

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
NATIONAL CANCER INSTITUTE  
124<sup>th</sup> NATIONAL CANCER ADVISORY BOARD**

**Summary of Meeting  
December 4–5, 2002**

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

**NATIONAL CANCER ADVISORY BOARD  
BETHESDA, MARYLAND  
Summary of Meeting  
December 4–5, 2002**

The National Cancer Advisory Board (NCAB) convened for its 124<sup>th</sup> regular meeting on Wednesday, December 4, 2002, in Conference Room 10 of Building 31, National Institutes of Health (NIH), Bethesda, MD. The meeting was open to the public on Wednesday, December 4, 2002, from 8:30 a.m. to 3:15 p.m. The meeting was closed to the public from 3:15 p.m. until adjournment at 5:00 p.m. The meeting was reopened to the public on Thursday, December 5, 2002, at 8:30 a.m. until adjournment at 12:00 noon. NCAB Chair Dr. John E. Niederhuber, Professor, University of Wisconsin Department of Surgery, 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. Susan M. Love  
Dr. Larry Norton  
Ms. Marlys Popma  
Dr. Franklyn Prendergast  
Dr. Amelie G. Ramirez  
Ms. Lydia G. Ryan

**President's Cancer Panel**

Dr. Harold P. Freeman  
Dr. LaSalle D. Leffall, Jr.

**Alternate Ex Officio NCAB Members**

Dr. Steven K. Akiyama, NIEHS  
Dr. Hugh McKinnon, EPA  
Dr. Peter Kirchner, DOE  
Dr. Thakor Patel, VA  
Dr. Richard Pazdur, FDA

**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—WEDNESDAY, DECEMBER 4, 2002**

**I. INTRODUCTION, WELCOME, AND ACCEPTANCE 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 a new Board member, Dr. Frank Prendergast, Director of the Mayo Clinic Comprehensive Cancer Center and a former member of the NCI Board of Scientific Advisors (BSA). 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.

**II. APPROVAL OF FUTURE MEETING DATES THROUGH 2004—  
DR. JOHN E. NIEDERHUBER**

Dr. Niederhuber called Board members' attention to future meeting dates listed in the Agenda. Dates have been confirmed through 2004.

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

**III. NCI DIRECTOR'S REPORT—DR. ANDREW von ESCHENBACH**

Dr. Andrew von Eschenbach, Director, NCI, reported that the Department of Health and Human Services (DHHS) is preparing for a transdepartmental initiative to address disparities in health care. The NCI has been asked to provide leadership in the genesis of this program by developing infrastructure and providing a specific focus on cancer. The principles and operational plans developed by NCI will be exported to health care in general. This underscores the importance of the NCI in transforming health care and accelerating the promise of biomedical research.

**Staff Changes**

Dr. von Eschenbach announced the appointment of Dr. Anna Barker as the NCI's Deputy Director for Strategic Scientific Initiatives. Dr. Barker served as a senior vice president at Battelle and went on to develop her own biotechnology company. She has been a leader within the American Association for Cancer Research (AACR) and helped develop that organization's report presenting a blueprint for action to expand cancer research. Dr. Barker's role at the NCI will be to promote the transition from discovery to intervention development through trans-Institute collaborations. The next steps in his effort to reorganize NCI leadership, Dr. von Eschenbach added, will be: (1) recruitment of a Deputy Director to provide leadership in the transition from intervention development to delivery of care through clinical research and direct testing of interventions; and (2) recruitment of a Deputy Director for Management to work closely with John Hartinger, the NCI's Chief Financial Officer, in implementing administrative and fiscal management policies.

Dr. von Eschenbach reported that Ms. Dorothy Foellmer has moved from the Office of Legislative Affairs to serve as his Chief of Staff. Susan Persons and Kathleen Chalmers are serving in the Office of the Director (OD) as Program Coordinators to work with the intramural and extramural programs. Recruitment is underway to select a Director for the Division of Cancer Treatment and Diagnosis (DCTD); Dr. Ellen Feigal is serving as Acting Director. Efforts have been initiated to fill the position of Director of the Division of Cancer Control and Population Sciences (DCCPS) following the departure of Dr. Barbara Rimer to join the faculty of the University of North Carolina School of Public Health and become Deputy Director of the Lineberger Cancer Center; Dr. Robert Croyle is serving as Acting DCCPS Director. The NCI is also searching for a replacement for Dr. Robert Hiatt, Deputy DCCPS Director, who is joining the University of California at San Francisco as Director of Population Sciences and Professor of Epidemiology.

Dr. von Eschenbach noted that K. Vish Viswanath has assumed Dr. Croyle's position as Acting Associate Director for Behavioral Research, and he welcomed Dr. Edward Trapido as Associate Director of the Epidemiology and Genetics Research Program.

Dr. von Eschenbach stated that reorganization of the Office of Communications is ongoing. Melvis Castro and Marianne Bright are serving as Acting Deputy Director and Acting Director, respectively. Mary McCabe is working in the Office of Education and Special Initiatives, and Jill Bartholomew has moved on to another agency.

Dr. Harold Freeman has continued to develop the staff of the Center to Reduce Cancer Health Disparities (CRCHD), having recently added Dr. Nadarajen Vydelingum to his staff.

### **NCI Planning Activities**

Dr. von Eschenbach noted that in addition to recruitment, the Institute has been devoting a great deal of effort to creating an effective management team through a series of retreats for senior staff. These retreats have addressed the development of a long-term strategic plan as well as focusing on team development. Randy White, who has been with the Center for Creative Leadership and helped develop leadership in the corporate and academic worlds, has been brought into these retreats as a consultant.

An important part of the strategic planning process, Dr. von Eschenbach added, is the Bypass Budget; the 2004 edition of this document has been made available to the Board and will soon be available on line. The Bypass Budget process is being examined with the aim of creating mechanisms to obtain input into its development from the larger cancer research community. The Bypass Budget not only continues its emphasis on the investigation of fundamental mechanisms within the cancer cell, but also emphasizes discovering interactions between cancer cells and the environment on the macro and micro levels and developing of new technologies required to increase understanding of these interactions.

Other planning efforts are ongoing, Dr. von Eschenbach reported. A P30/P50 Working Group charged with addressing future development of the Cancer Centers program and Specialized Programs of Research Excellence (SPOREs) has completed its deliberations and is developing a report that will be shared with the NCAB. Another process currently underway is addressing future development of the NCI's facilities in Frederick, Maryland, and the scientific agenda pursued there; these deliberations will be coordinated with the implementation of resources and programs associated with the completion of the new NIH Clinical Center. Use of these resources will be integrated to address both fundamental discovery and translational delivery research.

NCI's long-range planning, Dr. von Eschenbach continued, is being performed in concert with similar activities under Dr. Elias Zerhouni's direction at the NIH. One of the NCI's most important trans-NIH collaborations is with the new National Institute of Biomedical Imaging and Biotechnology (NIBIB) and its Director, Dr. Roderic Pettigrew.

Along with long-range strategic planning, the NCI is beginning to map out a long-range business plan to allocate resources required over time to meet the Institute's goals. The recently launched National Lung Cancer Screening Trial, for example, is an effort that requires front-loading of resources to rapidly accelerate accrual. Cancer Centers and SPORes are another example of activities that require long-range efforts to ensure availability of resources. Dr. von Eschenbach explained that, in planning terminology, the Institute is moving from mechanism-based fund accounting to enterprise accounting.

The critical aspect of the planning process, Dr. von Eschenbach stressed, is strategic planning. The NCI must be able to define strategic initiatives that can be integrated through collaboration with efforts of the broader community to move the cancer agenda forward. Dr. Alan Rabson, NCI Deputy Director, has been leading a program of inviting key stakeholders from the extramural community to visit the NCI. These visitors meet with leadership within the Institute with whom they have relevant relationships to discuss their needs and expectations and gain their input into the planning process; they also have the opportunity to meet with the NCI Director for one-on-one interaction.

Dr. von Eschenbach noted that the NCI has had an opportunity to develop many new programs during the last few years. However, with the end of the doubling of the NIH budget, the NCI will have to be realistic about new initiatives. While resources will not be insufficient, expansion will be restricted. A significant number of opportunities and needs have been identified through Progress Review Groups and other activities; the NCI will have to be very careful in addressing these needs in the context of commitments that are already in place.

Dr. von Eschenbach pointed out that the launch of the National Lung Screening Trial (NLST) has been successful in part due to a very effective process that has been referred to as "harmonization." The trial requires seamless integration of an arm within the Prostate, Lung, Colorectal, and Ovarian (PLCO) trial—which is supported by the Division of Cancer Prevention (DCP)—and the American College of Radiology Imaging Network (ACRIN) arm, which is supported by the DCTD. The trial is being conducted in more than 30 institutions and has accrued approximately 6,000 patients. The NCI is looking for additional partners to help bear the financial burden of this trial. The American Cancer Society (ACS), which committed \$1M per year for 5 years early on, has decided to front-load its \$5M to create a public relations and education campaign to promote the trial. The ACS is also using its national grassroots network of volunteers to recruit patients; the target of 50,000 patients should be achieved within 18 months.

Similar cooperative efforts are being pursued on other fronts, including collaboration with the Avon Corporation and with pharmaceutical and biotechnology companies to accelerate clinical trial efforts and collaboration with the Food and Drug Administration (FDA) to accelerate the development of interventions based on advances in genomics and proteomics. This is an area the National Dialogue on Cancer (NDC) has been looking into through its Research Task Force, under the leadership of Dr. Barker.



### **Recognition of Dr. Barbara Rimer**

Dr. von Eschenbach, in presenting a token of appreciation from the NCI to Dr. Rimer, mentioned that before joining the NCI staff, she had served a term as Chair of the NCAB. He stated that she has been an enormous asset to the Institute and that she will continue to play an integral role in the cancer research community. Dr. Rimer said that the reason for pursuing her new opportunity is her commitment to training and education. She thanked Dr. von Eschenbach for his support and expressed her commitment to his vision for the NCI. She urged the NCAB to address the recruitment of bright young people into public service as an important challenge for the Institute. She also recognized and thanked the NCI Executive Committee, OD, DEA, Office of Communications, DCCPS, and other NCI staff for the privilege of working with them. In pointing out the accomplishments of the DCCPS over the past few years, Dr. Rimer mentioned initiatives related to tobacco, genes and the environment, survivorship, behavioral research, quality and outcomes, communications, and expansion of the Surveillance, Epidemiology, and End Results (SEER) program. She identified dissemination of proven strategies and collaboration with partners around the world as the keys to improving population health.

### **IV. PRESIDENT'S CANCER PANEL REPORT—DR. LaSALLE D. LEFFALL**

Dr. LaSalle Leffall, Jr., Charles R. Drew Professor of Surgery, Department of Surgery, Howard University College of Medicine, Howard University Hospital, explained that this was his first appearance before the NCAB as Chair of the PCP. Dr. Leffall mentioned that he had served as a member of the NCAB from 1980 to 1986. He noted that another PCP member, Dr. Harold Freeman, was also in attendance; Dr. Leffall commended Dr. Freeman, his predecessor as PCP Chair, for his 11 years of leadership as well as for his distinguished career as a surgeon and oncologist. He added that the Panel's third member, Mr. Lance Armstrong, would be in attendance at meetings of the NDC and the PCP on Saturday, December 7, in Washington, DC.

Dr. Leffall explained that the PCP is charged with identifying barriers to optimal development and implementation of the National Cancer Program, soliciting testimony from the cancer community and the public on cancer-related research questions, and making recommendations to the President. In its 2001 report, the Panel examined the critical issue of barriers that prevent Americans from all receiving timely and effective cancer care. Testimony from nearly 400 people culminated in a report entitled *Voices of a Broken System: Real People, Real Problems*, which was presented to the NCAB last year.

One important conclusion of this report was that no person in America with cancer should go untreated, experience insurance-related delays in diagnosis and treatment, or be bankrupted by a diagnosis of cancer. While he was not a PCP member when this report was written, Dr. Leffall said, he fully embraces its conclusions and recommendations.

The PCP is now asking what roles other organizations can play in evaluating and implementing the Panel's recommendations. The December 7 PCP meeting is designed to gather feedback from NDC working groups on the recommendations contained in the 2001 PCP report. The partners collaborating in the NDC represent a wide range of stakeholders in access to and delivery of cancer care. The Panel hopes that this discussion will generate ideas for follow-up by the PCP and other stakeholders. Dr. Leffall promised to report to the NCAB in February on the December 7 PCP meeting.

Dr. Leffall invited NCAB members to attend the PCP meeting—from 2:00 to 4:00 p.m., at the Marriott Wardman Park Hotel in Washington—following the 1:30 adjournment of the NDC meeting. He

announced that the PCP is also planning an international meeting for May 25–27, 2003, in Lisbon, Portugal, to continue examining the gap between discovery and delivery. This meeting will follow the 12<sup>th</sup> *Reach to Recovery* International Conference in Lisbon. Two additional meetings will be held in September 2003.

Dr. Leffall reported that the PCP is developing a report on its July 2002 meeting in Washington State: *A Dialogue Between the Yakama Nation and the President's Cancer Panel*. The report will highlight cancer care issues and initiatives among American Indian tribes of the Pacific Northwest and provide recommendations for improving local care and translating findings to other tribes.

#### V. INTERIM FISCAL 2003 RPG FUNDING POLICY—MR. STEPHEN HAZEN

Dr. von Eschenbach introduced Mr. Stephen Hazen, Chief, Extramural Financial Data Branch, NCI. Mr. Hazen noted that the NCI is operating at FY2002 funding levels under a continuing resolution that will be in effect until at least January 11, 2003. All NIH components are continuing to make grant awards but are doing so under restraint. The Institute is optimistic that the President's requested 12 percent increase will be approved, but interim policies are required to account for uncertainty in the budget. These temporary policies will be revisited when the final budget has been approved.

Mr. Hazen reviewed principles that have guided the NCI Executive Committee in establishing temporary fiscal policies. Type 5 noncompeting grants are being paid at committed levels; cost-of-living increases promised in the Notice of Grant Award are being honored. This requires \$122M more than was paid for Type 5 grants last year.

To protect ongoing research represented by Type 2 competing renewal applications, the interim policy is to set the Type 2 R01 payline at the 17<sup>th</sup> percentile and the Type 1 payline at the 12<sup>th</sup> percentile. Type 2 grants will be paid at the same level as last year. Reductions from approved budget levels for Type 1 grants will be the same as those in effect in FY2002. No Request for Applications (RFA) awards will be made; payment for Type 1 awards will be restricted; and exceptions will not be funded. Provisional funding through March 2003 will be provided for any Type 2 R01s beyond the interim payline but within the 20<sup>th</sup> percentile, if they are having cash-flow problems.

Mr. Hazen reviewed a chart comparing funding policies for competing research project grants (RPGs) for FY2002, the interim period, and the President's budget request for FY2003. In 2002, the R01 payline was at the 22<sup>nd</sup> percentile, and 772 Type 1 and 2 grants were funded; 32 P01 grants were funded in rank order (there is no payline for P01s). Within the \$436M available for competing grants in 2002, almost \$25M was set aside for RFAs; the amount used for exceptions and supplements was \$88M. Other competing awards, including R03s, R21s, R33s, developmental grants, and exploratory grants, totaled 313.

The NCI estimates that if the interim funding policy were extended for a full year, 588 R01s and 24 P01s would be awarded, but the dollars available for competing awards would be reduced by about \$100M due to the commitment to Type 5s. The RFA set-aside would be \$25M, even though the NCI has published \$44M worth of RFAs due in FY2003. Under a flat budget or a budget significantly less than the President's request, RFAs will have to be reexamined. The interim policy significantly reduces funds available for exceptions and supplements as well as the number of other competing grants.

The NCI, Mr. Hazen noted, will continue to give preference to first-time R01 investigators. In 2002, these were funded at two points beyond the regular payline; during the interim, these will be funded at the same payline as Type 2s.

In 2002, Type 1 awards averaged a 10 percent reduction; this has not changed under the interim policy. Whereas Type 2s received an average 6 percent reduction in 2002, they will be held to current funding levels in the interim period.

## **VI. NIH DIRECTOR'S REPORT—DR. ELIAS A. ZERHOUNI**

Dr. von Eschenbach introduced Dr. Zerhouni by praising his passion for the scientific method, his contributions to the development of functional imaging, his service as a member of NCI's BSA, and his leadership since being appointed as Director of the NIH.

Dr. Zerhouni said he wanted to review his first 6 months as Director and share his thoughts on core directions his office has been formulating for the NIH. His first priority, based on feedback from the Congress and the Administration, is to develop a communication strategy to help the country understand what is being done with tax resources, especially in light of the doubling of the agency's budget. In terms of scientific challenges, Dr. Zerhouni stressed the need to focus on making a difference by translating basic research discoveries into real benefits.

Over the past summer, he reported, the Roadmap Initiative was created. More than 100 scientists came to NIH for brainstorming sessions on the following questions: What are the fundamental changes in how research is conducted? What are the roadblocks preventing discovery research and derivative research? What are some areas of opportunity that individual Institutes could not address alone but that fall within the mission of—and should be addressed by—the NIH as a whole?

Roadmap participants agreed that the way science is conducted has changed in a revolutionary way. The group developed four priority areas for addressing this issue.

The first priority is the need to enhance, develop, and diffuse new research methods into the conduct of science, such as bioinformatics, nanotechnology, and structural biology. Roadmap participants also stressed the need to improve the overall quality of research data. Many researchers suggested that access to technology is a stumbling block to their ability to conduct research. Dr. Zerhouni identified, for example, high-resolution robotics as one of the technological advances that have made the most difference in biomedical research over the past 10 years, contributing to a much greater density and quality of information as well as gains in the speed with which it is collected.

The second priority area that emerged from the Roadmap meetings concerns new pathways to discovery. Because of the complexity of biological systems, scientists have worked with simpler biosystems—for example, fruit flies, worms, and yeast—to understand basic mechanisms. New efforts to integrate disparate biological systems into a comprehensive system could lead to fundamental discoveries. The research community needs predictive models and mathematical approaches to identify crosscutting principles underlying the interactions and behaviors of complex biological systems under various conditions, such as disease. Dr. Zerhouni noted that this problem is illustrated by the recent focus on hormone therapy. Basic science in this field is inadequate because there has been no systems approach to discovering clustering or patterns of interacting biological pathways.

The third priority is to improve the clinical research enterprise to advance discoveries from bench to bedside and back, with the goal of preventing or delaying the onset of disease and improving patient care. Although, as Dr. Zerhouni observed, the NCI is more advanced than other Institutes with regard to bringing innovations to clinical research and clinical trials, in general, there are no common standards for clinical research, and there is no common language among clinical researchers. Networks exist, but they are not sufficiently interactive. Dr. Zerhouni pointed out that in his work on gene arrays in breast cancer, Dr. David Botstein had to select substantial portions of his sample from the Netherlands, because that country has a centralized clinical research data system that allows phenotype and genotype characterization; he could not find a large, well-characterized cohort in the United States. Dr. Zerhouni suggested that without improvements in the clinical research enterprise, the trust of Americans in the benefits of medical research would continue to erode.

The fourth priority relates to the likelihood that scientific teams of the future will be very different from those of the past 25 years: Teams will be larger, and scientific projects will be bigger and more interdisciplinary. There will be more coordination of projects among different laboratories within institutions and at diverse locations. Preparing for this future will require the participation of universities to develop new training pathways as well as a commitment from the scientific community to view associated scientific fields as intrinsic parts of the biomedical research process. Dr. Zerhouni said this may be the most difficult of the four priorities because it requires changes in the culture within which research is conducted.

### **Questions and Answers**

Dr. Larry Norton, Director, Medical Breast Oncology, Evelyn H. Lauder Breast Center, Memorial Sloan-Kettering Cancer Center, called attention to the need to keep up with the explosion of knowledge in the mathematical sciences. He suggested that one of the biggest problems facing biomedical research is trying to handle large amounts of data using eighteenth-century mathematical tools. On the issue of clinical trials, Dr. Norton agreed with Dr. Zerhouni's statement about the restrictions on correlation of data. There is a disconnect, he suggested, between the desire to protect individuals in terms of privacy and the desire to help those individuals by studying populations to learn about the relationships between environmental and behavioral factors.

Dr. Niederhuber asked whether the scientists who met during the summer discussed how scientists are trained and whether new approaches to training are needed to help young investigators function in the new scientific environment. Dr. Zerhouni replied that the scientists felt that training is at a crisis stage. One concern is a decrease in the number of physicians involved in clinical research. Another concern is that the lengthening of the time required to obtain a Ph.D. is postponing the achievement of an independent career. The number of grants awarded to first-time investigators has remained steady, but the average age of these new investigators is rising. Dr. Zerhouni said that the issues of training and multidisciplinary teams are ones he plans to raise with the Advisory Committee to the Director.

Dr. Susan M. Love, Adjunct Professor, Department of Surgery, University of California School of Medicine, argued that "baby boomer" researchers are being overlooked. The professional part of the life cycle is being extended as people live and work longer. Dr. Zerhouni noted that many physicians at the community level are well trained—or could be trained—in clinical research, but there are inadequate formal linkages between academic and community institutions. Dr. Zerhouni added that he does not subscribe to the division of research into basic and clinical areas; instead, he feels it is more useful to think in terms of original research and derivative research. Original research, which produces knowledge

that did not previously exist, can be basic or clinical; there is just as much derivative research in basic science as there is original research in clinical science. Dr. Love suggested that clinicians who have been practicing for long periods might be able to provide new insights that younger investigators may not perceive.

Another problem area, Dr. Love stated, is in the middle ground between basic and clinical research. The understanding of physiology and anatomy is not complete and, in some cases, not entirely accurate; attention has been focused on molecular biology and diverted from physiology. For example, she said, more is known about estrogen receptors than about what controls estrogen in different organs in postmenopausal women. Dr. Zerhouni replied that the cycle of reductionist and integrationist phases alternates in the history of science. He said that not everything is known about estrogen receptors, suggesting that new tools and pathways of discovery are needed to approach this complex question.

Dr. Jean B. deKernion, Professor and Chairman, Department of Urology, UCLA School of Medicine, asked Dr. Zerhouni to comment on how advances in the physical sciences can be brought into the realm of medical sciences—possibly through different approaches to education. Dr. Zerhouni said that this is a critical challenge, adding that substantial change is not likely to come from existing scientific teams but, rather, from a new generation. He suggested that the most promising approaches to the integration of the physical and biological sciences are not coming from medical schools. As an example, he cited a new program in biological engineering at the Massachusetts Institute of Technology (MIT). Two years ago, the program had only a few applicants; today, 40 percent of entering students want to go into that program. The program brings mathematics and physics together with biology and seeks to give biology the quantitative training that can bring understanding to the next level.

Dr. Amelie G. Ramirez, Associate Professor, Department of Medicine, and Deputy Director, Chronic Disease Prevention and Control Research Center, Baylor College of Medicine, asked about the role behavioral and social sciences have in multidisciplinary research. Dr. Zerhouni stated that progress in the twenty-first century will be determined by knowledge teams that cross disciplinary boundaries; the knowledge team must include social and behavioral scientists. A culture must be created within which multidisciplinary communication is intrinsic to research design. Fifty percent of disease burden, he said, relates to lack of understanding of behavioral factors.

Dr. Niederhuber expressed his thanks to Dr. Zerhouni for sharing his views with the NCAB, and Dr. Zerhouni responded by recognizing the great contribution rendered to the NIH and the nation by the NCAB and the 21,000 individuals who serve on other advisory boards, peer-review panels, and ad hoc committees. This is the only Federal agency, he noted, that has so much interaction with the various constituencies it serves.

## **VII. NEW BUSINESS I—DR. JOHN E. NIEDERHUBER AND NCAB MEMBERS**

Dr. Prendergast asked how quickly grant approval can be activated after the new budget has been approved. Dr. Kalt said that applicants should consult program directors at their institutions for advice on when and how to submit amended applications. As more information is developed, he added, it will be reported on the NCI Web site under Funding Policies. Dr. Niederhuber noted that communications have been received from individuals who have not reached the 20<sup>th</sup> percentile as to whether they should rewrite their applications. Dr. Kalt replied that should an application be resubmitted, the investigator will not be placed at risk; if the score given to a resubmission is lower than the score on the original application, the earlier score will be reactivated. Dr. Prendergast suggested that in order to reassure investigators, the NCI

respond promptly once a budget is approved to get the funding machinery activated. Dr. von Eschenbach said that the NCI is cautiously optimistic that the budget will be funded at or near the level requested by the President.

In opening the floor for new business, Dr. Niederhuber said that the NCI had asked him to raise two issues for the Board's consideration; he invited Dr. Kalt to describe these. Dr. Kalt stated that the Board is being asked to consider establishing an ad hoc subcommittee on bioinformatics vocabulary. For years, the NCI has maintained an in-house coding and classification system for its own research; elements of this system have been incorporated into a formal process to develop a nomenclature, called the NCI Enterprise Vocabulary System (EVS), which is used by all NCI components to characterize supported research. The EVS is housed with the NCI Center for Bioinformatics, headed by Dr. Ken Buetow. The system has attracted the attention of other cancer interest groups and research organizations. The NCI is looking for assistance in updating the system and harmonizing it with those used by partners throughout the cancer research community. A universal nomenclature will allow comparison of different data sets within and outside the NCI. The specific task for the subcommittee would be to advise the NCI on developing an appropriate infrastructure to address this globalization of bioinformatics vocabulary. If the Board agrees to help, the subcommittee will hold its first meeting during the February 2003 NCAB meeting. Dr. Niederhuber asked Board members interested in serving on this subcommittee to contact him; he asked Dr. Moon S. Chen, Professor, Department of Epidemiology and Preventive Medicine, and Associate Director for Cancer Prevention and Control, University of California–Davis, to serve as Chair *pro tem* of this group. He added that Dr. Frank Hartel, Director of EVS at the Center for Bioinformatics, will serve as the subcommittee's Executive Secretary.

The second item of business, Dr. Niederhuber continued, is reactivation of the ad hoc Subcommittee on Confidentiality of Patient Data, which would also have its first meeting in February. The group was first convened in 2000 to advise on NCI's efforts to establish best practices for ensuring patient confidentiality in cancer research settings. It provided comments on draft regulations based on the Health Insurance Portability and Accountability Act (HIPAA). The DHHS has now issued final regulations that need further assessment and comment from the NCAB. Dr. Niederhuber asked Dr. James O. Armitage, Professor and Chairman, Department of Internal Medicine, Oncology/Hematology Section, University of Nebraska College of Medicine, to serve as Chair *pro tem* and asked Board members to let him know if they are interested in serving on this subcommittee. Mary McCabe will serve as Executive Secretary.

### **VIII. LEGISLATIVE UPDATE—MS. SUSAN ERICKSON**

Ms. Susan Erickson, Acting Director, Office of Policy Analysis and Response, NCI, mentioned that the 107<sup>th</sup> Congress had adjourned on November 22, 2002, leaving a continuing resolution in place that will fund Government operations through January 11, 2003. The 108<sup>th</sup> Congress will be sworn in on January 7, 2003, and will have to approve a budget before the 11<sup>th</sup> or pass another continuing resolution.

Three bills passed by the 107<sup>th</sup> Congress have some relevance to the NCI: the Medical Devices User Fee and Modernization Act, which includes language stating that the NIH Director may conduct research into silicone breast implants; the Benign Brain Tumor Cancer Registries Act, which instructs state registries to collect data on benign as well as malignant tumors; and the Rare Diseases Act, which establishes an Office of Rare Disease Research at NIH.

The Republican Party will be in control of the Senate, and there will be new Committee Chairs. The full Appropriations Committee will be chaired by Senator Ted Stevens; the Labor, HHS, and Education Subcommittee by Senator Arlen Specter; the Health, Education, Labor, and Pensions Committee by Senator Judd Gregg; and the Public Health Subcommittee by Senator Bill Frist.

All unpassed bills from the 107<sup>th</sup> Congress have expired. Ms. Erickson said that some of these bills merit review because they indicate themes that can be expected to resurface in the new Congress. These themes include quality of cancer care, health disparities, prevention, and survivorship. Specific issues related to quality of care included standards of care, surveillance, communications, and core quality measures. Bills that addressed these issues included the Quality of Care for Individuals With Cancer Act and two bills addressing reauthorization of the National Cancer Act. Health disparity issues included the Patient Navigator model; early detection, treatment, and follow-up for medically underserved populations; and cultural competence in health care delivery. Some provisions of the prevention legislation focus on obesity. Since obesity is a risk factor for several cancers, this legislation could impact NCI. Survivorship issues included the potential to earmark funds for survivorship and establishment of an NCI Office of Cancer Survivorship (OCS). While this office already exists, legislation proposed in the 107<sup>th</sup> Congress would have given the OCS a statutory mandate to coordinate cancer survivorship research.

#### **IX. GENE EXPRESSION PROFILES PREDICT SURVIVAL OF LYMPHOMA PATIENTS AFTER CHEMOTHERAPY—DR. LOUIS M. STAUDT**

Dr. Louis M. Staudt, Chief, Lymphoid Malignancies Section, Metabolism Branch, Center for Cancer Research (CCR), NCI, presented recent work on the molecular diagnosis of cancer. This requires the use of gene expression profiling to define homogeneous disease entities. Gene expression profiling entails analyzing the entire genome of cancer cells and determining which genes are active and which are not. Gene expression varies considerably among tumors from different cancer patients, and it is this variation that is correlated with the clinical behavior of patients during treatment. Dr. Staudt explained that a well-defined cancer subtype must have a common normal cell of origin, a common mechanism of malignant transformation, and a uniform clinical behavior. The ultimate criterion is its clinical utility: whether it defines optimal therapeutic choice for patients and identifies new molecular targets for therapy.

Dr. Staudt indicated that the remainder of his presentation would focus on the clinical application of gene expression profiling in lymphoid malignancies, particularly diffuse large B-cell lymphoma, mantle cell lymphoma, and chronic lymphocytic leukemia (CLL). The tool used for gene expression profiling is a DNA microarray; the lymphochip microarray used in Dr. Staudt's laboratory was generated from DNA clones provided by NCI's Cancer Genome Anatomy Project (CGAP). A single microscope slide holds 20,000 spots, each representing a human gene. Thus, a large subset of the human genome can be studied at one time. Data analysis is performed by applying a variety of mathematical algorithms, such as hierarchical clustering, to a large data set. This helps organize the data by grouping genes that are similarly expressed across cancer samples and grouping cancer samples that have related patterns of gene expression.

After organizing genes in this fashion, gene expression signatures of various biological processes can be identified. Such gene expression signatures may represent a cell type or a stage within cell differentiation. The proliferation gene expression signature is a functional signature well represented in most microarray data; this signature includes genes that are expressed at high levels when the cell is dividing, and low levels when the cell is quiescent. Gene expression signatures of individual signaling pathways that may be abnormal in cancer have also been identified, such as that of the NF- $\kappa$ B pathway.

Dr. Staudt stated that gene expression signatures provide an “executive summary” of the cancer biopsy: The signatures may indicate whether the particular lymphoma sample is very proliferative, whether the cells are in a particular stage of differentiation, whether or not a large number of T cells are infiltrating the tumor, and whether a signaling pathway is active.

Dr. Staudt indicated that diffuse large B-cell lymphoma is the most common type of non-Hodgkin’s lymphoma, an aggressive malignancy derived from a mature B-cell subtype in the secondary lymphoid organs. While 40 percent of cases are treatable, this rate has not changed in the last 20 years despite attempts to change chemotherapy regimens. This prompted investigators to consider whether a malignancy with one morphologic diagnosis could represent many molecular diseases. Diffuse lymphomas were easily classified into two groups following preliminary gene expression profiling studies. Each group expresses a different set of genes and derives from a different type of normal B cell: One group derives from a normal germinal center B cell (GCB), while the other resembles an activated blood B cell (ABC) and may derive from a postgerminal center B cell.

Dr. Staudt explained that the Lymphoma/Leukemia Molecular Profiling Project (LLMPP) is an international group of seven institutions—including NCI’s Intramural Research Program (IRP)—that has as its goals establishing a molecular classification of human lymphoid malignancies and defining molecular correlates of clinical parameters that are useful in prognosis and in choosing optimal therapy. Through this consortium, a large number of lymphoma samples were collected for additional studies, allowing better mathematical and statistical analyses of the data. In these studies, a third group of large B-cell lymphoma tumors became apparent. Research is in progress to determine whether this group truly represents a distinct subgroup of diffuse lymphomas. The LLMPP studies, however, confirmed early findings regarding clinical differences in long-term survival of patients classified according to their gene expression profiles (GCB, a 60 percent 5-year survival; ABC, a 35 percent 5-year survival). Dr. Staudt emphasized that diffuse lymphoma is at least two different diseases, with different cells of origin, mechanisms of malignant transformation, and oncogenic events.

The LLMPP microarray data were further analyzed to determine the genes whose expression patterns correlated with favorable or poor outcomes. Results indicated that the genes that dictated level of survival were part of the gene expression signatures. The number one signature that predicted a poor outcome was the proliferation gene expression signature: More highly proliferative lymphomas were harder to cure. In contrast, the number one signature that predicted a favorable outcome was the GCB signature, probably because lymphomas derived from these cells do not have an antiapoptotic mechanism that prevents cell death. Two other signatures were found to be of critical importance for survival: MHC Class II molecules involved in antigen presentation to the immune system and the “lymph node signature,” which is a host reaction to the tumor in the lymph node. A single gene, *BMP-6*, was found to predict poor outcome.

Dr. Staudt noted that the advantage of this approach is that an outcome predictor score can be calculated and assigned to each patient. A high score predicts a poor outcome, while a low score predicts a favorable outcome. He explained that the predictive elements were then combined into a multivariate model, and patients were ranked according to their outcome predictor scores and divided into four quartiles to calculate 5-year survival rates. Based on this model, the top two quartiles had a 5-year survival rate of 70 percent, whereas the other two quartiles had 5-year survival rates of only 36 and 15 percent, respectively. Dr. Staudt stressed the clinical importance of the outcome predictor scores. A clinical test using the 17 characterized outcome predictor genes could identify biologically high-risk patients who might benefit from alternative therapeutic approaches.



A less common form of non-Hodgkin's lymphoma, but one that is universally fatal, is mantle cell lymphoma. In terms of length of survival following diagnosis, this disease is clinically heterogeneous. Analysis of mantle cell lymphoma microarray data showed variable expression of proliferation signature genes—a 13.5-fold difference in the expression of proliferation genes among the samples. Samples were again divided into four quartiles to calculate survival. In the most favorable quartile, the median survival is 6.7 years, and in the least favorable, it is 0.8 years. Dr. Staudt stated that, using this quantitative measure of tumor cell proliferation that can accurately predict the survival of patients, clinical trials of bone marrow transplant or high-dose chemotherapy should be pursued in patients with high tumor proliferation rates.

CLL is the most common human leukemia; it derives from a subtype of mature B cells. Two clinically distinct subtypes of CLL have been identified in recent years. One subtype has mutated immunoglobulin (Ig) genes, while the other has unmutated genes. Patients with the latter subtype have a progressive disease and need early treatment, whereas patients with the mutated genes have stable disease and require late or no treatment. Dr. Staudt explained that he was interested in finding molecular correlates of the two CLL subtypes because Ig gene sequencing could not be practically translated into a routine diagnostic test. He indicated that *ZAP-70* is the most differentially expressed gene between the Ig-mutated and Ig-unmutated CLL subtypes. Based on their *ZAP-70* gene expression, patients can be classified into two groups equivalent to their Ig mutational status in predicting time to disease progression. Thus, *ZAP-70* expression could be used as a diagnostic test: Low gene expression would merit a “watch and wait” strategy, while high gene expression would indicate early and intensive treatment. This approach is being investigated in clinical trials.

Dr. Staudt indicated that the ultimate goal is to be able to conduct small, tailored DNA microarrays for decision making in cancer treatments (e.g., multiagent chemotherapy, upfront bone marrow transplant, or new molecular targets). He then explained that in terms of new molecular targets, the NF-κB pathway appears to be a good candidate. This pathway prevents apoptosis, and the activity of the pathway can be tracked by determining the status of genes that are downstream targets of the NF-κB transcription factor. Analysis of NF-κB target gene expression in GCB- and ABC-diffuse large B-cell lymphomas showed a preferential expression of such genes in the ABC subtype. This finding was confirmed biochemically. Further studies showed that dominant inhibition of the NF-κB pathway kills ABC cells. The NF-κB pathway is a new therapeutic target for the most clinically intractable subgroup of diffuse large B-cell lymphomas. Dr. Staudt stated that these findings constitute a rational basis for a clinical trial of an available inhibitor of the NF-κB pathway, PS-341, in diffuse lymphoma patients. This agent might have synergistic activity with chemotherapeutic agents because the NF-κB pathway is known to block the action of standard chemotherapy.

Dr. Staudt focused the last portion of his presentation on how gene expression profiling will be translated to the clinical setting. He indicated that for some clinical trials, gene expression profiling (e.g., *ZAP-70*) could be implemented immediately. However, in most instances, a “molecular diagnosis cycle” would be required, entailing genomic-scale gene expression profiling to build molecular predictors of response and create a diagnostic test for routine clinical use. Dr. Staudt explained that this translational process must be a cycle, because some patients might not be cured—hence, the need for testing new therapies, reiterating the discovery cycle of correlates of survival, and creating new diagnostic tools. The benefits of applying genomic-scale gene expression profiling include: generating new outcome predictors for each arm of the trial; identifying subsets of patients who respond better to one treatment arm than the other, allowing subsequent patient-specific therapy and preventing promising new drugs from being

discarded; and allowing clinical trials to be compared with respect to patient enrollment, providing a scientific basis for clinical trial design and analysis.

Dr. Staudt concluded his presentation by listing barriers to implementing molecular profiling in clinical trials. Most patients receive their diagnostic biopsy in a community setting; molecular profiling in a clinical trial would require a second biopsy, which may not be feasible or reimbursable. Biopsy specimens must retain integrity of biomolecules; frozen biopsies are usually not stored. New methods are under investigation that may allow the preservation of biomolecules at room temperature. Finally, patients and physicians alike must be educated about the value of molecular profiling of cancer. NCI-designated Cancer Centers could lead the way in this process.

### **Questions and Answers**

Dr. Ralph Freedman, Professor, Department of Gynecologic Oncology, M. D. Anderson Cancer Center, asked whether gene expression profiling could identify patients who would not benefit from therapy and whether the paradigm described for lymphomas could be applied to other cancer types. Dr. Staudt replied that in the case of diffuse lymphoma, patients may or may not be cured, and this is predictable through gene expression profiling. In mantle cell lymphoma, nobody is cured, but chemotherapy may be administered to improve quality of life rather than survival. In this case, the information obtained through gene profiling may be considered a clinical management benefit. Regarding the application of this molecular tool to other cancer types, Dr. Staudt indicated that breast cancer is one tumor type for which the probability of metastasis can be predicted from the initial diagnostic biopsy. Approximately 70 outcome predictor genes have been identified for breast cancer. Thus, patients with the most favorable profiles may be spared some therapy. Similarly, outcome predictor genes have been identified for brain and prostate cancer.

Dr. Armitage expressed concern about the impact of the HIPAA regulations on clinical trials involving gene expression profiling. He mentioned that if the requirement of having patients' permission to study their biopsies had been in force years ago, the studies presented by Dr. Staudt would not have been conducted. He indicated that the "law of unintended consequences" might hurt more people because it does not allow the advancement of knowledge. Dr. Staudt echoed Dr. Armitage's concern and requested that NCI as well as the NCAB address with high priority any impediments imposed by HIPAA.

Dr. Prendergast asked whether clinical trial design and the meaning of *standard of care* should be revisited. He wondered when it might become unethical to continue conducting clinical trials as currently done and whether profiling tools should be used to segment the patient population before conducting clinical trials. Dr. Love expanded on Dr. Prendergast's questions by asking Dr. Staudt whether he believed gene expression profiling was ready for the clinical setting. Dr. Staudt replied that for CLL, routine diagnosis could be performed today. For mantle cell lymphoma, identification of who does and who does not have highly proliferative tumors should be performed through quantitative determinations. For diffuse large B-cell lymphoma, new therapies are needed. Regarding the stratification of patients for different treatments, Dr. Staudt indicated that this would vary for different cancer types on a case-by-case basis.

Dr. von Eschenbach acknowledged the contributions of Dr. Staudt and stated that this work could be seen as a model that reflects NCI's agenda in terms of assembling teams and expanding on the concept of NCI faculties that has been promoted as part of the IRP. He explained that while NCI needs to assemble a bioinformatics and emerging technology agenda around the scientific discovery process, there

are issues outside NCI's control, such as patient confidentiality and policies that need to be addressed by Congress. Dr. Niederhuber added that Dr. Staudt's presentation was also exemplary in terms of the partnership between the IRP and the extramural program.

## **X. LUNCH—OPEN DISCUSSION**

Dr. Niederhuber proposed an NCAB retreat to discuss ways in which the Board could help the NCI Director and Division Directors in planning for the future. He asked Board members to suggest themes and issues that could be addressed during a retreat.

Dr. Prendergast raised the issue of the potential of new HIPAA privacy rules to disrupt the research enterprise. The cost of implementing these new regulations should not be underestimated. Assistance to the NCI in developing policy positions on this issue would be useful to the research community as a whole.

Dr. Niederhuber said that many people have raised questions concerning cooperative groups. He asked Dr. Norton for comments on whether this might be an appropriate area for the NCAB to consider. Dr. Norton indicated that cooperative groups are an important part of the infrastructure of clinical research and must play a role in streamlining the process. Because the NCAB represents all aspects of the cancer research community, it is in a position to bring a broad perspective to the table. Issues that need to be discussed include the public's understanding of clinical trials and community expectations about the benefits of trials. Access to tissue samples is a critical issue, not just in terms of HIPAA regulations, but also in terms of the mechanics of obtaining, processing, and storing tissue, which places a burden on an already overburdened clinical care system. Dr. Norton suggested that this issue is broader than the interests of scientists; the public would probably demand better access to tissue if they understood the implications. Thus, he concluded, issues related to clinical trials should not be limited to the role of cooperative groups but should be placed in a broader context.

Dr. Niederhuber agreed that providing advice on tissue acquisition would be a major accomplishment. He suggested that the issues of tissue acquisition on a national level could be combined with a discussion of central Internal Review Board (IRB) issues.

Dr. Armitage noted that Cancer Centers often have to justify their plans to store tissue, when it would make more sense that institutions be required to demonstrate their ability to store tissue before receiving Cancer Center funding. Receipt of NCI funding should be contingent on collection of tissue samples.

Dr. Armitage stated that although the NCI is primarily a research institution, the Government's mandate in establishing the Institute was not limited to supporting research, but also included a mandate to ensure that cancer care is delivered. The NCI could have an impact on educating both young physicians and the American people about cancer and cancer research. Dr. Armitage also suggested that the NCAB discuss possible roles the NCI could play in addressing the cancer burden in the developing world.

Dr. Love said that one problem with access to tissue is that pathologists often feel they "own" tissue samples. Standardized consent forms could help ensure that patients and pathologists are comfortable with storing tissue.

In response to Dr. Armitage's comments about the responsibility to ensure delivery of care, Dr. von Eschenbach agreed that the Congress and the American people have expectations that new knowledge will be applied and outcomes measured. The development of the NCI's scientific agenda and business plan will incorporate a strong sense of accountability and responsibility, and the NCI will be responsive to the Office of Management and Budget (OMB) and the Administration with regard to performance-based evaluation. Dr. von Eschenbach suggested that the NCI has an opportunity to demonstrate that the continuum of discovery, development, and delivery has a positive impact on people's lives. An example of this approach is his charge to the P30/P50 Working Group to address questions of how Cancer Centers interact with their communities to deliver state-of-the-art care in the context of clinical trials and other projects.

Another infrastructure issue, Dr. von Eschenbach continued, is the need to facilitate enabling technologies, especially those related to tissue acquisition. An NDC research task force has been focusing on this issue, and Dr. Barker has been involved in writing a White Paper on components of that effort.

Dr. Barker indicated that the task force included broad representation from all of the sectors involved in cancer research, intervention development, and care delivery. The group focused on how to harvest the potential of genomics and proteomics and identified about 20 important barriers. Of the three barriers the group selected for detailed examination, the first was the issue of tissue access, which is critical to those researching molecular targets—whether for cancer, diabetes, or other diseases. There are about 207 million tissue samples in the country today, but most of them are not usable, having been acquired without quality control; other samples are good, but the researchers are not willing to share them. The new HIPAA rules are an additional factor for which a national strategy has not been developed. What may be needed is a distributed repository and a national database. This could make it possible to get information without direct access to tissue. This is an area in which the NCI could take a leadership role.

Other issues the group is addressing, Dr. Barker continued, include surrogate endpoints and ways to increase the investment of the private sector in drug discovery and development. She mentioned the example of cholesterol as a surrogate for cardiovascular disease. The cancer research community, she noted, may have done itself a disservice by convincing the FDA that cancer biomarkers must be on the causal pathway. Drug development is a high-risk activity for the private sector because the trials are long and there are many targets to be explored. The NCAB could help the NCI understand how to build needed relationships.

Dr. Barker concluded by stating that the NCI is beginning to play a role as a systems integrator with responsibility for developing national strategies. The Board could make a huge contribution by providing leadership on behalf of the various sectors members represent.

## **PROGRAM REVIEW OF DIVISION OF CANCER EPIDEMIOLOGY AND GENETICS**

### **XI. INTRODUCTION—DR. JOSEPH FRAUMENI**

Dr. Joseph Fraumeni, Jr., Director, Division of Cancer Epidemiology and Genetics (DCEG), NCI, presented DCEG's operating philosophy of identifying through epidemiologic analysis the causes of cancer and discovering new approaches to cancer prevention. The DCEG devotes resources to identify the roles played in cancer etiology by environmental factors, inherited genes, and genetic susceptibility. Particular emphasis is placed on transdisciplinary, population-based research to uncover the interactions between genes and the environment and identify opportunities for preventive interventions.

Dr. Fraumeni described the DCEG as a highly interactive group of scientists whose transdisciplinary team approach to their investigations is designed to complement extramural activities. The DCEG has the capacity to respond to and investigate emerging public health concerns and scientific opportunities, as well as undertake long-term, high-risk studies that will inform biologic concepts, clinical decision making, and public policy.

## **XII. GENES AND SUSCEPTIBILITY TO CARCINOGENS: THE MELANOMA STORY— DR. MARGARET TUCKER**

Dr. Margaret Tucker, Chief, Genetic Epidemiology Branch, DCEG, NCI, presented information gathered from the clinical investigation of families at high risk for melanoma. Some 50 families, comprising more than 1,200 individuals, have been prospectively followed for up to 25 years to identify risk factors and genes for susceptibility to cancer. Hypotheses developed at this level are then applied to larger populations.

Dr. Tucker explained that the incidence of melanoma has increased dramatically in the general population since SEER began collecting data in the early 1970s. One approach the DCEG has taken in investigating familial melanoma etiology is to photograph an individual's moles over time. Researchers have been able to change the natural history of melanoma by documenting the progression of and removing potentially fatal dermatological melanocytic lesions. With these data, researchers are able to quantify the risk of developing melanoma based on the numbers of dysplastic nevi ("abnormal" moles) present. Another approach has been to identify genes for susceptibility to cancer; possessing mutations (or alterations) in such a gene confers a 30- to 70-fold increased risk for developing melanoma. Two major susceptibility genes have been identified in the high-risk families: the tumor suppressor cyclin-dependent kinase inhibitor 2A (*CDKN2A*) and the oncogene cyclin-dependent kinase 4 (*CDK4*). Other genes are being sought.

Dysplastic nevi, increased numbers of banal nevi, light complexion, freckling, sunburn, and solar damage are other well-established melanoma risk factors in the general population. DCEG staff are developing screening algorithms to predict risk, as well as methods to assess sun exposure over an individual's lifetime using residential history. The average annual intensity of ultraviolet B (UVB) radiation received by each individual can also be estimated. Risk increases with proximity to the equator: The 20 percent increased average UVB intensity between Atlanta and New Orleans translates to about 40 and 30 percent increases in melanoma risk for men and women, respectively. Spending time outdoors increases risk of melanoma, even among individuals who tan well. Having a dark tan confers a sun protection factor (SPF) of only 2 to 4, which has important implications for the message communicated to the general population about sun exposure and sun protection.

The International Melanoma Genetics Consortium was created in 1997 to pool data and perform population studies on high-risk families in order to identify new genes and modifiers of risk. The Consortium's first project was to estimate the risk of melanoma associated with having a *CDKN2A* mutation. Using a logistic regression model incorporating survival analyses, three variables—gender, tumor suppressor *p14ARF* aberrations, and population melanoma incidence rates—were analyzed in 80 families. The most important variable for developing melanoma was residential location. Based on these findings, the Consortium reassessed its previous genetic testing recommendations and concluded that it was still premature to offer *CDKN2A* testing as a predictive factor for melanoma. Dr. Tucker closed by stating that the Consortium is attempting to obtain a residential history for those families not uniformly followed over the years to quantify exposure to sun.

## Questions and Answers

Dr. Norton asked whether there is a correlation between the expression of melanoma susceptibility genes and residential history. Dr. Tucker replied that expression studies have not been systematically done on familial melanomas with known mutations because early intervention has resulted in removal of lesions too small to be used as histological material for such studies.

In response to a question from Dr. deKernion about cancer caused by holes in the ozone layer, Dr. Tucker explained that UV monitors were being used to quantify changes in the amount of UV radiation reaching Australia and South America. Dr. Samir Abu-Ghazaleh, Gynecologic Oncologist, Avera Cancer Institute, asked about the distribution pattern of melanomas on the body. Dr. Tucker indicated that the pattern in high-incidence families resembles that of the general population; for males, the most common site for melanomas is the back, while for females, it is primarily the lower leg, followed by the back.

### **XIII. INDOOR POLLUTION AND CANCER: RADON AND OTHER HAZARDS— DR. JAY H. LUBIN**

Dr. Jay H. Lubin, Mathematical Statistician, Biostatistics Branch, DCEG, NCI, began by describing the health hazards presented by radon gas. Radon is released from the radioactive decay of uranium in rocks and soil and accumulates in houses without adequate ventilation and in underground mines. Once radon is inhaled, the first few cell layers of the lungs are exposed to alpha irradiation.

In 1999, the Biological Effects of Ionizing Radiation (BEIR) Committee of the National Academy of Sciences published a report predicting that about 12 percent of all U.S. lung cancer deaths were due to residential radon, making it the second leading cause of lung cancer. The mean concentration of radon in U.S. homes is 46 Becquerels per cubic meter (Bq/m<sup>3</sup>). The Environmental Protection Agency (EPA) action level is 148 Bq/m<sup>3</sup>; approximately 5 percent of U.S. homes exceed this concentration.

In the mid-1980s, DCEG instituted a set of studies to look at the cumulative effects of residential and occupational radon exposure. An increase in risk for lung cancer with increased exposure to radon was demonstrated in underground miners. Significantly, there were 450 cases of lung cancer in miners who had experienced a cumulative exposure to radon—comparable to that of individuals living in high-radon houses. Case control studies were performed to directly estimate the residential exposure/response relationship, as well as the effects on females and children. One such study involved an area of rural China in which radon levels are five times the U.S. average (225 Bq/m<sup>3</sup>), and the villagers live in underground dwellings. As with the studies of the miners, the results of this study show an increase in risk of lung cancer with increased radon concentrations.

Workshops sponsored by the Department of Energy and the Commission on European Communities evolved into annual meetings and three exposure/risk pooling projects covering North America, Europe, and, with the inclusion of the China studies, a world pooling project that should encompass some 15,000 lung cancer deaths. The North American project comprises 7 studies, each with 200 or more lung cancer cases and 1-year radon detectors as pooling criteria. DCEG initiated two of the studies and made major contributions to a third. Results of the North American pooling again demonstrate that increased radon concentration correlates with an increased risk for developing lung cancer.

Dr. Lubin concluded his presentation by stating that DCEG also has an interest in air pollution from indoor sources like tobacco smoke, cooking fumes and oils, and coal, as well as from exposure to pesticides and electromagnetic (EM) fields. He briefly described some of the studies in these areas, including one to evaluate the amount of pesticide in the dust from collected vacuum cleaner bags.

### **Questions and Answers**

Dr. deKernion asked for comment on the relationship between smoking and radon exposure. Dr. Lubin explained that radon had had a twofold greater impact on miners who did not smoke than on smokers. In response to two questions from Dr. Abu-Ghazaleh, Dr. Lubin stated that installing pipes is effective for ventilating radon from houses. While all histological types of lung cancer are seen following radon exposure, there seemed to be a greater dose response with small-cell carcinoma and adenocarcinoma than with squamous cell carcinoma. In response to a question about outlying data points in one North American pooling study in Iowa, Dr. Lubin explained that there is no intrinsic difference in radon levels in Iowa; however, this study took the most comprehensive radon measurements.

Dr. Norton asked what action from the risk/exposure data could be taken to the American population. Dr. Lubin answered that EPA is well aware of the public health risk and that it is now virtually impossible to sell a house without first testing for radon. Congress has also recognized the risk to U.S. miners by instituting the Radiation Effects Compensation Act. Dr. Lubin replied to a question from Dr. Pettigrew that there was no evidence that there was a safe level of radon exposure. Dr. Pettigrew asked about the EM exposure studies, and Dr. Fraumeni answered that two studies had been published. Neither demonstrated a relationship between cell phone use and brain tumors or EM field exposure and acute childhood leukemia.

### **XIV. TRENDS IN CANCER AND LIFESTYLE: THE ESOPHAGEAL ADENOCARCINOMA EPIDEMIC—DR. WONG-HO CHOW**

Dr. Wong-Ho Chow, Chief, Senior Investigator, DCEG, NCI, reviewed risk factors associated with the dramatic increase in incidence rates of esophageal adenocarcinoma in Caucasians and African Americans in the United States between 1974 and 1998. Among white males, the rate increased 400 percent, making adenocarcinoma the dominant esophageal cancer in this group. Rates for black males have also more than doubled in this period. The incidence rates for gastric cardia adenocarcinoma have also increased, whereas rates for squamous cell carcinoma of the esophagus and adenocarcinoma in other parts of the stomach have declined.

Dr. Chow explained that about 75 percent of cases of esophageal adenocarcinoma are due to a combination of three risk factors: history of gastrointestinal reflux disease, obesity, and cigarette smoking. A comprehensive, multicenter, population-based case control study undertaken in three areas across the United States demonstrated that the risk for developing esophageal adenocarcinoma increased consistently with increased frequency of reflux symptoms. Reflux disease incidence rates measured in U.S. male veterans between 1974 and 1994 parallel those of esophageal adenocarcinoma. Dr. Chow stated that it is generally accepted that reflux-related esophageal adenocarcinoma develops from a progression of histologic and genomic changes caused by the chronic mucosal injury associated with reflux disease. Ten to twenty percent of patients with reflux disease will develop metaplastic layers called Barrett's esophagus. The risk of adenocarcinoma in these patients is 30 to 125 times that of age-matched controls.

Risk of esophageal adenocarcinoma increased consistently with increasing body mass index (BMI). Obesity may increase abdominal pressure, resulting in reflux disease. The percentage of obese adults in the United States nearly doubled between 1960 and 1994, but the gender and racial patterns of the increase differ from those for esophageal adenocarcinoma. One theory as to why males have a higher rate of esophageal adenocarcinoma is that they tend to carry excess weight in the central abdominal area, causing a greater increase in abdominal pressure than in women, who tend to distribute excess fat in the hips.

The risk for developing esophageal adenocarcinoma is doubled in both smokers and ex-smokers, and the risk for ex-smokers is not reduced until 30 years after they quit smoking. Dr. Chow noted that smoking-related cancer incidence should be leveling due to the decline in smoking prevalence since the mid-1960s.

Dr. Chow discussed other factors thought to influence risk of esophageal adenocarcinoma. Infection with *Helicobacter pylori* in the stomach has been shown to reduce the risk of esophageal adenocarcinoma, possibly by reducing the secretion of gastric acid and, consequently, acidic reflux. The progressively declining prevalence of this bacterium due to antibiotic use and improved living conditions might have contributed to the rise of acidic reflux, Barrett's esophagus, and more recently, esophageal adenocarcinoma. The consumption of fruits, vegetables, and fiber correlates with a reduced risk, as does the use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs). Dr. Chow cautioned that the latter findings need to be confirmed.

Dr. Chow concluded her presentation by describing further research initiatives and follow-up studies planned by DCEG in collaboration with other NCI Divisions, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and academic institutes and health maintenance organizations in the United States and other countries.

### **Questions and Answers**

Dr. Freedman asked Dr. Chow to comment on behavior modification with respect to this disease. Dr. Chow stated that other intramural and extramural studies are underway to address this issue. In response to a question from Dr. Niederhuber, Dr. Chow explained that occupations were generally not identified as risk factors for esophageal adenocarcinoma.

In response to a question from Dr. Moon Chen, Professor, Department of Epidemiology and Preventive Medicine and Associate Director for Cancer Prevention and Control, University of California–Davis Cancer Center, about the lower incidence of stomach cancer in Asian populations, Dr. Chow explained that the populations studied in the work she presented were primarily white and African-American, but DCEG is studying Asian populations as well.

Dr. Abu-Ghazaleh asked whether there was a link between lifestyle and other esophageal/gastric cancers. Dr. Chow replied that certain risk factors, like smoking, increase the risk for both esophageal and stomach cancers. Alcohol consumption was a risk factor for esophageal squamous cell carcinoma but not adenocarcinoma. In her study, risk was not associated with use of snuff, chewing tobacco, or a pipe.

Dr. Richard Pazdur, Division Director, Division of Oncology Drugs, FDA, asked Dr. Chow to elaborate on the increased use of over-the-counter medications to treat reflux symptoms. Dr. Chow replied that from her earlier studies, it was clear that the increased risk of developing esophageal



adenocarcinoma appeared only in individuals with a history of reflux disease and not among those who used the medications but had no documented reflux disease. This issue is being evaluated in further studies at the DCEG and other institutes.

## **XV. INTEGRATING GENOMICS INTO EPIDEMIOLOGY: THE CORE GENOTYPING FACILITY—DR. STEPHEN CHANOCK**

Dr. Stephen Chanock, Director, Core Genotyping Facility (CGF), Advanced Technology Center, NCI, discussed the application of genomics to large-scale, population-based epidemiology studies in NCI's IRP. Currently, the CGF is dedicated to the analysis of variation in candidate genes in studies designed to investigate genetic susceptibility to cancer. As an example, Dr. Chanock noted that only a small proportion of breast cancer cases could be attributed to known germline gene mutations. It is now possible to ascertain the additional genetic contributing factors, such as common genetic polymorphisms. The majority of studies to be conducted at the CGF are population-based and intended to dissect the complex contribution of many genes. For instance, single nucleotide polymorphisms (SNPs) are estimated to number in the millions and are defined as occurring in greater than 1 percent in at least one population, but the majority have no phenotype. While it is not possible to predict a disease outcome from one SNP, many variants have been shown to be associated with medical conditions—for example, bladder cancer associated with the *NAT2* variance. Combinations of linked SNPs (alleles) inherited as a unit are defined as haplotypes, which in turn can be applied to population-based genetic association studies. Some haplotypes are known to confer selective advantages under certain conditions, such as the protective effect of the sickle cell variant against malaria.

Efforts are underway to characterize SNPs and haplotypes for analysis in molecular epidemiology studies. The CGF has been developed to handle a large number of samples and provide an increasing number of candidate SNPs, with a bias towards those resulting in a functional change (e.g., alterations in gene expression or amino acid coding sequence) or those that contribute to common haplotypes.

In 2002, the CGF received 25,000 samples from 24 epidemiological studies. So far, 14,000 samples from 10 of these studies have been analyzed, resulting in the delivery of 450,000 SNP genotypes and 300,000 microsatellite genotypes (short tandem repeats [STRs]). In the next 2 years, the CGF is expecting to receive approximately 80,000 samples from about 50 studies of 20 different cancers, necessitating the efficient execution of a high-throughput bioinformatics pipeline and a sophisticated laboratory information management system (LIMS).

A critical resource, developed in the CGAP, is the SNP500Cancer project (<http://snp500cancer.nci.nih.gov>). The purpose of this program is to conduct sequence verification of SNPs for molecular epidemiology studies, particularly since a substantial number of putative SNPs reported in the literature and public databases are not polymorphic in major ethnic groups in the United States. Dr. Chanock explained that making bioinformatic analysis accessible to researchers is essential for choice, validation, and analysis of genetic variants in molecular epidemiology studies. Data generated in the CGF will also be an invaluable tool for studies in population genetics. It is planned that genotype data from the estimated 40,000 controls will be made available on the Web site, along with estimates of haplotypes and nucleotide diversity. Sequencing primers and probes for genes of high interest to the cancer research community can also be obtained from the SNP500Cancer Web site in order to perform validated assays under ready-optimized conditions, using both real-time amplification technologies (TaqMan and EPOCH) and MALDI-TOF.

Dr. Chanock concluded by stating that the CGF is actively pursuing strategies to utilize DNA pooling and whole-genome amplification, as well as to decrease the amount of DNA needed to perform assays. Similarly, assessment of new, more efficient technologies is ongoing. To enable this, the CGF has established collaborations with academic institutions and industry for the development of new technologies, particularly those that will increase throughput at a lower cost per genotype.

### **Questions and Answers**

In response to questions from Drs. deKernion, Norton, and Hoover about the use of the Core Facility, Dr. Chanock replied that the CGF was established to analyze samples from epidemiological studies from the IRP. He explained that the concept could be “franchised” to other Cancer Centers; issues of regional facilities versus duplicated resources and state-of-the-art technology could be discussed at a retreat workshop.

Dr. Niederhuber asked whether CCR’s facilities at NCI–Frederick could serve as a national resource for tissue acquisition and emerging technologies. Drs. von Eschenbach and Barrett responded that this is an issue under consideration.

Dr. Prendergast asked for elaboration on the rationale used by CGF in selecting its microarray technology. Dr. Chanock explained that one opportunity of the Core Facility is its ability to compare state-of-the-art technologies and select the most suitable ones for its use. For example, after comparing different platforms, CGF selected TaqMan based on its ease of use and efficiency; different screening assays are being tested for particular applications. Considerable effort is also being directed at utilizing the MALDI-TOF platform. Much of the information on developing the assays, as well as the CGF’s experience with the technology, will be available on both the SNP500Cancer and the future CGF Web sites.

### **CLOSED SESSION**

*This portion of the meeting was closed to the public in accordance with the provisions set forth in Section 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.

There was a review of intramural site visits and tenured appointments, committee discussions, and recommendations. There was also a discussion of personnel and proprietary issues. Members absented themselves from the meeting during discussion for which there was potential conflict of interest, real or apparent.

**DAY TWO—THURSDAY, DECEMBER 5, 2002**

**PROGRAM REVIEW OF DIVISION OF CANCER PREVENTION**

**XVI. OVERVIEW—DR. PETER GREENWALD**

Dr. Peter Greenwald, Director, DCP, NCI, introduced the research topics to be discussed and briefly summarized the major activities of the DCP. The main focus of the DCP is the identification and validation of biomarkers of risk and carcinogenesis in people and of clinical trials to learn how to prevent the process from moving towards invasive cancer.

Dr. Greenwald reviewed the numerous extramural projects funded under the FY2002 budget and briefly mentioned the qualifications of DCP staff. He then described the programs that specifically focus on prevention of specific cancers and reviewed the number of patients presently enrolled in each Phase III clinical prevention or early detection trial. The main clinical prevention trials sponsored by DCP are conducted via the Community Clinical Oncology Program (CCOP). The main Phase III trials include the breast cancer prevention Study of Tamoxifen and Raloxifene (STAR), the prostate cancer Selenium and Vitamin E Cancer Prevention Trial (SELECT), and the NLST, jointly sponsored with DCTD.

**XVII. PRECLINICAL CHEMOPREVENTION—DR. JAMES CROWELL**

Dr. James Crowell, Chief, Chemopreventive Agent Development Research Group, DCP, NCI, reviewed the cancer preventive agent development program and the accomplishments in a number of program areas. He explained that the goal of the program is to screen agents systematically, using well-validated model systems, and characterize the efficacy, safety, and mechanism of action of these agents. In addition, the agents are qualified for clinical investigations by developing the chemistry, manufacturing, and control documents required for filing an Investigational New Drug (IND) application with the FDA for Phase I clinical trials.

Dr. Crowell mentioned that the research supported by this program is often undertaken in collaboration with other NCI Divisions. These projects provide resources, such as access to agents and INDs, for scientific advancement of chemoprevention through investigator-initiated projects supported by a variety of other funding mechanisms.

Potential cancer preventive agents are identified through experimental carcinogenesis and epidemiological research, pharmaceutical and biotechnology collaborations, and an NCI program called Rapid Access to Preventive Intervention Development (RAPID). The latter provides contract resources to academic researchers who have discovered a novel potential cancer preventive agent but lack the resources or ability to carry out the drug development required to bring the agent to clinical trials. Dr. Crowell highlighted the agents, including vaccines, supported by RAPID. He then reviewed specific agents being studied in collaboration with pharmaceutical companies.

He commented that there are a number of well-validated animal models available to study the efficacy of preventive agents for almost every epithelial cancer and that the use of genetically engineered animal models to study the efficacy of various agents has increased. He then reviewed preclinical data on several preventive agents that provided justification for their use in clinical trials. Celebrex, a selective COX-2 inhibitor, was shown to prevent the incidence of colon and bladder cancer in two different animal models. Combination therapy with an NSAID and difluoromethylornithine (DFMO), two agents with

independent mechanisms of action, prevents multiple tumor formation in a mouse model for cancer of the small intestine. Dr. Crowell also commented on an aerosolized glucocorticoid that reduced the incidence of tumors in a rat lung model. This agent is presently showing promising results in clinical trials.

Dr. Crowell observed that despite the significant role genetic engineering plays in drug development, basic pharmacologic and pharmacokinetic studies are fundamental to this process. As an example, he described indole-3-carbinol, a compound normally found in cruciferous vegetables that is effective in preventing breast cancer in rats but that broadly induces phase I liver enzymes and might alter the metabolism of other drugs. One of the byproducts formed from this compound during digestion has, however, been shown to be efficacious in the prevention of breast cancer and does not significantly induce phase I enzymes. This agent is also being studied for its ability to prevent the replication of human papillomavirus (HPV).

Dr. Crowell concluded his presentation by listing a number of agents that target specific organs. He stated that the use of pharmacologic, nutritional, endocrinologic, and immunologic interventions to block, reverse, or delay the process of carcinogenesis is a novel approach to risk reduction and cancer control.

### **Questions and Answers**

In response to a question regarding the interaction between the DCP and industry in terms of drug discovery and development efforts, Dr. Crowell explained that collaborations with pharmaceutical companies generally do not entail studying their lead compounds unless the collaboration will help an agent proceed to clinical trials more quickly and easily. The collaborations generally involve proof-of-principle studies on second- or third-generation agents.

Dr. Crowell stated that in the past 10 years, approximately 55 Phase I studies have been supported, and there are presently 22 active Phase II clinical trials. Dr. Greenwald added that tamoxifen is the best example of a preventive drug currently in use based on data obtained from clinical prevention trials.

Dr. Greenwald commented that the Board should be updated on the EDNR study at a future meeting. He mentioned that there are hundreds of biomarkers available for exploration, but there has been little validation in terms of correlating the behavior of biomarkers with incidence of disease. The EDNR program is aimed at validating biomarkers.

Dr. Norton asked whether there are going to be any changes in the strategy of the existing cooperative groups to ensure that clinical trials of future preventive agents will not take as long as the trials that justified the use of tamoxifen. Dr. Greenwald responded that, presently, a group of expert scientists meets several times a year to provide advice as to which agents should be given priority to proceed to Phase III clinical trials.

### **XVIII. PHASE II PREVENTION TRIALS—DR. ERNEST HAWK**

Dr. Ernest Hawk, Chief, Gastrointestinal and Other Cancers Research Group, DCP, NCI, reported on the Phase II aspect of drug development for cancer prevention. He identified the three objectives of the Phase II Program: (1) identify and prioritize the most promising compounds for Phase III trials;

(2) improve mechanistic insights into carcinogenesis and chemopreventive efficacy; and (3) standardize and validate surrogate endpoint biomarkers.

Dr. Hawk commented that there are 40 ongoing Phase II prevention trials, involving 50 investigators. He also listed the 25 clinical sites participating in these studies. Dr. Hawk then described a number of clinical endpoints used to calculate the ability of an agent to prevent or reduce the incidence of disease. In addition to the pathological endpoints, changes at the cellular, molecular, and biochemical levels are assessed. Dr. Hawk reviewed a number of molecular targets specific to colorectal cancer chemoprevention. These targets have been shown to be relevant contributors to carcinogenesis in animal models. Celecoxib, a COX-2 inhibitor, is an example of a promising new compound brought into clinical development as a chemopreventive agent via a successful collaboration with a pharmaceutical company.

Dr. Hawk highlighted the cohorts involved in Phase II cancer prevention trials. These cohorts include individuals at both moderate and high risk of developing cancer because these trials can be conducted using smaller numbers of individuals and for shorter periods, providing an efficient, albeit preliminary, evaluation of an agent's efficacy.

Dr. Hawk explained that evidence obtained from both *in vitro* and *in vivo* preclinical studies, as well as from observational databases on the activity of the same agents in relation to other indications, are reviewed when determining whether an agent should be advanced to Phase II clinical trials. In addition, information gained from Phase III trials impacts how a Phase II trial is conducted, and information gained from Phase II trials is used to improve how experiments are conducted in animal models.

Dr. Hawk shared results from four Phase II clinical trials. The first trial tested 2 different doses of celecoxib in 83 patients over a period of 6 months. Compared with placebo, patients treated with celecoxib showed either no change (lower dose) or a reduction (higher dose) in the colorectal adenoma burden. Next, Dr. Hawk discussed a Phase II lung cancer prevention trial that tested Sialor<sup>®</sup> in 110 current or former smokers with prevalent bronchial dysplasia. After 6 months of treatment, there was a significant reduction in progressive disease among those treated with the drug, as shown in evaluations focusing on either specific lesions or the randomized cohort.

The third study investigated the ability of selenomethionine to reach its target organ: the prostate. This trial studied a small cohort of patients before they underwent scheduled prostate surgery and analyzed serum and organ selenium levels over a period of 14 to 31 days. Dr. Hawk noted that the statistically significant increase in prostate selenium was important in providing support for this agent's evaluation in a Phase III prostate cancer prevention trial. The objective of the fourth study was to analyze the ability of tamoxifen to modulate biomarkers used to assess efficacy of breast cancer prevention. Dr. Hawk indicated that this study is ongoing. Should the study identify biomarkers modulated by tamoxifen, this model system could be used to identify and prioritize other agents for entry into Phase III clinical trials.

Dr. Hawk summarized innovations in NCI's Phase II program. He listed a number of novel agents, methods of agent delivery, new cohorts, and new technologies to improve the accuracy and reliability of efficacy assessments, particularly noninvasive assessments. Dr. Hawk concluded by emphasizing the role of the Phase II program in promoting risk markers, molecular targets, and response markers identified through basic prevention science to meaningful clinical benefits that can inform and transform practice at the level of public practitioners and policy makers.

## Questions and Answers

In response to a comment from an NCAB member, Dr. Hawk agreed that issues of drug availability, rather than knowledge of reasonable molecular targets, often limit progress in Phase II prevention studies. The main problem is the lack of access to agents that act on specific targets. Dr. Hawk pointed out that several groups at NCI are attempting to work with industry to improve the availability of such agents.

Dr. Greenwald commented that the tamoxifen breast cancer prevention trial is tracking other endpoints, including its preventive effects on ovarian cancer. However, data are preliminary, and a conclusion has not been drawn. When asked about the use of new biostatistical methods to answer the unique dilemmas and complexities that result from these clinical trials and interventions, Dr. Greenwald replied that there is a biostatistical research group at NCI working on methods to determine the best trial design or alternative trial design, how to integrate information gained from different fields, and when to use modeling when the data from one trial are sufficient to make projections on another trial. Dr. Greenwald suggested this group should present its findings to the NCAB.

Regarding a question about combining cancer prevention studies to make better use of the patient population resource, Dr. Greenwald responded that analyzing the effects of one agent on more than one endpoint would be difficult. Likewise, the conduct of trans-NIH prevention trials, although logical, poses an organizational challenge.

Dr. Greenwald indicated that cooperative groups have been successful in the accrual of patients for prevention trials because they have had access to patients' family histories, and relatives at higher risk are interested in participating in such trials. Dr. Greenwald pointed out that a bigger issue to overcome for success in prevention trials is the training of physicians for their role in disease prevention.

Dr. Norton commented that studies should investigate the effects that alternative medicines have on the prevention of cancer. At this time, there is no related information, and alternative treatments may do nothing, be preventive, or actually cause harm.

Dr. Greenwald agreed that as validated biomarkers that correlate with the incidence of cancer become available, primary care physicians, oncologists, and the public in general will need to be informed to help prevent specific cancers in the manner that high cholesterol and high blood pressure are now treated to prevent heart disease.

## **XIX. NUTRITIONAL SCIENCE—DR. JOHN MILNER**

Dr. John Milner, Chief, Nutritional Science Research Group (NSRG), DCP, NCI, indicated that growing evidence points to the ability of foods and food components to increase physical and cognitive performance as well as reduce the risk for a variety of diseases, particularly cancer. He mentioned that in the United States, six of the major causes of death are related to dietary habits. Dr. Milner commented that 90 percent of cancers are associated with some environmental condition and are not related to familial inheritance.

Dr. Milner listed a number of essential and nonessential nutrients that may modulate genetic and epigenetic events. The nonessential nutrients encompass compounds derived from plants, animal tissue, and fungi, as well as byproducts from the normal flora of the gastrointestinal tract. Indole-3-carbinol, a

compound found in cruciferous vegetables, has been shown to dramatically reduce estrogen receptor expression, and studies are underway to analyze combination therapy using indole-3-carbinol with tamoxifen to prevent breast cancer.

Dr. Milner indicated that the effects nutrition has on protecting against or increasing the risk for disease are related to the genes present in the individual consuming the food. Nutrients have been shown to modify DNA stability and methylation state. Nutrients can also alter posttranslational events, resulting in changes in the structure, phosphorylation state, or glycosylation state that could alter the function of the protein. Any of these changes regulated by food components could result in behavioral alterations of the cell.

Dr. Milner explained that the majority of nutritional data have been based on observation, but more recently, the focus has changed to taking a scientific approach when attempting to identify who will or will not benefit from changes in nutrition. The NSRG created two cooperative grant mechanisms attempting to bridge nutritional research to that based on genetics and molecular biology. Dr. Milner commented that of 30 applications received, 6 P20 planning grants were funded, and 14 applications are presently under review for funding through a U54 cooperative specialized center award mechanism.

Dr. Milner reviewed the concepts behind some RFAs to be funded in FY2003. One RFA called for research projects that would identify molecular targets for nutrients in prostate cancer prevention. Another RFA, "Diet, DNA Methylation, and Other Epigenetic Events and Cancer Prevention," requested proposals that would examine the effects of bioactive food components. A supplemental announcement issued in collaboration with the Center for Bioinformatics will promote the discovery of gene-nutrient targets. The goal of the announcement would be to identify animal and human markers associated with nutritional studies. The markers would be identified in a microarray facility at the DCP, and the information would be posted on a Web site and made accessible to other scientists.

Dr. Milner noted that in addition to creating RFAs, the NSRG is involved with several other activities. The NSRG has sponsored a number of workshops, created a listserv, and developed a new gene-nutrient Web search engine. Dr. Milner closed by emphasizing the need to promote the available funding mechanisms in nutritional research and cancer prevention to the next generation of scientists.

### **Questions and Answers**

Dr. Milner commented that the RFAs recently issued were developed to foster a relationship between nutritionists and scientists in molecular biology and genetics. The number of M.D./Ph.D. programs available in nutrition is low. More graduate-level training needs to be established to improve scientific research in nutrition.

Dr. von Eschenbach commented that the NCI is emphasizing nutritional research as a trans-Institute initiative because, along with the physical activity component, it integrates into one comprehensive area similar to the research field on tobacco and cancer. Ways to encourage behavioral changes with respect to nutrition and physical activity must be studied in a manner similar to the models used to discourage smoking.

Dr. Norton asked whether, based on the information presented by Dr. Milner, patients in chemoprevention clinical trials should be on a controlled diet. Dr. Greenwald responded that in the SELECT trial, control patients were offered vitamins that did not have selenium or Vitamin E. However,

the majority of trials depend solely on randomization to ensure that diet does not affect the agent being studied. Dr. Greenwald remarked that at this time, knowledge of the effects of nutrients on cancer is too limited to regulate the diet of patients in clinical trials. In addition, controlling for diet in clinical trials would be very costly.

Dr. Norton asked whether instructing patients during the informed consent process about nutrients to avoid could allow them to sabotage a study. Dr. Milner agreed that patients could impair a trial if they decided to eat the nutrients they had been instructed to avoid. Dr. Greenwald commented that patients are tracked, and measurements are taken on the nutrients they ingest to ensure that the trial is not jeopardized.

An NCAB member commented on the need to provide proper nutrients to patients in clinical trials to avoid having them take other supplements that could interfere with the therapy or even exacerbate the state of the disease.

Ms. Marlys Popma, Executive Director, Republican Party of Iowa, asked whether any studies were underway to determine how diet might decrease the incidence of cancer in the aging population. Dr. Greenwald indicated that at present, there are no studies on nutrients and aging. Dr. Milner added that a conference addressing the use of supplements and dietary components in relation to aging and health would be held in January 2003.

Dr. von Eschenbach commented that there is a complementary medicine program within NCI as well as another program within the NIH and both groups cooperate and collaborate. The program within NCI has a more focused portfolio.

## **XX. PREVENTIVE ONCOLOGY TRAINING—DR. DOUGLAS WEED**

Dr. Douglas Weed, Chief, Office of Preventive Oncology, DCP, NCI, reviewed the new initiatives, training tracks, and other efforts sponsored by the Cancer Prevention Fellowship Program (CPFP). He defined the mission of the CPFP as providing NCI fellows with training in cancer prevention and control through formal coursework, mentored research, and professional development activities.

Dr. Weed explained the structure and activities of the CPFP, which include an annual national competition for placements, training in a molecular laboratory, two courses in cancer prevention and control, and a strong focus on mentored research and professional development. Over the past 15 years, the CPFP has trained more than 130 fellows. In 2002, the Program selected 16 new fellows from more than 100 applications. The physicians and scientists who applied to the Program were diverse in age, gender, and ethnic background.

Dr. Weed indicated that the fellows are encouraged to pursue a Master of Public Health (M.P.H.) degree through an accredited program during the first year of their fellowship. Once the fellows have received their M.P.H.s, and before starting their research, they attend a 6-week summer curriculum in cancer prevention and control and the molecular aspects of cancer prevention. When the fellows join a research group or laboratory, the CPFP provides them with stipends and meeting travel, cancer prevention training, and professional development funds, while the mentors provide the fellows with research training, scientific guidance, computer access, and workspace. Dr. Weed stated that an increasing number of Divisions within the NCI, as well as the CCR, have research programs in cancer prevention and are mentoring Cancer Prevention Fellows.



Dr. Weed indicated that the leadership and professional development workshops are major components of fellowship training. The Grantsmanship workshop focuses on teaching fellows how to apply for funding and which grants to apply for, both while they are at NCI and when they leave the Institute.

Dr. Weed commented that fellows trained in the CPFPP have remained active in leadership roles in cancer prevention at NCI, academic institutions, Cancer Centers, and government and private institutions. Current fellows have been recruited to work with past fellows, and several fellows have returned to give lectures in the summer curriculum.

Dr. Weed explained that the two new specialty tracks—the Clinical Prevention Research Track and Ethics of Prevention and Public Health Track—available to fellows applying for entry into the program in 2003 were designed to recruit specific individuals to the CPFPP to meet the special needs of the field. The purpose of the Clinical Prevention Research Track is to recruit more clinicians into the Program and train them in translational research, clinical prevention trials, the clinical trial protocol review process, the drug development approval process, and other relevant clinical activities. The Ethics of Prevention and Public Health Track was created to develop leaders in the field of public health ethics, with a focus on cancer prevention.

Dr. Weed concluded that every aspect of the CPFPP has an evaluation component. A progress report submitted by the fellows on their research is evaluated on a biannual basis; the summer curriculum is evaluated at every level; and applicants evaluate the advertising and recruitment aspects of the program.

### **Questions and Answers**

Dr. Weed remarked that most Cancer Centers in the United States have R25 cancer prevention training programs available, but those programs are smaller than the program at NCI. Dr. Weed added that fellows who are not accepted into the CPFPP due to budgetary constraints are often referred to one of the other training programs.

Dr. Weed indicated that three nurses are currently in the program, but CPFPP is attempting to recruit other nurse scientists into the program, as well as scientists from any discipline who show an interest in cancer prevention.

Dr. Weed affirmed that the summer cancer prevention and control curriculum is an independent program available to any scientist interested in being trained in cancer prevention.

### **XXI. NEW BUSINESS II—DR. JOHN E. NIEDERHUBER AND NCAB MEMBERS**

There was no new business conducted at this time.

### **TRANSDIVISIONAL RESEARCH ON HUMAN PAPILLOMAVIRUS (HPV): DEFINITION AND INTERVENTION OF A CANCER-CAUSING AGENT**

### **XXII. INTRODUCTION—DR. JOSEPH FRAUMENI**

Dr. Fraumeni stated that scientists from separate divisions of NCI communicate, interact, and collaborate in studies that range from basic scientific discoveries to translational research and clinical applications, as well as public health applications. The presentations by Drs. Schiffman, Solomon, and

Lowy exemplify how trans-NCI collaborations are playing a vital role in setting the national research and public health agenda for cervical cancer. Moreover, this transdivisional research shows promise in reducing the burden of a preventable disease in all segments of American life as well as in developing countries where the disease rates are especially high.

### **XXIII. THE CENTRAL CAUSE OF CERVICAL CANCER—DR. MARK SCHIFFMAN**

Dr. Mark Schiffman, Chief, Interdisciplinary Studies Section (ISS), Environmental Epidemiology Branch, DCEG, NCI, stated that HPV is the central cause of virtually every case of cervical cancer worldwide. As long as 100 years ago, researchers had observed a relationship between cervical cancer and “venereal disease.” Dr. Schiffman explained that pathology studies had originally associated venereal warts with cervical cancer. In the past 20 years, molecular techniques have identified the two most important types of HPV—HPV16 and HPV18—associated with cervical cancer and cervical cancer-derived cell lines.

Dr. Schiffman indicated that the acceptance of HPV as a carcinogen has been quite recent. Of the 100 types of HPV, 4 (HPV16, HPV18, HPV31, and HPV45) account for most cases of cervical cancer, while approximately 15 types have been shown to cause cervical cancer. If a vaccine is ever developed, it will have to focus on generating immunity to these 4 most common types of HPV, if not all 15 types associated with cervical cancer. Dr. Schiffman stressed that HPV is sexually transmitted and extremely common, and that the incidence of cervical cancer is controlled mainly through screening and treatment.

Dr. Schiffman noted that the set of standards used to identify HPV as the cause of cervical cancer was based on epidemiologic criteria applied to the study of other infectious diseases. These epidemiologic criteria include biological plausibility, strength of association, specificity of association, consistency of associations on replication, and the time sequence of the variables. Dr. Schiffman explained that the cohort studies that provided the time sequence data required a large number of participants and followed the participants for 2 to 10 years. One cohort study included more than 20,000 women who were followed over 10 years; it determined that women who were HPV-positive at the start of the study were at a much higher risk for developing precancerous lesions or cancer as compared to women who were HPV-negative.

These studies showed that HPV causes cervical cancer, and the next step was to understand the history, or timeline, of HPV-induced cervical cancer. The majority of women are able to clear the virus and gradually build up immunity to HPV after they have been infected. In cases in which women have persistent forms of HPV, the result is often precancerous lesions or cancer.

Dr. Schiffman reported that HPV16 causes 50 percent of cervical cancer worldwide, which is why it was chosen as the primary vaccine target. Subcohort studies on women in Costa Rica found that 30 percent of women remained positive for HPV16 after 5 to 7 years—a higher figure than for other types of HPV—and almost half of the women with persistent HPV16 infection developed precancerous or cancerous lesions. He stressed that persistence of an oncogenic type of HPV is the key to precancer progression and subsequent cancer invasion.

Dr. Schiffman mentioned that there are a number of cofactors—such as immunosuppression, smoking, parity, and long-term use of contraceptives, among others—that place HPV-positive women at higher risk for cervical cancer. In addition, to better understand how to predict who is at high risk for developing cervical cancer, there is an interdisciplinary working group across the NCI. One goal of the

ISS is the identification of biomarkers that will accurately predict when women are at high risk for developing cancer. Dr. Schiffman concluded his presentation by stating that another goal of his Section is to analyze the genome of HPV to determine the genes or sequence variants that are associated with the oncogenic forms of HPV.

#### **XXIV. HPV TESTING AND DIAGNOSTIC SCREENING—DR. DIANE SOLOMON**

Dr. Diane Solomon, Project Officer, Atypical Squamous Cells of Undetermined Significance (ASCUS) LSIL Triage Study (ALTS), Breast and Gynecologic Cancer Research Group, DCP, NCI, presented developments over the past 2 decades that have improved cervical cancer screening and diagnosis, as well as patient management.

Dr. Solomon explained that a major advance in the field of cervical cancer screening came in 1988, when the Bethesda System provided a uniform set of terms for reporting cytologic abnormalities found through Pap smears. Dr. Solomon reviewed the different grades of abnormal cervical diagnoses. Low-grade squamous intraepithelial lesions (LSILs) represent abnormalities caused by transient HPV infections that would likely regress but could progress to high-grade squamous intraepithelial lesions (HSILs) as a result of persistent infection. Dr. Solomon explained that in a minority of women, the cytologic diagnosis does not correspond to the actual clinical state of the cervical tissue.

The group of equivocal diagnoses was referred to as ASCUS. Dr. Solomon remarked that in 1992, the NCI and American College of Obstetricians and Gynecologists (ACOG) held a workshop that provided the impetus to conduct a clinical trial to compare management strategies for women with equivocal (ASCUS) and low-grade (LSIL) cytologic abnormalities.

Throughout the 1990s, advancements in technology improved cytologic sample collection, and HPV testing evolved to increase assay sensitivity. ALTS was designed to take advantage of these new technologies.

In an effort to find the best management strategy for women diagnosed with ASCUS or LSIL, participants in ALTS were randomized into one of three arms: immediate colposcopy, follow-up with HPV triage, or conservative management. The conclusion from this study was that triage of women based on an HPV DNA test was an efficient strategy to detect precancerous lesions without sending all women to colposcopy.

Based on these results, the American Society of Colposcopy and Cervical Pathology (ASCCP) recommended that women diagnosed with ASCUS could be managed with repeat Pap smears, colposcopy, or HPV DNA testing, but HPV testing was the preferred approach if a residual cervical sample was available. However, women diagnosed with LSIL should undergo colposcopy, because neither HPV testing nor cytology follow-up performed efficiently as a triage (second) test for those women.

Dr. Solomon mentioned that over the past year, two groups—the ACS and the U.S. Preventive Services Task Force (USPSTF)—have revised screening guidelines for cervical cancer based on an increased understanding of the biology of cervical cancer precursors and improvements in screening. Dr. Solomon closed by commenting that the future direction of screening includes determining: the most appropriate age for screening women with both Pap smear and HPV DNA testing; how to manage HPV-positive women with normal cytology; how to identify new areas for clinical research; and how to

generate rapid but inexpensive diagnostic tests. A meeting sponsored by both the DCP and the NCI as a whole will be held in the winter of 2003 to discuss these issues.

## **XXV. DEVELOPMENT OF HPV PROPHYLACTIC VACCINES—DR. DOUGLAS LOWY**

Dr. Douglas Lowy, Chief, Laboratory of Cellular Oncology, CCR, NCI, presented research related to vaccine development against HPV. He acknowledged that investigators and collaborators from multiple Institutes at NIH, as well as other institutions, had carried out the research. Dr. Lowy commented that any vaccine that interferes with HPV infection would be both protective against cancer and a cost-effective health measure.

Dr. Lowy explained to the Board that due to the oncogenic nature of HPV, a vaccine targeted to a structural subunit of HPV would be most effective in inducing high titers of neutralizing antibodies that would act to prevent rather than treat infection. L1 is the most abundant structural protein of the virus, can self-assemble to form viral particles, and contains the most immunogenic epitopes. Dr. Lowy reported that vaccination with intact L1 virus-like particles and using an oral papillomavirus model (BPV-4) provided complete protection in naive cows. In addition, transfer of IgG from an immunized animal to a naive animal induced protection against viral challenge, suggesting that the protection was due to neutralizing antibodies. Dr. Lowy mentioned that the two disadvantages of this vaccine were that it is not therapeutic and it does not protect against other types of HPV.

Dr. Lowy reviewed human trials testing the safety and immunogenicity of a vaccine against HPV16. The antibody titer in the vaccinated participants was found to be 40 times higher than that seen in individuals infected with HPV, and the titers remained high for up to 6 months. These data were similar to those reported in studies conducted by pharmaceutical companies and indicate that the vaccine induced a durable antibody response. A proof-of-principle efficacy trial reported by Dr. Laura Kowski in November 2002 used a similar vaccine with adjuvant therapy and found protection from persistent HPV16 infection for a follow-up period of 1½ years.

Dr. Lowy commented that if an individual was infected with HPV at another site in the body, vaccination could prevent infection of the cervical tissue and transmission to sexual partners. He remarked that these data indicate that these vaccines are safe and induce protection against specific HPV strains. However, protection against other strains, as well as the duration of the protection, needs to be explored.

Dr. Lowy mentioned that to fully protect women against oncogenic HPV, the vaccine would need to include viral particles from more than one type of HPV. Two pharmaceutical companies are planning trials that will include viral particles from HPV16 and HPV18. Additional nononcogenic HPV types known to be responsible for genital wart infections, HPV6 and HPV11, are included in the vaccine produced by one of these companies. An alternative approach would be to use the structural L1, L2, E7, and E2 proteins in a chimeric vaccine that would be both protective and therapeutic.

Dr. Lowy concluded his presentation by stating that Pap screening should continue after any vaccination program is started, as the protection will initially be type-specific and will not be absolute.

Dr. Allan Hildesheim, ISS Environmental Epidemiology Branch, DCEG, NCI, did not make a presentation due to inclement weather and time constraints. However, Dr. Lowy mentioned that he and Dr. Hildesheim had attempted to combine their presentations.

## **XXVI. DISCUSSION—DR. RALPH S. FREEDMAN**

Dr. Freedman commented that the strategies for handling ASCUS and LSIL vary based on the expertise of the medical group, especially for women who are HPV-positive but have normal Pap smears. Dr. Solomon concurred that management strategies need to be developed for women who are diagnosed as LSIL- or HPV-positive, especially in the 2 years following the initial diagnosis.

Dr. Freedman asked how woman who have been treated for cervical cancer and present with HPV post radiation should be managed. Dr. Solomon proposed that HPV DNA testing would be extremely useful in determining the persistence of the virus in these patients.

Dr. Freedman stressed that screening education needs to be improved nationally, targeting geographical areas that do not provide Pap screening. Dr. Solomon responded that there are groups at NCI investigating how to reach unscreened populations of women.

Dr. Freedman commented that the neutralizing-antibody approach to vaccine development is more realistic than the peptide strategy, considering the problems associated with the cost required to augment the peptide response. Dr. Lowy added that the benefit of neutralizing-antibody vaccines is that second-generation vaccines founded on the original neutralizing antibodies could be developed based on results from the original vaccine, while peptide and purified-protein vaccines require multiple immunizations.

Dr. Lowy commented that women are typically infected with more than one type of HPV, explaining that in many places in the world, females are monogamous, and nonmonogamous males transmit the disease to them; any increase in the number of a man's sexual partners corresponds with increased risk to the women.

Dr. Freedman asked whether studies were underway to investigate cofactors that place women at higher risk for infection. Dr. Hildesheim stated that markers of genetic susceptibility, disease progression, and immune response will be investigated in a study conducted by Dr. Sophia Wong.

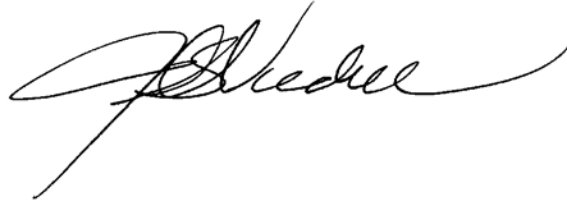
Dr. Lowy noted that the ability to induce cell-mediated immunity against nonstructural viral proteins is being actively investigated, but there are methodological problems that make a therapeutic vaccine more challenging than a protective vaccine.

There being no further business, the 124<sup>th</sup> meeting of the National Cancer Advisory Board was adjourned at 12:00 noon on Thursday, December 5, 2002.

February 11, 2003

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Date



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John E. Niederhuber, Chair

February 11, 2003

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Date



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Marvin R. Kalt, Executive Secretary