interest and pointed out that some members of the community might perceive that these recommendations suggest that Cancer Centers take a lead role in all aspects of the fight against cancer. She also expressed concern about the public misperception that the NCI has endorsed the clinical care at Cancer Centers as the best available. Dr. Nienhuis said that the Working Group is aware of the appearance of a possible conflict of interest but feels strongly about the central role of Cancer Centers in facilitating and integrating research. The Group is not suggesting that Cancer Centers take control of the cancer community, but that they serve as hubs within their regions to develop interactions that would promote dissemination and delivery of knowledge. Dr. Simone added that 80 percent of clinical research is done in the community setting; the Working Group is in favor of making it possible for small institutions that lack the management resources of larger institutions to be given an opportunity to participate in the program. He also acknowledged the problem of public perception that NCI designation of a Cancer Center implies quality, and he avowed that the level of NCI involvement in quality-of-care issues needs to be determined.

Dr. Norton raised the issue of coordination versus comprehensiveness. The Working Group report suggested establishing "Junior Cancer Centers" that do not have all of the components necessary to create a comprehensive program. Dr. Norton wondered whether the same concept could be applied to the SPORes program. Institutions that are strong in one area, such as training, but weak in others, such as tissue resources, might be able to contribute to the program; new communication technologies could enable the creation of "virtual" Centers as an alternative to Centers that bring all necessary components together in one place. Dr. Nienhuis said the Working Group had discussed the idea of creating "extended Centers" or virtual Centers; the proposed primary P30 Centers and network of associated Centers is a step toward that goal. Dr. Simone added that the Group concluded that P50s cannot continue to grow at the current rate, and other resources will need to be developed; this might not be limited to financial resources, but could include other resources that partner institutions could provide.

Dr. deKernion asked for comments on whether Cancer Centers are positioned to take advantage of advances in mathematics, physical science, and nanotechnology. He also asked how a two-tiered

system of review for P50s is compatible with the stated desire to streamline review; whether the suggestion to provide salary support for clinical trial physicians was conceived in the context of the current budget; whether the Working Group had considered the issue of education for physicians interested in participating in clinical trials; and whether any thought had been given to a timeframe in which these recommendations should be reexamined. Dr. Simone replied that Centers should be encouraged to explore new technologies. The Group felt that the two-tiered review is needed to ensure that each P50 is reviewed by specialists in relevant fields and that this should not be incompatible with the overall goal of streamlining the review process. The recommendation about salaries for clinical trial physicians does not mean additional money is requested but, rather, that the provision of salary support should be explicitly permitted. The reevaluation of the process, Dr. Simone noted, should involve individuals with no professional stake in Cancer Centers but who have sufficient knowledge of what one should expect from a research enterprise. Dr. Nienhuis added that Centers should be evaluated on how effectively they develop and train individuals for effective careers in clinical research.

Dr. James Armitage, Dean, University of Nebraska College of Medicine, commented that the Cancer Centers program is the most important thing the NCI has accomplished in terms of its impact on the field of medicine.

Dr. Elmer Huerta, Director, Cancer Risk Assessment and Screening Center, Washington Cancer Institute, emphasized the importance of following up on the Working Group's recommendations that focus on increasing outreach to and involvement with the community. Dr. Nienhuis noted that the Working Group does not want to reduce the focus on discovery in Cancer Centers but encourages a new focus on community outreach within the Centers.

Dr. Ralph Freedman, Professor, Department of Gynecologic Oncology, M. D. Anderson Cancer Center, expressed concern that the recommendations may reduce the emphasis on R01-supported scientists within Cancer Centers who are essential to mentorship for future generations of researchers. Dr. Simone said that the lack of discussion of basic science in the report did not indicate an intention to reduce its importance in Cancer Centers.

Dr. Chen suggested making knowledge dissemination a measurable criterion for evaluating P50s and using the P50 as a mechanism for exploring multidimensional problems, such as health disparities. Dr. Simone replied that the Group had discussed the idea of function-based SPOREs in addition to disease-based projects.

Dr. Frank Prendergast, Director, Mayo Comprehensive Cancer Center, expressed concern that cancer centers in the United States that are not NCI-designated Cancer Centers are at a disadvantage because the clinical demands on them are growing, their resources for academic activities are shrinking, and the best investigators are drawn to the NCI-designated Centers. He stated that the relationship between Cancer Centers and SPOREs is, in most cases, a good one. The Center has purview over the clinical aspects of the SPORE while the SPORE director maintains autonomy, and the letter and intent of the SPORE mechanism is honored. Dr. Simone stated that the Cancer Centers have succeeded because they have evolved over time, and both the Centers and the P50s will have to continue to evolve in the future. Drs. Nienhuis and Simone concluded by saying that the Working Group's report is not the last word—the essence of the recommendations will be adopted by NCI staff with assistance from the broader community.

Dr. von Eschenbach thanked Drs. Nienhuis and Simone and the entire Working Group for their extraordinary work. He explained that NCI staff directly involved in the Cancer Centers and SPOREs programs will be asked to study the report and present their perspectives on these issues to the Executive Committee, where a more extensive discussion will take place. Input from the broader community will be solicited, and the process of aggressively developing an implementation strategy will begin. In the next few months, this will be one of the most important undertakings of the Institute.

Dr. Love asked whether the NCI is considering a strategic plan that will organize the extramural program around Cancer Centers in a “hub and spoke” type of system. Dr. von Eschenbach stated that the reason the Working Group was formed was that the Cancer Centers exist and are clearly drawing resources. The NCI is acknowledging this reality and taking steps to ensure that these resources are leveraged and kept in balance.

Motion. A motion to accept the report of the P30/P50 Working Group was seconded and passed unanimously.

VII. AMERICAN ASSOCIATION FOR CANCER RESEARCH UPDATE— DR. SUSAN BAND HORWITZ

Dr. Horwitz, President of AACR and Falkenstein Professor of Cancer Research, Department of Molecular Pharmacology, Albert Einstein College of Medicine, New York, reported on the activities of the AACR. In her introduction, Dr. Horwitz noted that the AACR was established in 1907 and has almost 20,000 members in more than 60 countries. The organization’s mission is to prevent and cure cancer through research, education, communication, and collaborations. Dr. Horwitz sought to emphasize in her talk the ways in which the AACR can collaborate with the NCI to achieve mutual goals.

Dr. Horwitz spoke on the strengths of the AACR, citing in particular the excellent scientific programs and the high scientific caliber of the membership. She explained that a scientific retreat, chaired by Dr. Philip Sharp, was held in February 2002, to set priorities for future AACR activities. At this exciting and productive meeting, several areas clearly commanded focus for future advancements in cancer research. Enhancing cross-disciplinary scientific communication and developing priorities topped the AACR’s list, followed by the reinvigoration of chemical biology to align this field more directly with the goals and needs of the cancer research field. Advancements in biological imaging were recognized as opening new avenues for assessing real-time tumor effects by pharmacological agents, and this was seen as one approach for accelerating the development of drugs for clinical use. The meeting participants felt that AACR should prioritize the translation of new discoveries into real benefits for cancer patients. Dr. Horwitz finished reviewing the list of priorities by commenting on the importance of promoting scientific communication and international collaboration. Her subsequent presentation outlined the AACR activities that will help address and realize these priority areas.

Dr. Horwitz briefly summarized the action plan compiled by the Clinical Cancer Research Committee’s Special Task Force on Strategic Planning. The primary focus is to accelerate clinical trials based on surrogate and intermediate markers. Dr. Horwitz remarked on the AACR’s intention to work with the FDA on these proposals.

Dr. Horwitz also reported on the AACR scientific think tank that was held in January 2003. This meeting was organized to prioritize research areas and suggest approaches to catalyze cancer eradication.

Priority areas included: molecular epidemiology and proteomics, bioinformatics and computational molecular biology, and cancer gene discovery and validation.

AACR's journals give voice to the scientific accomplishments of its members and the entire cancer research community. The latest of five journals, *Molecular Cancer Therapeutics*, began in 2001. Dr. Horwitz noted that more emphasis is being placed on electronic publications to enable individual scientists to mine data across scientific disciplines that are relevant to their particular research.

Dr. Horwitz went into some detail about the meetings organized by the AACR. She described the large annual AACR meeting as not only another avenue to communicate the highest-quality endeavors in all areas of cancer research, but also as a means to bring together cancer researchers from academia and industry—within and outside AACR membership. Furthermore, she explained that the meeting provides a platform for AACR to recognize, with awards, outstanding scientists and to announce career development awards. This year, the Avon Foundation has funded four \$50,000-per-year new career development awards, each for 2 years. In addition, the annual meeting of the AACR provides an opportunity to applaud and support public education. Dr. Horwitz recognized Dr. Anna Barker for her 15 years of involvement in this area and noted that 1,500 people eagerly attended the Public Forum Program that Dr. Barker chaired last year.

Dr. Horwitz also mentioned the Scientist↔Survivor Program, in which scientists partner with cancer survivors who attend sessions and have the opportunity to ask questions throughout the week of the annual meeting. Dr. Horwitz described this program as an important educational experience not only for the cancer survivor, but also for the cancer researcher who may spend a great deal of time studying cancer, but not necessarily with the people affected by the disease.

Next, Dr. Horwitz detailed two midsized annual meetings organized by the AACR. One, entitled *Molecular Targets and Cancer Therapeutics*, held in the United States and in Europe in alternate years, is a collaboration among the AACR, NCI, and the European Organization for Research and Treatment of Cancer (EORTC). The other meeting, entitled *Frontiers in Cancer Prevention Research*, started last year and had more than twice the expected number of attendees. Both meetings have been very successful. A new meeting is being planned for this year called, *Frontiers in Basic Cancer Research*. Although small, this meeting promises to be up-to-date on issues of proteomics, protein networking, and basic cancer research.

Dr. Horwitz continued by describing small AACR meetings that focus on cutting-edge and emerging science. The AACR selects topics from areas in which it feels that a meeting can make a definite difference. These meetings generate considerable interest and enthusiasm.

AACR task forces form the intellectual springboard for developing these meetings. Dr. Horwitz highlighted two: the "Pediatric Oncology" and the "Aging and Cancer" task forces. The relationship between aging and cancer, although recognized, has not led to an increased enrollment of people over 60 years old in clinical trials. Certainly, a greater knowledge of the process of aging will improve our understanding of cancer. Dr. Horwitz felt that this could be an area of fruitful collaboration between the NCI and AACR.

In addition to these meetings, the AACR organizes workshops to train and educate scientists. Dr. Horwitz mentioned opportunities to participate in two such workshops: Methods in Clinical Cancer

Research and Methods in Molecular Biology in Clinical Oncology. Dr. Horwitz reiterated the organization's commitment to education.

Dr. Horwitz also addressed the globalization of science and AACR's involvement with cancer groups in other countries. She noted that the public has become more demanding and more knowledgeable, and that the AACR is aware of the urgency of educating the next generation of scientists.

In closing, Dr. Horwitz cited a 3-year-old poll about attitudes of Americans towards cancer research. Although underestimating their personal risk of cancer, most Americans support significant increases in Federal research spending to find a cure for cancer. Dr. Horwitz noted that the number of people with malignancies in the United States is approximately 1.4 million, and in 2002, this meant a cost of \$172B. By 2015, this cost could exceed \$500B per year.

Dr. Horwitz encouraged continuing and expanding collaborations between AACR and the NCI. The scale of the cancer burden is appreciated by both organizations, and the challenge is to respond with energy, creativity, and urgency. Among her list of suggested collaborations, Dr. Horwitz included public education, training, scientific conferences, and importantly, a dialogue about scientific priorities. Dr. Horwitz concluded by envisioning AACR as a catalyst for discovery and innovation, working with government, academia, industry, and the general public to fulfill its goal of curing and preventing cancer.

VIII. ANNUAL NCI REPORTS—DR. MARVIN KALT

Report on Inclusion of Women and Minorities in Research

Dr. Kalt reminded the Board that the Health Research Extension Act, also known as the NIH Revitalization Act of 1993, ensures that women and minorities are included in proportional numbers in all applicable clinical research studies. The Act requires that the Advisory Councils of each NIH Institute prepare biennial reports describing the manner in which the Institute has complied with this section of the Act. Dr. Kalt's presentation summarized the most recent NCI report; the format was designed by a central committee at NIH overseen by the Office of Research on Women's Health.

Information on this policy is published in *The NIH Guide to Grants and Contracts* on both the NCI and NIH Web sites. Dr. Kalt explained that consideration of the population in studies involving human subjects is part of the merit evaluation of every grant application and review, and applications with unacceptable plans are not funded. Subject accrual is a component of each grant recipient's annual report and is included in the final published results. For the purposes of this report requirement, the NIH mandates that all the results from Phase III treatment trials, behavioral trials, and epidemiological studies are reported in a single table, and these are aggregated for the biennial report.

Dr. Kalt presented data showing that accrual to treatment trials is robust and proportionate to subjects' recognition that participation has a direct benefit on their health. Accrual to prevention and screening trials is more challenging with respect to underserved populations. NCI funds basic research to address the issues of methodology and recruitment and conducts outreach programs on proportionate accrual at national meetings.

In 1997, in anticipation of the year 2000 census, the Office of Management and Budget (OMB) redefined race by racial and ethnic standards—"Hispanic" was to be reported as an ethnicity rather than a race—and stated that all Government agencies put this practice into effect by January 2003. This has had

an effect on the proportional inclusion data collated for reporting. Data on three categories (race, ethnicity, and gender) must now be included, resulting in two different inclusion enrollment forms, depending on when the study started to collate these data.

Dr. Kalt presented extramural accrual data from FY 2001 and FY 2002 showing the racial/ethnic breakdown of enrolled subjects using both the old and new formats. He clarified that the relatively large number of Asian subjects enrolled was the result of specific population studies in Japan and China. Breakdown by gender revealed an overrepresentation of females in aggregate due to the large number of epidemiological studies performed in breast and gynecologic cancers. Cumulative enrollment data from trials sponsored by the Cancer Therapy Evaluation Program (CTEP) over the same period demonstrates a more proportional gender balance, as CTEP sponsors more studies that affect both genders. The CTEP data also present good representation from all the minority groups in proportion to their burden of disease.

Results from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial of almost 155,000 subjects were presented to demonstrate reasonable representation by both gender and individual racial and ethnic group. Dr. Kalt concluded by presenting intramural data on 1.2 million subjects from the Division of Cancer Epidemiology and Genetics (DCEG) showing that breakdown by sex and gender is extremely well balanced in intramural research trials.

Motion. A motion to approve the Biennial Inclusion Report as presented was seconded and approved unanimously.

Distribution of Awards by Division

This topic was not discussed by the Board at the meeting. A report summarizing the distribution of the FY 2002 budget among the various NCI research programs is included in the Board Book.

Questions and Answers

In response to a question from Dr. Samir Abu-Ghazaleh, Gynecologic Oncologist, Avera Cancer Institute, Dr. Kalt stated that people from the Middle East can choose their preferred racial designation. This would primarily be “white,” but almost one-third of the people asked to complete the forms choose not to identify their racial designation.

Dr. Chen asked whether there was any way to standardize classification for all the participants other than self-identification. Dr. Kalt replied that people can be informed that their response will be confidential—a part of building trust with subjects accrued to trials—but, despite NCI’s best efforts, it is not an issue that can easily be resolved.

Dr. Huerta congratulated the NCI and the NIH for collating these data, as they will be extremely useful in the future.

CLOSED SESSION

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).

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 that it would represent the appearance of a conflict. Members were asked to sign a conflict of interest/confidentiality certification to this effect.

The en bloc vote for concurrence with all other IRG recommendation was affirmed by all serving Board members present. During the closed session of the meeting, a total of 1,672 applications were reviewed requesting support of \$490,392,199. Funding for those 1,616 applications was recommended at a level of \$476,674,550. The meeting adjourned at 5:40 p.m.

DAY TWO—WEDNESDAY, FEBRUARY 12, 2003

**IX. STOMACH AND ESOPHAGEAL CANCER PROGRESS REVIEW GROUP REPORT—
DRS. ERNEST HAWK, TIMOTHY EBERLEIN, AND BRIAN REID**

Dr. Ernest Hawk, Chief, Gastrointestinal and Other Cancers Research Group, Division of Cancer Prevention (DCP), NCI, was unable to attend.

Dr. Timothy Eberlein, Bixby Professor and Chair, Department of Surgery, and Director, Alvin J. Siteman Cancer Center, reported on the Stomach and Esophageal Cancer PRG. The initial meeting of the PRG convened in May 2002 to discuss population management. Four populations—at-risk, early-stage, late-stage, and metastatic disease—were identified for three diseases: squamous cell carcinoma of the esophagus, esophageal adenocarcinoma at the gastroesophageal junction, and adenocarcinoma of the stomach. Dr. Eberlein presented the PRG's 10 priority recommendations to advance research and address stomach and esophageal cancers.

Dr. Eberlein commented that in the United States, the incidence of these three diseases is very low, while the morbidity and mortality associated with these cancers is very high. Although only 35,000 new cases of esophageal and stomach cancer are diagnosed in the United States each year, stomach cancer has the fourth largest incidence of malignancy worldwide and is the second leading cause of cancer death. Cancer of the esophagus is the sixth leading cause of cancer death worldwide. These statistics provide an impetus for the NCI to take the lead in studying these diseases and form partnerships with international groups.

The incidence of adenocarcinoma of the esophagus (ACE) is on the rise among males and females in white and black populations in the United States. Dr. Eberlein remarked that studying different ethnic groups afflicted with esophageal or stomach cancer could provide useful epidemiological information associated with the prevention of or risk factors associated with these diseases. The initial recommendation made by the PRG was, therefore, to establish a network to conduct interdisciplinary, population-based studies identifying populations at risk for developing stomach and esophageal cancer. This network also would determine the prevalence and natural history of preneoplastic disease.

Dr. Eberlein discussed the neoplastic progression of both stomach and esophageal cancers. Progression is a multidecade process. Advances have been made in understanding how genomic instability is associated with the disease and identifying risk factors—such as obesity or gastroesophageal reflux disease (GERD)—that can be protective against one disease but predictive of another. Based on these findings, the PRG's second recommendation was for the development and evaluation of prevention strategies based on the mechanisms of host/environment interactions that lead to metaplasia and neoplasia of the stomach and esophagus.

Dr. Eberlein observed that 25 percent of patients with gastric cancer who are eligible for surgery are not recommended for surgery. Thus, the PRG's third recommendation focused on the development of a program to educate patients, their families, health care providers, and the public about risk factors, risk reduction, and treatment options and outcomes for gastroesophageal cancers.

Dr. Eberlein reported that subsequent recommendations focused on the identification and development of therapeutic targets based on the molecular and biological characteristics of a specific tumor. The 5-year survival rates for stomach and esophageal cancers in the United States are 22 and 14

percent, respectively. The PRG recommended that novel therapeutics be developed and tested and that existing treatments be optimized based on the understanding of the molecular mechanisms of premalignant disease.

Dr. Eberlein explained that recent advances in the understanding of the human genome, combined with the analysis of endoscopic biopsies during each stage of disease, enable researchers to correlate molecular changes with therapeutic treatments. The ability to analyze biopsies derived from all populations affected with stomach and esophageal cancers also provides the opportunity to identify molecular changes associated with the malignancy that could aid in defining at-risk populations as well as predict therapeutic responses. The PRG recommended that host- and molecular/biological-tumor characteristics be defined to customize treatments, as well as predict patient survival or recurrence of malignancy. In addition, molecular, cellular, and epidemiological factors of gastroesophageal tumors should be profiled to identify diagnostic, prognostic, predictive, preventive, and therapeutic targets.

Dr. Eberlein noted that patients with gastroesophageal tumors often have major functional problems associated with their disease and treatment, including total esophagectomy or gastrectomy, difficulty eating, and managing recurrence of malignancy after radiation therapy. To address these issues, the PRG recommended that disease-specific, patient-oriented methods to assess quality of life, quality of care, and cost effectiveness of treatment be developed for use with clinical trials and observational studies.

Dr. Eberlein commented that risk factors such as obesity, GERD, diet, infection with *Helicobacter pylori*, and molecular markers associated with malignancy can be used to develop prevention strategies. The PRG recommended identifying and validating genetic, biochemical, and biological markers to help identify at-risk patients. The PRG also recommended the development of new noninvasive and minimally invasive technologies for the screening and surveillance of premalignant and malignant gastroesophageal lesions. The final recommendation was for the development of preclinical models to understand the biology of these cancers and create preventive, diagnostic, and treatment strategies.

Dr. Eberlein concluded his presentation by stating that these recommendations provide an ideal opportunity to combine the resources of the Federal Government—Department of Defense, State Department, Fogarty International Program—with the leadership of the NCI to make progress on a group of malignancies that affect people in the United States and abroad.

Dr. Brian Reid, Member, Human Biology and Public Health Sciences Divisions, Fred Hutchinson Cancer Research Center, described the platform created to address the recommendations made by the PRG: the Stomach/Esophageal Neoplasia Translational Research Network (SENTRNet). Because of the low incidence rate and high mortality rate of these cancers in the United States, collaborations are essential, especially with international agencies. SENTRNet is a multidisciplinary, inter-institutional partnership that provides the platform for all of the researchers and institutions involved.

Dr. Reid explained that SENTRNet provides centralized centers for administration, informatics, and pathology, built on associations with several clinical centers that provide patients and gastroenterologists. Virtual tissue repositories would be created to share tissue samples. Translational laboratories would perform molecular characterization on the biopsies in the tissue repositories, and analytical centers would identify risk and protective factors through patient questionnaires. Dr. Reid

mentioned that a multicenter study approach has already led to the identification of risk factors associated with esophageal adenocarcinoma.

To describe how SENTRNet would enable progress, Dr. Reid presented research data from endoscopic population studies, the PRG's first priority. Through collaboration between gastroenterologists and research laboratory scientists, genetic abnormalities associated with risk for progression to cancer within 2 years were identified. Another collaboration determined that use of nonsteroidal anti-inflammatory drugs (NSAIDs) resulted in a decrease in the number of p53 lesions, a genetic abnormality predictive of progression to cancer. Dr. Reid commented that this initial work supported the PRG's second recommendation for the development of prevention strategies.

In terms of the PRG's recommendation regarding patient and provider education, Dr. Reid explained that it was difficult to find advocates, and that their major complaint was that neither they nor their providers were up to date on treatments for their conditions. Educating the public and providers about who is at risk for developing gastroesophageal cancers, how to monitor that risk, and what protective factors are available is a PRG priority that will be addressed through the Cancer Information Service.

Dr. Reid explained that recommendations on therapy, identification of molecular targets, and molecular profiling all focused on improving both existing therapies and novel treatment strategies. He described how initial findings on cancer-specific molecular targets have identified patients at risk for recurrence and have aided in improving treatments. Studies on photodynamic therapy in patients with Barrett's esophagus identified somatic genetic mutations in patients who did not respond well to treatment. Dr. Reid noted that microarray analysis of endoscopic biopsies from these patients was performed to identify gene expression patterns altered after therapy, or even after recurrence.

Dr. Reid noted that before creating SENTRNet, a review of existing programs (e.g., SPOREs and Cancer Cooperative Groups) was conducted; it was determined that these could not adequately address the issues raised by the PRG. Dr. Reid concluded by emphasizing that the NCI funding of SENTRNet, along with collaborations with other grant mechanisms in the Federal Government, could address many of the recommendations identified by the PRG.

Questions and Answers

Dr. Chen asked Dr. Reid to describe the efforts that have been made to inform minorities of the risk factors and preventive measures for these cancers. Dr. Reid indicated that there is a lack of awareness about these cancers and very few advocacy groups are available to pass this information to the individual groups. Dr. Chen recommended partnering with the NCI-funded Special Populations Networks—especially those working with African Americans, Hispanics, and Asian/Pacific Islanders.

Dr. Niederhuber asked about Dr. Reid's roles at the University of Washington and the Fred Hutchinson Cancer Research Center. Dr. Reid stated that he is the Principal Investigator for the multidisciplinary Barrett's esophagus research program at the Fred Hutchinson Cancer Research Center. Dr. Reid mentioned other members of the multidisciplinary program and their association with either the University of Washington or the Fred Hutchinson Cancer Research Center.

Drs. Love, Huerta, Norton, Barker, and Niederhuber all complimented Drs. Reid and Eberlein on developing the SENTRNet program. Dr. Huerta commented that the high numbers of immigrants in the

United States, both from Latin America and Asia, provide a great opportunity to study minority populations under this program.

Dr. Norton asked why SENTRNet was not developed to be more like a SPORE, as this format has many advantages. Dr. Eberlein indicated that a SPORE would be constrictive considering the limited number of institutions that would be able to provide the basic scientists, clinicians, gastroenterologists, and pathologists with expertise in stomach and esophageal cancers. However, SENTRNet would like to use some of the concepts from SPOREs, such as the funding mechanism.

In response to a question from Dr. Freedman about intramural and extramural research interest in gastroesophageal cancers, Dr. Greenwald commented that scientists at the NCI have been studying stomach and esophageal cancers in Colombia, China, and the United States, and their involvement in SENTRNet would be valuable. Dr. von Eschenbach agreed with earlier comments and recommended that the Board focus on looking at the integration strategy to find better mechanisms to synergize extramural efforts with intramural activities.

X. MERIT AWARDEE PRESENTATION: MODULATORS OF PROSTATE CANCER METASTASIS—DR. BRUCE ZETTER

Dr. Bruce Zetter, Vice President for Research, Boston Children’s Hospital, and Charles Nowiszewski Professor of Cancer Biology, Harvard Medical School, presented promising early research results on prostate cancer metastasis using urine as a source of potential biomarkers. His work has focused on tumor metastases, which occur despite the highly efficient clearance of the millions of cells that can be released from a tumor into the bloodstream each day. Eventually, one or two migrating tumor cells cause a metastatic lesion. Dr. Zetter reviewed the concepts envisioned for this process and then described screening results using urine as the biofluid of choice for detection of circulating cancer markers.

Previously, circulating tumor cells were thought to form metastatic colonies at organ sites where they had become randomly trapped. Dr. Zetter reported that a specific interaction is now thought to occur between the tumor cells and the venular endothelial cells within the organ to be colonized as well as to adhesive molecules in the organ stroma. Subsequently, the tumor cells extravasate to form a cuff of cells around an arteriole, and subsequent micrometastases can develop into macrometastases. Dr. Zetter explained that the process is not, however, the ordered event originally envisioned. Mutations of gene regulators can cause dramatic changes in overall gene expression, some of which are random and others that might “preordain” a process under which tumors progress to the metastatic state.

Dr. Zetter remarked on the importance of distinguishing the genes that change during tumor progression from the ones that change in the benign tumor stage. This information can have diagnostic or therapeutic implications. Dr. Zetter referred to a recent article published by Dr. Todd Golub’s group in *Nature Genetics* describing a group of 17 genes that seem to represent a “signature” for metastasis. Dr. Zetter has been interested in studying those proteins that are expressed as tumors and that undergo the transition from benign to metastatic. He stated that these proteins may prove to be good prognostic markers.

Dr. Zetter described how current diagnosis of prostate cancer using the prostate-specific antigen (PSA) marker cannot distinguish between localized and metastatic cancer. Dr. Zetter also defined the terms prognosis and prediction by explaining that patients want information about what will happen in the

course of their disease—i.e., prognostic markers—whereas insurance agents want information that could lead to a change in the treatment of the patient—i.e., predictive markers. There is a need for markers, other than PSA, that have prognostic and/or predictive value in prostate cancer.

Dr. Zetter decided to study proteomics rather than genomics to avoid the requirement for cell capture. He also recognized that modifications of proteins can be detected in circulating fluid—although, as a drawback, proteomic studies in general have a lower level of sensitivity than genomic studies. Dr. Zetter also decided to use urine because it can be collected noninvasively. Doctors do not mind asking for it; patients do not mind providing it; and importantly, institutional review boards do not mind this type of biological sample collection. Dr. Zetter discussed some of the challenges in urinary proteomics, such as low protein concentration and small number of proteins, but ultimately, he felt that the information potentially provided by urinary proteins should be extremely important.

Dr. Zetter reported that his laboratory analyzes urine proteins using two-dimensional gels, although within the next 2 years, he hopes to use new mass spectrometry technology to directly identify the approximately 300 urine proteins they are now studying. Four analysis groups are currently being collected: controls, untreated prostate cancer patients, treated patients, and patients who have been treated and who again have high PSA levels suggestive of disease recurrence. The level of each of the identified proteins can be followed in individual patients; however, protein patterns have not yet been accepted by diagnostic companies, and protein identification is required. Dr. Zetter described the identification of three different proteins with diagnostic potential: tetranectin, osteopontin, and thymosin beta 15. Future plans include exploring the role of these proteins by investigating the phenotype and metastatic potential of cancer cells into which these proteins have been introduced. An ELISA—enzyme-linked immunosorbent assay—has been developed for thymosin beta 15 and may be useful in identifying patients who will become PSA return patients. Dr. Zetter concluded by remarking that the urinary proteome is a potential tool for biomarker discovery and that pattern analysis may augment use of individual markers.

Dr. Zetter thanked the Board for providing an opportunity for MERIT awardees such as himself to present their work.

Questions and Answers

In response to questions, Dr. Zetter noted that he did not try to concentrate prostate secretions in urine samples because he wanted to develop a model that might be of use for cancer situations other than that of prostate cancer. He noted that urine proteins are a reflection of blood proteins and not an independent source of early markers. He also explained that his research group uses both creatinine and overall protein levels to standardize the different urine samples. Dr. Zetter confirmed the importance of knowing both filtration and protein levels to make comparisons between patients' urine proteins.

In a discussion following the questions, Dr. Zetter encouraged the NCI to help stimulate cross-platform analysis within cancer studies. He felt that a centralized effort will be required to integrate prostate cancer studies that research the genome and proteome in both tissues and secretory fluids. Dr. Zetter also encouraged the NCI to help promote development of tools to commercialize basic findings that have clinical application. On this last point, he referred to his own experience developing an ELISA after he realized that immunohistochemistry was less valued by diagnostic companies.

XI. SUBCOMMITTEE REPORTS/NEW BUSINESS II—NCAB MEMBERS

Ad Hoc Subcommittee on Confidentiality of Patient Data

Dr. Armitage reported that the Ad Hoc Subcommittee on Confidentiality of Patient Data is arranging a meeting in June with an expert on the Health Insurance Portability and Accountability Act (HIPAA) before making any recommendations to the Board. In the interim, the Subcommittee plans to poll Cancer Centers and groups to identify what they perceive to be the major problems associated with the implementation of HIPAA. These problems will be discussed at the June meeting.

Minutes of the Ad Hoc Subcommittee on Confidentiality of Patient Data have been prepared, edited, and approved by the Subcommittee's Chair and Executive Secretary, and submitted to the NCAB and the NCAB Executive Secretary under separate cover.

Subcommittee on Planning and Budget

Minutes of the Subcommittee on Planning and Budget have been prepared, edited, and approved by the Subcommittee's Chair and Executive Secretary, and submitted to the NCAB and the NCAB Executive Secretary under separate cover.

Subcommittee on Clinical Investigations

Minutes of the Subcommittee on Clinical Investigations have been prepared, edited, and approved by the Subcommittee's Chair and Executive Secretary, and submitted to the NCAB and the NCAB Executive Secretary under separate cover.

Ad Hoc Subcommittee on Bioinformatics Vocabulary

Minutes of the Ad Hoc Subcommittee on Bioinformatics Vocabulary have been prepared, edited, and approved by the Subcommittee's Chair and Executive Secretary, and submitted to the NCAB and the NCAB Executive Secretary under separate cover.

Motion. A motion was made to approve the minutes of the four subcommittee meetings presented. The motion was seconded and unanimously approved.

There was no new business conducted at this time.

XII. ADJOURNMENT—DR. JOHN NIEDERHUBER

There being no further business, the 125th meeting of the National Cancer Advisory Board was adjourned at 10:50 a.m. on Wednesday, February 12, 2003.

6/10/03

Date

/s/

John E. Niederhuber, Chair

6/10/03

Date

/s/ Dr. Long for

Marvin R. Kalt, Executive Secretary