DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL CANCER INSTITUTE
127th NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
September 9-10, 2003

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

NATIONAL CANCER ADVISORY BOARD
BETHESDA, MARYLAND
Summary of Meeting
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The National Cancer Advisory Board (NCAB) convened for its 127th regular meeting on Tuesday, September 9, 2003, in Conference Room 10 of Building 31, National Institutes of Health (NIH), Bethesda, MD. The meeting was open to the public on Tuesday, September 9, 2003, from 8:30 a.m. to 3:40 p.m. The meeting was closed to the public from 4:30 p.m. until adjournment at 5:30 p.m. The meeting was reopened to the public on Wednesday, September 10, 2003, from 8:30 a.m. until adjournment at 11:10 a.m. NCAB Chair Dr. John E. Niederhuber, Professor, Departments of Oncology and Surgery, University of Wisconsin-Madison, presided during both the open and closed sessions.

NCAB Members

Dr. John E. Niederhuber (Chairperson)
Dr. Samir Abu-Ghazaleh
Dr. Moon S. Chen, Jr.
Dr. Kenneth H. Cowan
Dr. Jean B. deKernion
Dr. Ralph S. Freedman
Dr. Elmer E. Huerta
Dr. Eric S. Lander
Dr. Susan M. Love
Dr. Arthur W. Nienhuis
Dr. Larry Norton
Ms. Marlys Popma
Dr. Franklyn G. Prendergast
Dr. Amelie G. Ramirez
Ms. Lydia G. Ryan

President's Cancer Panel

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

Alternate *Ex Officio* NCAB Members

Dr. Steven Akiyama, NIEHS
Dr. Peter Kirchner, DOE
Dr. Hugh McKinnon, EPA
Dr. T.G. Patel, VHA
Dr. Richard Pazdur, FDA
Dr. John F. Potter, DOD

Members, Executive Committee, National Cancer Institute, NIH

Dr. Andrew von Eschenbach, Director, National Cancer Institute
Dr. Alan Rabson, Deputy Director, National Cancer Institute
Dr. Anna Barker, Deputy Director, Strategic Scientific Initiatives
Dr. J. Carl Barrett, Director, Center for Cancer Research
Ms. Nelvis Castro, Deputy Director, Office of Communications
Dr. Robert Croyle, 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
Dr. Paulette Gray, Acting Director, Division of Extramural Activities
Ms. Janice Mullaney, Acting Deputy Director for Management, Office of the Director
Dr. Dinah Singer, Director, Division of Cancer Biology
Ms. Sandy Koeneman, Executive Secretary, Office of the Director

Liaison Representatives

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

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DAY ONE: TUESDAY, SEPTEMBER 9, 2003

I. INTRODUCTION, WELCOME, AND APPROVAL OF JUNE 2003 MINUTES— DR. JOHN NIEDERHUBER

Dr. Niederhuber began by asking for a moment of silence to think of the patients with cancer and those who have passed away from cancer. He welcomed members and *Ex Officio* members of the Board; representatives of liaison organizations; members of the President's Cancer Panel (PCP); Dr. Paulette Gray, Acting Director, Division of Extramural Activities (DEA), National Cancer Institute (NCI), and Executive Secretary, NCAB; other NCI staff; and members of the public. Dr. Niederhuber introduced and welcomed Dr. Monica Leibert, new Liaison Representative to NCAB from the American Urologic Association. He invited the public to submit to Dr. Gray, in writing and within 10 days, comments regarding items discussed during the meeting.

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

Motion. A motion was requested and made to approve the minutes of the June 2003 NCAB meeting. The motion was seconded, and the minutes were unanimously approved by the Board.

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

Dr. Niederhuber called Board members' attention to future meeting dates listed in the Agenda, which had been confirmed through 2005. Because of conflicts in 2004 with the American Society for Clinical Oncology's (ASCO) Annual Meeting in June and the beginning of Hanukkah in December, the June NCAB meeting has been rescheduled for June 1-3, 2004, and the December meeting for November 30, 2004-December 1, 2004.

III. DIRECTOR'S REPORT—DR. ANREW von ESCHENBACH

Dr. von Eschenbach reported on several initiatives that typify NCI's strategy of focusing on aggressive collaborative interactions within government and with extramural entities to create leverage regarding the application of resources. The goal is to develop a critical mass of intellectual capital around specific issues and initiatives. Cancer is seen as an opportunity to lead many of the transformations that have to occur within the scientific discovery process as well as in the development and delivery of state-of-the-art interventions. Dr. von Eschenbach cited one initiative that was discussed at a meeting with the Surgeon General prior to the NCAB meeting as one example. Opportunities for cooperation and collaboration were explored in the area of prevention to address the epidemic of obesity in the United States. A particular focus was an initiative described as energy balance, which is the interaction of nutrition/diet and physical activity, and the impact of that interaction on the problem of cancer and, by extension, the relation to other diseases such as type 2 diabetes and cardiac diseases.

Dr. von Eschenbach noted that the rescheduling of the July meeting of the American Association for Cancer Research (AACR) in Washington, DC, enabled substantial participation on the part of NCI and its staff. He commented on the meeting's success as a scientific forum and on the impressive number of young investigators who were present and participated. He commended AACR's work in providing opportunities that nurture and develop young scientists and clinical investigators, and noted NCI's participation in helping to bring that about.

Dr. von Eschenbach cited the trans-NIH initiative to address the problem of health care disparities as another example of NCI's role in collaborative and cooperative relationships and how effort and progress made in the cancer agenda can be disseminated to have a much broader impact. As background, he explained that at a Department of Health and Human Services (DHHS) retreat, health care disparities had been identified as one of five strategic initiatives that would be embraced as a trans-HHS effort. One NCI-sponsored Progress Review Group (PRG) led to the development of a model for strategic and implementation planning to address health care disparities as they relate to cancer. The NCI was asked to provide the model and the infrastructure that could be adapted to address disparities for the entire area of health care. Dr. von Eschenbach reported that the trans-HHS initiative is moving forward effectively and with much enthusiasm. A meeting of the Health Care Disparities Roundtable recently was held, and a PRG was convened.

Looking ahead, Dr. von Eschenbach noted that significant opportunities for collaboration are emerging from the PCP study in the area of survivorship, with particular attention to issues regarding childhood cancer survivorship. This will be an initiative on NCI's agenda in the coming years. He reported that the NCI has just released a cancer statistics report in collaboration with the Centers for Disease Control and Prevention (CDC), American Cancer Society (ACS), and North American Association of Central Cancer Registries. The report indicates that death rates for lung, breast, prostate, and colorectal cancers continue to decline. However, the report also points out that the rate of decline has apparently stabilized for many of those cancers, indicating that continued vigilance is needed to accelerate the rate of decline. How to capitalize on the progress in biomedical research to have a greater impact on people's lives is an important challenge that will require commitment and a focus on cancer as a disease process to determine how to have the greatest influence.

Dr. von Eschenbach reported that a Training Commission is being established within the NCI to review efforts with regard to the development of young investigators in the areas of basic, translational, and population sciences and clinical research. A lecture series, called "The NCI Director's Seminar Series," is beginning and will feature external speakers and leaders. A presentation by Dr. Mark McClellan, Commissioner, U.S. Food and Drug Administration (FDA), will kick off the Series in January. There also have been a number of important think tanks that have been formed. A series of focus groups have been held under the direction of Dr. Dinah Singer, Director, Division of Cancer Biology, NCI, to engage the broader community in dialogue and discussion of critically important needs and the formulation of a strategic scientific agenda to address them.

Furthering collaborations and cooperative efforts with the international community also is an important part of NCI's agenda, according to Dr. von Eschenbach. Efforts within the NCI have been successful in the areas of training and exchange of scientists. Building on that foundation, the NCI is engaged in creating strategic initiatives with other international cancer agencies. One of these is a recent workshop with Italian scientists and the Italian Health Ministry to explore collaborations in the area of pharmacogenomics. Another is a program to help solve the problem of care for pediatric patients in Iraq. This is being done through NCI's collaboration with the Middle East Cancer Consortium, and the effort is already underway with development of a Cancer Center in Amman, Jordan. Iraqi pediatric cancer patients will be identified and moved to the border by a voluntary agency, then transported to the Cancer Center for care paid for by the King of Jordan. Dr. von Eschenbach pointed out that this effort has enabled the NCI, with Cancer Center Director Dr. Samir Khalife's leadership, to formulate a larger agenda to help rebuild much of Iraq's infrastructure in terms of personnel needed to recreate an oncology program. Other countries and other volunteer agencies will be brought into the process as well.

Dr. von Eschenbach emphasized the importance of finding vehicles for communicating NCI initiatives, engagements, and involvements to both the medical community and the public. The NCI Web Site, http://www.cancer.gov, has provided one vehicle, and Dr. von Eschenbach reported that he has created the Director's Corner on the site to provide weekly updates on initiatives that the NCI has undertaken as well as the rationale and expectations for many of those initiatives.

Dr. von Eschenbach stated that he has asked the NCAB to create a Subcommittee to work with the Director, NCI, and NCI leadership in developing the National Advanced Biomedical Technology Initiative. As background, he cited the extraordinary progress achieved in curing testicular cancer since 1976, when he began his career as a urologic oncologist. As evidence of this progress, he mentioned the survivorship experience of cyclist Lance Armstrong, who succeeded in battling metastatic testicular cancer diagnosed in 1996, to win the Tour de France for the fifth consecutive time by 2003. Dr. von Eschenbach expressed his belief that the progress that has been made since 1971, and enactment of the National Cancer Act together with the evolving understanding of cancer as a disease process with many opportunities for intervention, validate the goal of eliminating suffering and death from cancer by 2015. He noted that the NCI has had an extensive strategic planning process that engages the entire community in defining initiatives and a scientific agenda, and continues to drive toward those opportunities. He stated, however, that maintaining the current exponential growth and trajectory of the biomedical research agenda will require further integration of science with technology to provide even better tools for investigators, hence the proposal to create a Subcommittee to help develop the National Advanced Biomedical Technology Initiative.

Dr. von Eschenbach stated that the proposed Subcommittee, if approved, will be Chaired by Dr. Eric Lander, Director, Whitehead Institute/Massachusetts Institute of Technology Center for Genome Research. With input from Dr. Niederhuber and the Board, Dr. Lander will develop a task force to conduct a series of focus groups to consider emerging technologies and how they relate and could be applied to cancer research. The focus groups will work from the point of view of needs assessment in terms of defining areas where technology can significantly contribute to the acceleration of biomedical research and where those applications could apply. In addition to needs assessment, the focus groups will examine opportunities for incorporating technologies that are developing in disparate fields that could be incorporated into a biomedical research agenda. He asked Dr. Lander to comment on the Subcommittee's role. Dr. Lander explained that the initiative has grown out of NCI's past and current leadership in recognizing the importance of developing infrastructure, such as the Cancer Genome Anatomy Program. The purpose of the forthcoming task force will be to reach out to the community through the focus groups to ascertain the needs of the different communities and opportunities that exist, then suggest to the NCI the kinds of programs that may be needed. Dr. Niederhuber stated that a functional statement for the proposed Subcommittee was being developed for Board action.

Personnel Changes

Dr. von Eschenbach announced that Dr. Edward Maibach has joined the NCI senior leadership team in the position of Associate Director for Strategic Dissemination. Other recruitments are underway and will be reported to the Board as they are finalized.

Budget Update

Mr. John Hartinger, Associate Director, Office of Budget and Financial Management, NCI, reminded the Board that NCI budget for Fiscal Year (FY) 2003 was $4.6B, a $400M or 10 percent increase over FY 2002. The Research Project Grant (RPG) line increased by 10 percent, and the Institute

will fund about 1,360 competing awards, 100 more than in FY 2002. The number of grant applications to the NCI rose once again by about 7-9 percent, a different trend from that of other Institutes. Other programs (center, training, prevention) grew in the range of 11-12 percent. The Specialized Programs of Research Excellence (SPOREs) experienced a 25 percent increase to a level of about $125M, up from about $95M in FY 2002. The Intramural and Management and Administration lines were held to a 2-5 percent growth for FY 2003.

Mr. Hartinger reviewed the status of the FY 2004 budget in Congressional deliberations. The House has approved a budget of $27B for the NIH and $4.7B for NCI, a 3.9 percent or $178M increase for the NCI. In the Senate, an amendment for a $1.5B addition to the NIH budget has been proposed in committee and will go to the full Senate for action. No funds have been allocated for Building and Facilities. Mr. Hartinger noted that the NCI Executive Committee (EC) is proceeding with plans for 2004 despite the uncertainty. Division Directors have proposed many initiatives, and Dr. von Eschenbach will meet with each Director to review details of the budget. Mr. Hartinger pointed out that a 3.9 percent increase would present challenges to maintaining the grant payline at the 20th percentile and funding some of the other initiatives.

In a follow up to payline discussions at the meeting of the Subcommittee for Planning and Budget, Mr. Hartinger explained that although the current estimate of $517M for competing grants in FY 2004 would permit an actual growth in the number of funded RPGs to about 1,431, the expected 7-9 percent increase in applications received would hold the payline at the 18th or 19th percentile. To raise it to the 20th percentile would require additional millions. The Subcommittee is considering various options for maintaining the 20th percentile in the face of an increasing number of applications and higher average costs.

Mr. Hartinger discussed implications of the NIH Roadmap initiatives outlined by Dr. Elias Zerhouni, Director, NIH, at the June meeting. He noted that initiatives were due to the NIH today from all nine of the implementation working groups (the NCI is a member on all of them). Funding for these Roadmap initiatives will come in part from the $35M line in the FY 2004 President's budget. In addition, Dr. Zerhouni has a 1 percent transfer authority, which could add to the uncertainties surrounding the Institutes' budgets for 2004. Finally, Mr. Hartinger reported that the FY 2005 Bypass Budget is in its final stages and is expected to be completed soon.

Questions and Answers

Dr. Ralph Freedman, Professor, Department of Gynecologic Oncology, University of Texas, asked how the budget implications for the proposed new initiative would be addressed, particularly as they relate to the 2005 budget. Dr. von Eschenbach explained that the biotechnology initiative would be developed in parallel with a business planning strategy. He noted, however, that there are opportunities for funding outside of the normal budgetary stream. Dr. Jean deKernion, Professor and Chairman, Department of Urology, University of California School of Medicine, asked whether special funding initiatives would be included in the Bypass Budget or submitted as an independent request for funding. Dr. von Eschenbach explained that in the formulation of a business plan, opportunities and needs will be identified and mapped to the investment requirements. Various mechanisms and opportunities for acquiring the investment would be looked at and pursued as part of the implementation strategy.

Dr. Larry Norton, Director, Medical Breast Oncology, Memorial Sloan-Kettering Cancer Center, asked how intellectual property (IP) rights would be dealt with for the biomedical technology initiative. Dr. Anna Barker, Deputy Director for Strategic Scientific Initiatives, NCI, noted that IP rights would raise

specific issues and pose special problems, particularly regarding the development of therapeutics. She noted that the NIH is planning to participate in a study proposed by the National Academy of Sciences to seek to resolve some of these issues. In the meantime, the problem will have to be approached creatively, including looking at models being used in other places. Dr. von Eschenbach added that the IP issue is being addressed at the NCI level in general because it applies to initiatives already in progress. It also is being addressed at the NIH level in the Public-Private Partnership Committee, which he chairs. In addition, the Office of General Counsel now has a lawyer dedicated to helping the NCI address issues of IP and transfer. Dr. Lander agreed that new tools and infrastructure must be made broadly available in terms of IP considerations and price. He noted that although the proposed Subcommittee would not be charged with specific IP considerations, it would address the issue throughout its discussions, because the biomedical technology initiative will be measured by the fact that the tools are transforming for cancer research, not that they exist in theory. Dr. Barker added that an important consideration will be to develop a strategy for maximizing the availability of precompetitive data and technology.

IV. PRESIDENT'S CANCER PANEL—DR. LaSALLE LEFFALL, JR.

Dr. LaSalle Leffall, Jr., Charles R. Drew Professor of Surgery, Howard University College of Medicine, and Chair, PCP, reminded the Board that the Panel's meetings in 2003 were designed to examine the issues and challenges associated with cancer survivorship. He noted that the nine million people in America alone who have survived cancer attest to progress in understanding and treating cancer, but present a new challenge for the National Cancer Program. Dr. Leffall reviewed the findings from the first meeting, which was held on May 28-30 in Lisbon, Portugal, where it became apparent that the term "cancer survivor" and the concept of "survivorship" are viewed differently in Europe compared with the United States. Europeans do not talk openly about cancer. It is still considered a death sentence by many, and public visibility of survivors is uncommon. Advocacy for survivorship concerns by celebrities such as Lance Armstrong is almost unknown.

On July 28, the Panel co-hosted, with the Lance Armstrong Foundation, a followup event in Paris entitled "Living Beyond Cancer: Celebrating Life." The goals of the event were to: (1) catalyze a change in attitudes toward cancer and those diagnosed with it; (2) support European organizations and institutions in their efforts to increase cancer awareness; (3) promote the concept of celebrating living beyond cancer, that those diagnosed with this disease should no longer bear a stigma of fatality; and (4) mobilize and empower an increasingly large population that is surviving the disease.

Dr. Leffall noted that the first of the meetings in the United States was held in Denver on September 5 to address survivorship issues and challenges among pediatric cancer survivors, defined as those diagnosed from birth to age 14. He called attention to the high survival rate of children with cancer, with estimates that show there are 200,000 pediatric cancer survivors alive today, defined as individuals who were less than 20 years old at diagnosis. However, this group also experiences unique emotional and social concerns associated with aggressive therapy during periods of rapid growth, which causes significant chronic and late health effects. Dr. Leffall pointed out that defining the needs of pediatric survivors and developing recommendations to address them have implications for future cancer research, clinical care, and service delivery.

Dr. Leffall stated that the Denver meeting began with a presentation by Dr. Joseph Simone, Chair, National Cancer Policy Board, summarizing the findings of the Institute of Medicine (IOM) report "Childhood Cancer Survivorship: Improving Care and Quality of Life." This was followed by discussion of the report and testimony on cancer survivorship experiences from those diagnosed with cancer as

children or family members. A Town Hall meeting was held that same evening. Among the issues identified from the testimony were:

- The need for better information and communication regarding long-term effects of cancer treatment
- Better coordination of care post-treatment, both in terms of documentation of medical history and coordination among primary care physicians, specialists, and other health service providers
- A comprehensive survivorship health center outside the treatment setting where survivors can go for information, resources, and support without reliving the treatment experience
- Training of health care professionals about special issues associated with treating or counseling people with a history of cancer
- Greater recognition of the burden of the cancer on families and caregivers, who may receive inadequate counseling and support
- Better educational support during treatment and a consistent process for integrating children back into the educational system following treatment
- Accessible support groups for the children and their families.

Dr. Leffall concluded by noting that he would report on the findings of the September 22 meeting in Austin, TX, on adolescents and young adults and the November 4 meeting in Birmingham, AL, on adults, at the December NCAB meeting.

V. LEGISLATIVE REPORT—MS. SUSAN ERICKSON

Ms. Susan Erickson, Acting Director, Office of Policy Analysis and Response, NCI, reported on the status of Congressional action on the FY 2004 appropriations legislation, in which the Senate proposes $27.99B for the NIH and $4.77B for the NCI, and the House proposes $27.66B for the NIH and $4.77B for the NCI. Discussion is underway in the Senate on 40 amendments. House and Senate Appropriation Committee reports filed in June require the NCI to report on four topics: brain tumors, pancreatic cancer, blood cancers, and prostate cancer. The NCI also was asked to be prepared to address several topics at the FY 2005 appropriation hearings, including: (1) the effectiveness of harm reduction for those tobacco users who are unable to quit, (2) existing and future efforts to better understand chronic myeloproliferative disorders, and (3) a progress report on neurofibromatosis.

Since the June NCAB meeting, NCI staff participated in the June 17 hearing on molecularly targeted cancer treatments held by the Senate Cancer Coalition and the July 10 hearing on the topic "NIH: Moving Research From the Bench to the Bedside." On the latter topic, the focus was technology transfer, and Dr. Barker gave testimony on the NCI-FDA collaboration to accelerate the approval of drugs to treat cancer. Ms. Erickson noted that cancer survivorship also was of great interest to Congress, as indicated by the companion bills introduced in the House and Senate. The bills provide for the expansion and coordination of activities of the NIH and CDC with respect to research and programs on cancer survivorship.

VI. TUMOR IMMUNOLOGY AND IMMUNOTHERAPY WORKSHOP REPORT—DR. JAMES ALLISON

Dr. James Allison, Professor, Department of Immunology, University of California, Berkeley, explained that the workshop was convened on January 22-24 at the request of Dr. von Eschenbach to discuss the latest research in tumor immunology and the opportunities, hurdles, and barriers related to effectively translating the basic science. Co-Chairs were Dr. Allison and Dr. Drew Pardoll, Professor and Co-Director, Division of Immunology and Hematology, Johns Hopkins University (JHU) School of

Medicine.

As background, Dr. Allison noted that cancer immunotherapy has been regarded with skepticism because of the failure of apparently promising approaches such as lymphokine-activated killer cells and tumor-infiltrating lymphocytes in gaining widespread utility and because of the disappointing results from recent Phase III trials on cancer vaccines. However, some immunotherapies, such as the graft-versus-leukemia reaction after allogeneic bone marrow transplantation, IL-2, and monoclonal antibodies, have been established as successful. Other immunotherapies, such as T-cell transfer and anti-CTLA-4 for melanoma and genetically modified vaccines, show promising early and mid-stage results. It has been established that cancer patients have both antibodies and T cells that can recognize antigens expressed by their tumor. However, the tumor-specific T cells usually are in a tolerant or hypoactive state and therefore ineffective. Dr. Allison noted that a major goal of current immunotherapy is to manipulate T cell regulatory pathways to break tolerance. Current approaches to breaking tolerance include targeting activated dendritic cells, enhancing T cell antigen receptor signal, enhancing co-stimulatory signals required to make T cells react efficiently, blocking immunological checkpoints, and infusing *in vitro*-developed nontolerant T cells to the tumor.

Dr. Allison briefly described research in the laboratories of Dr. Pardoll and others to achieve enhanced antigen presentation by dendritic cells. He then described work in his laboratory to block immunologic checkpoints using anti-CTLA-4 as a strategy for enhancing T cell responses. He noted that this strategy proved to be successful in a number of animal models, but not all of them. Subsequent testing in the B16 melanoma model showed that anti-CTLA-4 alone was ineffective, but the combination of CTLA-4 and GM-CSF tumor cell vaccine created a synergy that eradicated established B16 melanoma. Vitiligo was the only side effect. An antibody to human CTLA-4, made by GenPharm/Medarex, Inc., was tested in monkey models and proved to be safe. Dr. Allison presented data from Phase I trials. Two out of seven patients with hormone-refractory prostate cancer had a PSA drop of more than 50 percent after a single injection of antibody. One patient required a second injection at 5 months and again experienced a reduction in PSA.

Next, Dr. Allison presented data from a trial conducted by intramural NCI scientist Dr. Steven Rosenberg, in which immunization with a peptide was combined with anti-CTLA-4 administered in 3-week cycles. One patient with extensive lung, subcutaneous, and brain metastases experienced a complete response that has lasted 18 months so far. In the small sample of 14 patients, there were 2 complete responses, 1 partial response, and 4 mixed responses. Dr. Allison pointed out that autoimmunity was one side effect in the trial. One patient in the trial acquired autoimmune hepatitis and hypopituitarism, but both were resolved with treatment. He noted that this suggests the need to begin thinking about combining good vaccines. The challenge is to try to develop rational vaccines to be used with a checkpoint blockade to achieve good therapeutic responses without autoimmunity.

Dr. Allison concluded the scientific background for the workshop recommendations by showing that many of the molecules involved in T cell regulation are now defined, largely through R01 projects funded by the NCI. The molecules have unique inflections and function at different sites and on different components of T cell responses, but sets of them could rationally be combined to unleash T cells in a controlled manner, according to Dr. Allison. He added that great strides have been made in the past 5 years; the challenge is to take this information to the clinic.

On behalf of Dr. Pardoll, who could not be present, Dr. Allison continued the presentation of immunologics development from the clinical perspective and workshop recommendations. He discussed the following barriers to the development of immunologics: (1) the strategies are complex, involving

engineered peptides, proteins, or plasmids; (2) the regulatory burden is so high that it is difficult to develop immunologics at academic institutions; and (3) the pharmaceutical industry does not work well with biologics. This results in conservative development approaches and a lack of sustained commitment to development. Leadership in biologics development remains within the public/academic sector. Dr. Allison listed aspects of corporate culture that hamper ultimate immunologics development. He expressed the workshop's view that these and other issues limit the interest of corporations; hence, the NCI needs to be involved in a greater degree to help with the translation of immunologics.

Dr. Allison noted that NCI's solution to empower academia for therapeutics development was the Rapid Access to Intervention Development (RAID) Program. He presented the workshop views on the benefits of the RAID Program and suggestions for improving it. The concept, and NCI's Biological Resources Branch (BRB), which administers the program, was viewed as excellent. The great flexibility in interaction with academic groups and absence of interference with developing corporate relations were commended. The conclusion was that the program should be preserved and better resourced; however, the progress of agents through the program was considered to be too slow. Suggestions for improvement dealt largely with improving the consistency of the initial review for better project selection and accelerating the entire process. With regard to the latter, recommendations included adequately staffing the BRB for more efficient completion of projects and addressing the problems related to reagent production.

Dr. Allison noted that some of the most interesting immunologic agents are not being developed in the most promising fashion by the companies that have them, and he discussed reasons for this. Moreover, the companies have not been liberal in giving agents to academic investigators to develop for reasons of cost, loss of control, liability issues, and reluctance to have their agents used in combination with agents owned by others. In addition, independent investigators often cannot access key decisionmakers within the companies to make their case. Dr. Allison noted that instances of enlightened reagent transfer do occur between companies and academic institutions. He gave the example of an arrangement between CellGenesys and JHU that allowed JHU to use the K562-GM-CSF vaccine, which had been licensed to CellGenesys, for combination trials independent of the company's single-agent trials to the benefit of both parties.

Dr. Allison explained that the solution proposed by the workshop was that the NCI be proactive in getting the most interesting immunologic agents into the clinic in the most promising settings. Suggestions in that regard were: (1) a decision network "board" to prioritize important biologic agents and review proposals for their clinical testing, (2) NCI and FDA interaction with companies to make agents and/or expertise to produce them and make them available to the NCI with liability protection, and (3) integration of the production aspect with an expanded and streamlined RAID Program. Workshop participants also suggested that the NCI consider a mechanism similar to a SPORE to fund inter-institution research projects with a goal of translating agents quickly.

Questions and Answers

Dr. Frank Prendergast, Director, Mayo Comprehensive Cancer Center, noted that a few academic institutions have Good Manufacturing Practice (GMP) certified production facilities and asked about mechanisms that could be made available by the NCI to empower inter-institutional collaborations that could help sustain those entities and provide agents more rapidly. Dr. Barker replied that discussions and a needs analysis are underway to address the problem of making the pipeline for small molecules and biologics more efficient and effective. She also agreed with the need for prioritization, and noted that a fall meeting is being considered. Dr. Norton suggested that, because the very early development of

agents through Phase I testing would be a service to the industry, an expansion of RAID via a consortium of pharmaceutical industries might be considered in the spirit of public-private partnerships. Dr. deKernion commented that a funding mechanism should be considered for contracting to underutilized facilities in a number of smaller companies with GMP facilities.

VII. NCI TUMOR IMMUNOLOGY AND IMMUNOTHERAPY STRATEGIC INITIATIVES—DRS. JOHN SOGN, ALLAN MUFSON, AND EDWARD SAUSVILLE

Dr. John Sogn, Deputy Director, Division of Cancer Biology (DCB), NCI, explained that although tumor immunology is supported to some extent in all four NCI extramural program Divisions, the bulk of support comes from the Cancer Immunology and Hematology Branch (CIHB), DCB, and the Developmental Therapeutics Program (DTP), Division of Cancer Treatment and Diagnosis (DCTD). He introduced Dr. R. Allan Mufson, Chief, CIHB, and Dr. Edward Sausville, Associate Director, DTP, DCTD, to outline NCI plans in response to the Tumor Immunology and Immunotherapy Workshop recommendations.

NCI Activities in Support of Tumor Immunology and Immunotherapy Research

Dr. Mufson provided an overview of the ongoing support that the NCI provides to basic research in tumor immunology and immunotherapy. He pointed out that a greater understanding of the basic biology of the immune system and its response to tumor cells will allow for the successful use of immunotherapy alone or in combination with other therapies against cancer, and that the NCI is committed to furthering basic research in this area. Dr. Mufson pointed out that the NCI provides significant support for investigator-initiated research, innovative collaborations, resources and reagents, and new imaging technologies relevant to solving problems in tumor immunology. He briefly reviewed NCI, DCB, and CIHB activities and initiatives. Within the NCI, the six scientific Branches of the DCB are responsible for facilitating basic research in cancer biology. The CIHB is responsible for tumor immunology and immunotherapy research, and currently funds 152 R01 research grants worth $42M and 5 P01 grants worth $5.7M in that area. This represents 40 percent of CIHB-awarded funding. In addition, the CIHB funds 15 of DCB's Activities to Promote Research Collaborations, 11 of which are immunology/immunotherapy collaborations. The CIHB also developed and administers the Mouse Models of Human Cancer Consortium.

In addition to direct support for tumor immunology research, the NCI supports research resources valuable to the tumor immunology community, such as the Tetramer Facility operated by the National Institute for Allergy and Infectious Diseases. The DCB has contributed to this facility over the past 3 years, spending $250K in 2003. In addition, the BRB maintains a repository of cytokines and antibodies, which are available to the immunology research community. The NCI also develops initiatives to promote the development of new technologies to study immune function, including two Requests for Applications (RFAs) and one Program Announcement (PA) in imaging relevant to immune function, and one PA in human immunology, all of which were issued in 2002 and 2003.

Dr. Allison noted that NCI's commitment to the future of tumor immunology and immunotherapy is evident in ongoing initiatives for which increased funding has been requested in the Bypass Budget for FY 2004. Included in this request is $10M to fund three initiatives that define the molecular signatures of immune cells in the cancer microenvironment and $8.3M to fund five cancer vaccine development initiatives.

Update on RAID—Rapid Access to Intervention Development

Dr. Sausville reminded the Board that the NCI has had an extensive commitment to therapy development since the 1970s as represented by the Drug Development Group. Screening and development of preclinical data were conducted primarily at the Frederick Cancer Research and Development Center (FCRDC) and advanced safety testing at contract sites around the country, leading to an NCI-held investigational new drug (IND) and NCI clinical trial. In l998, the RAID Program was initiated to address opportunities that were emerging primarily from academia. In RAID, the plan was to use the same contract resource mechanisms but leading to an investigator-held IND with responsibility for conducting the trial vested with the investigator.

Dr. Sausville then reviewed NCI's biologics production/acquisition strategies, budget, and staffing level. Biologics are acquired from collaborating companies and through production at NCI-FCRDC and contracted production at other off-site facilities with onsite FCRDC quality assurance/quality control (QA/QC). Dr. Sausville noted that the BRB biologics budget has tripled since FY 1997, but the level of BRB staff who manage the program has remained constant over that same period, with some augmentation of contractors. RAID had the goal of promoting compounds originating in academic centers. It provided preclinical contract research resources to academic or academic/small business partnerships, allowing studies to occur under investigator or academic center sponsorship. Examples of the RAID tasks essentially overlap and are parallel with those in the BRB, and the goal was to bridge the gap between a lead discovery and a drug that might be studied in clinical trials. Unique features of RAID were the partnering of NCI internal and contract research resources to allow access to NCI in-house expertise with a tangible output—data suitable for IND submission, data for licensing to third parties, and products for clinical trial. The IP remains with the originating investigator, with the possibility for contractor staff to be in compliance with Bayh-Dole regulations. The funding goal was $10M to $15M per year for contract research.

One impetus for RAID was that study sections do not fund developmental tasks. Another was to allow investigator-initiated science to define the clinical investigation agenda. Hypothesis-driven investigations were emphasized, and IP would normally remain in investigators' hands. RAID was not envisioned as a pipeline for NCI INDs, nor was it designed to provide unconditional commitment. Milestones were built in, and poorly performing projects were subject to re-review. RAID also was neither an assistance mechanism for the pharmaceutical industry nor a grant program to a particular laboratory. RAID logistics also were unique in that: (1) reviews were to be conducted within 2-3 months of application, although biologics were subject to a second-level review for technical production feasibility; (2) strength of hypothesis, scientific novelty, and cost/benefit value were the criteria for review; and (3) the Review Committee could recommend all or only some of the proposed steps. RAID was envisioned as an interactive collaboration of the NCI with the participants. Dr. Sausville noted that the BRB Oversight Committee was created to help prioritize the many different projects not only from the RAID Program but also from the intramural program and other federal agencies that would seek to produce novel, high-quality biologics. The Oversight Committee also addressed the issue of technical feasibility.

Dr. Sausville provided data on RAID projects by type and costs to date for the program. Of 225 applications received, 84 projects were approved. They are about evenly split between small molecules and biologics and cover a wide range of projects, many of which are immunologically relevant. Total cost to date for the 84 projects is $42,685K, which is about on track for the $10M to $15M per year projection over the life of the project. Examples of successful biologics projects are an Epstein-Barr virus supernatant to attempt to immunize transplant patients against EBV-related lymphomas, a monoclonal

antibody capable of dissolving light-chain amyloid disease, and a monoclonal antibody that is cytotoxic to various forms of lymphoma. Another 10 RAID biology/immunology-related projects will be ready for IND filing by the end of 2003.

Next, Dr. Sausville discussed timelines for RAID projects, noting that median time to completion for immunology-related molecules are 8-12 months slower than the small molecules. That holds true for total projects, preclinically oriented projects, and projects for clinical development. However, Dr. Sausville pointed out, the median time to completion is between 2 and 3 years, which is competitive with some industry approaches. He noted that delays occur because of quality, safety, and reproducibility concerns, and because many incoming biologics projects have problems that require fixing by the BRB. These include expression systems, analytical approaches, regulatory and safety issues, IP concerns, and delays in Material Transfer Agreements. Dr. Sausville concluded that clear collaboration is needed with investigators who have worked through a number of different milestones if the program is to be as rapid as it could be. He noted that the NCI aims to work with investigators so that good ideas can be supported, and he welcomed the prospect of expanding RAID in a way that is appropriately partnered with extramural colleagues. He directed attention to the Web Site http://dtp.nci.nih.gov for a more detailed discussion of RAID.

Questions and Answers

Dr. Arthur Nienhuis, Director, St. Jude Children's Research Hospital, expressed the hope that mechanisms will be developed over time to extend the expertise that has been developed within the RAID Program to maximize the benefits of GMP facilities that have been constructed at various academic institutions. He asked to what extent the secondary review process for biologics begins to impose a bias on what the NCI is willing to undertake within the RAID Program. Dr. Sausville agreed that once a facility is developed with a certain type of product, it continues to be the in-house forte. He expressed the view that no one place can possibly represent all of the expertise necessary to provide the different items suitable for clinical research, and that a nationally coordinated program that engages existing GMP manufacturing facilities and builds in Centers of Excellence in a particular type of product might be the answer. In response to a question from Dr. Freedman, Dr. Sausville estimated that between 5 percent and 10 percent of the products that enter the Program have been licensed by their originating party to a commercial firm. He reiterated that RAID was designed to promote the early phase clinical testing, to the point where the product is attractive to the commercial sector for development to the approval stage.

Dr. Ellen Feigal, Acting Director, DCTD, noted that the NCI is aware of and working to address issues raised by the workshop, namely, the need to think strategically on a national scale about what molecules might be combined for greater efficacy and tie that to what is entering the pipeline. The NCI also is working directly on the problem of providing greater access to molecules. Dr. Prendergast asked whether a database of the GMP facilities and capabilities exists nationally. Dr. Barker replied that the issue is on the agenda of the fall planning sessions.

Dr. Niederhuber commented that institutions can often afford the one-time expense of building a facility but cannot adequately maintain staffing. Dr. Sausville agreed that the valuable contributions a well resourced and staffed facility could make are often not valued in academia. QA/QC, assay sequencing of agents, and verification of the master cell bank are tasks traditionally associated with the pharmaceutical industry. He noted, however, that if the academic sector chooses to participate, a way must be found to provide resources because the price of not doing so ranges from flawed reagents to patient care disasters.

Dr. von Eschenbach thanked Drs. Allison and Pardoll and workshop participants for providing a focus on issues and needs in a very important part of the NCI portfolio. He looked forward to continued interaction and dialogue as tumor immunology and immunotherapy initiatives are developed to address many of the issues that were raised. The need for tools will be addressed, and initiatives as they are created will be integrated across the various disciplines and areas of emphasis. Dr. von Eschenbach pointed out that the workshop framed an important role for the NCI in terms of its leadership opportunity. In areas such as immunology, the NCI must provide the leadership and help create the opportunities to leverage resources for accomplishing what the Institute alone cannot do through the funding of specific initiatives. He commended the RAID Program as a source of pride and an important initiative and expressed gratitude for the work of Dr. Sausville and DTP staff. Dr. von Eschenbach noted that staff are exploring ways to increase the capacity of the Program without jeopardizing the quality and to leverage the leadership of RAID to integrate the capacity that exists in the private and academic sectors for even greater impact. He remarked that the RAID Program has become an important focus for the NIH Roadmap initiative. A collaborative effort is being discussed with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and the conversation will be expanded to other Institutes as well.

VIII. NIH REORGANIZATION COMMITTEE REPORT—DR. FRANK PRENDERGAST

Dr. Prendergast prefaced his summary of the IOM report entitled "Enhancing the Vitality of the National Institutes of Health: Organizational Change to Meet New Challenges," with the observation that the research in general and the NIH in particular is being subjected to substantial scrutiny as a consequence of the doubling of the NIH budget, as well as the high expectations of the public and the large number of stakeholders. The report was the product of the Committee on Organizational Structure of the NIH, Chaired by Dr. Harold Shapiro, and drawn broadly from across the country. The Committee met over a 9-month period, heard testimony from a large number of people, and conducted interviews with a substantial number of intramural NIH staff. Dr. Prendergast commented that there was unanimity among members regarding the genuine sense of NIH and NCI success over the years, including effective management of the biomedical enterprise for the country.

Dr. Prendergast noted that the mandate from Congress for this study was to determine the optimal NIH organizational structure, given the context of 21st century biomedical research. The study revolved around five questions: (1) Are there general principles by which the NIH should be organized? (2) Does the current structure reflect these principles, or should the NIH be restructured? (3) If restructuring is recommended, what should the new structure be? (4) How will the proposed new structure improve NIH's ability to conduct biomedical research and training, and accommodate organizational growth in the future? (5) How would the proposed new structure overcome current weaknesses, and what new problems might it introduce?

Dr. Prendergast briefly summarized the 14 recommendations of the Committee:

- Any efforts to consolidate or centralize management functions at the NIH, either within the NIH or the DHHS level, should be considered only after careful study.
- A public process should be developed for proposed changes in the number of NIH Institutes and Centers (ICs).
- Strengthen clinical research. In this regard, the Committee recommended that several intramural and extramural programs be combined in a new entity to subsume and replace the National Center for Research Resources, to be called the National Center for Clinical Research and Research Resources.
- Enhance and increase trans-NIH strategic planning and funding.

- Strengthen the Office of the Director (OD), NIH.
- Establish a public process for creating new offices and programs in the OD, NIH.
- Establish a discrete program, the Director's Special Project Program, within the OD, NIH, to fund the initiation of high-risk, exceptionally innovative research projects offering high potential payoff.
- Promote innovation and risk-taking in intramural research.
- Standardize data and information management systems.
- Set terms and conditions for IC Director appointments and improve the IC Director review process.
- Set terms and conditions for the NIH Director appointment.
- Reconsider the status of the NCI.
- Retain integrity in appointments to advisory councils and reform advisory council activity and membership criteria.
- Increase funding for research management and support.

Questions and Answers

Drs. Niederhuber and Norton observed that very few groups representing the cancer research community came before the Committee or provided input. Dr. Norton expressed the view that the report would be improved by the inclusion of documentation of the need for many of the changes that were recommended. Dr. Prendergast pointed out that the report was a consensus document and contained few definitive recommendations for actual structural change. He commented on the need for a clearer articulation of NIH accomplishments to the public and to Congress (e.g., the many trans-NIH initiatives that have been already undertaken).

Dr. von Eschenbach commented on what has happened since the report was released. He noted that the authorizations for the NIH and the NCI are being examined by Congress this year, and the authorization committees (Energy and Commerce Committees in the House; Health, Education, and Labor in the Senate) have scheduled a joint hearing on October 2, specifically around the IOM report. A 2-day retreat of IC Directors has been held to discuss the implications of the recommendations and inform Dr. Zerhouni in a way that enables him to assemble an appropriate response and be adequately prepared for the hearings. Dr. von Eschenbach noted that the NCI and its special authorizations by virtue of the National Cancer Act of 1971 were discussed, and he was able to provide historically specific information to clarify what could be misconceptions or misinterpretations of the authorizations. He agreed that it is important for the NIH to communicate to the public and Congress and that there be mechanisms to manage these activities. Dr. Prendergast emphasized the need for vigilance by individual groups that are stakeholders when issues such as these arise.

IX. WORKING LUNCH

Update on NIH Loan Repayment Program—Dr. Carolyn Strete

Dr. Carolyn Strete, Chief, Cancer Training Branch, Office of Centers, Training and Resources, NCI, stated that the purpose of the NIH Loan Repayment Program (LRP) is the recruitment and retention of highly qualified health professionals who conduct clinical and pediatric research. The LRP is a contractual agreement whereby recipients agree to participate in pediatric or clinical research for 2 years in return for the offer of repayment of up to $35K of the principal and interest of eligible educational loans. In addition, 39 percent of the loan repayment is allowed per year toward federal tax liability.

Dr. Strete then presented outcomes of the FY03 competition, including gender and race/ethnicity

data (information) as requested by the Board at a previous meeting. A total of 242 applications received this fiscal year had a primary assignment to the NCI; an additional 68 applications with primary assignments to other Institutes/Centers had dual assignments to NCI because of scientific overlap. She noted that the 242 applications received priority scores. The majority, or 83 percent (189) of the applications, were in the clinical area and 18 percent (42) were in pediatrics. Noting that gender and race/ethnicity were self-reported, Dr. Strete told the Board that in both science categories, males accounted for more than 50 percent of the applicants. In the total number of scored applications by race and ethnicity, the majority were white (72 percent), Asians made up 10 percent, African Americans 6 percent, Latinos 3 percent, and Other (Hawaiian and Pacific Islanders, American Indians, Alaskan Indians) 4 percent. By race and ethnicity and program type, the award distribution was: White—70 percent for clinical and 81 percent for pediatric; African American—7 percent for clinical and 2 percent for pediatric; Latino—2 percent for clinical and 5 percent for pediatric; Asian—11 percent for clinical and 7 percent for pediatric; Other—4 percent for clinical and 5 percent for pediatric. By award status, 54 percent of the clinical applications were funded, compared with 67 percent for pediatrics.

Dr. Strete observed that the NCI had a large population of grants from which to select. In the clinical area, one-half of the applications had scores between 1.0 and 2.0. About 74 percent of pediatric applications had scores in that range. In terms of awards by gender, 64 percent of males and 36 percent of females were selected. Award distribution by race/ethnicity and program type were: White—77 (41 percent) for clinical and 23 (55 percent) for pediatric; African American—4 (2 percent) for clinical and none for pediatric; Latino—2 (1 percent) for clinical and 2 (5 percent) for pediatric; Asian—12 (6 percent) for clinical and 2 (5 percent); and Other—5 (3 percent) for clinical and 1 (2 percent) for pediatric. Distribution of award dollars by fiscal year and type in FY 2002 was $4,165K total, $1,461K for pediatric and $2,704K for clinical. In FY 2003, the total was $8,222K, with $1,689K in pediatric awards and $6,533K in clinical awards. Dr. Strete noted that the latest competition cycle began on September 1, with a December 31 deadline. She reported that the 106 individuals who were not successful in this year's competition received feedback on how their applications could be improved. The Web Site for additional information is http://www.lrp.nih.gov.

Questions and Answers

Dr. Niederhuber asked and received confirmation from Dr. Strete that the NIH Loan Repayment Office is planning mechanisms to evaluate the Program. Dr. Niederhuber noted that it would be important in characterizing this community to know what type of support the individuals had as they are going through their training.

Impact of HIPAA on Oncology Research—Dr. Amelie Ramirez

Dr. Amelie Ramirez, Associate Professor, Department of Medicine, Baylor College of Medicine, presented preliminary findings of the *Ad Hoc* Subcommittee on Confidentiality of Patient Data inquiry into the impact of the Health Insurance Portability and Accountability Act (HIPAA) on oncology clinical research. The Committee selected the public comment mechanism to seek information from NCI-affiliated comprehensive and clinical Cancer Centers, cooperative groups, and SPOREs. Another goal was to positively influence the implementation process.

Dr. Ramirez reviewed methodology for the inquiry and the response. Letters requesting the names of HIPAA experts and IRB members were sent to Cancer Center Directors, Principal Investigators, and Cooperative Group Chairs. A Web-based public comment feedback form was developed addressing four general content areas: (1) areas most likely to affect research, (2) suggestions for modifying the

Privacy Rule, (3) clarification of the Rule that would be helpful, and (4) additional comments. The Cancer Centers, Cooperative Groups, and SPOREs provided a contact list of 226 HIPAA experts. Dr. Ramirez noted that although 83 responses were received, many of the submissions pooled multiple individuals; therefore, the sample is actually broader. Evaluation of the responses involved grouping and quoting similar comments to identify recurrent themes and issues. Among the general findings, Dr. Ramirez noted, was that the complex regulatory language is open to wide interpretation and various institutions established different requirements in implementing the Rule. Unintended consequences that were reported included the following: (1) conducting research is more challenging; (2) potential study participants are confused; (3) additional documentation leads to long delays and selection bias; (4) collaboration across institutions is more complicated, especially multi-center studies; (5) there are additional barriers to the use of identifiable specimens; and (6) the use of large databases is more restricted.

Dr. Ramirez pointed out that many of these problems may be mitigated when the DHHS releases all of the plans outlined by the document, particularly those related to specimen banks and research databases. On behalf of the Subcommittee, Dr. Ramirez proposed that the NCAB write a letter to the Department detailing the results of the study and suggesting changes that would address the most pressing problems. The most important change would be to provide specific guidance on how to make data from specimen resources and other research databases available to users without separate authorizations for each project.

Dr. Ramirez asked for other comments from the Board to be added to the Subcommittee's assessment. Dr. Freedman expressed concern that a patient's care could be impaired because documentation on that patient cannot be transferred according to the Rule. Dr. Prendergast commented on the potential for research cost increases because of the complexity of the consent forms and added workload.

Motion. A motion was made that the *Ad Hoc* Subcommittee on Confidentiality of Patient Data be charged to draft a letter to the DHHS to reflect the concerns of the Board regarding the HIPAA Privacy Rule. The motion was seconded and passed.

P01 Review Process Report—Dr. Olivia Bartlett

Dr. Olivia Bartlett, Chief, Research Programs Review Branch, DEA, pointed out that the challenge for the DEA is to maintain a high-quality review and standard for all applications in the face of an increasing P01 workload, reviewer recruitment challenges, the need to maintain scoring consistency and avoid priority score compression, reviewer and staff time investment, and review costs. To address these challenges, an NCI P01 Working Group was convened to examine the review format and other aspects of program project (P01) review and make recommendations to the EC. The Working Group was Co-Chaired by Ms. Diane Bronzert, Associate Director, Office of Referral, Review and Program Coordination, DEA, and Dr. Sogn. It included representatives from the four NCI program Divisions, the NCI Budget Office, and the DEA. P01 review practices were benchmarked across the NCI, and three P01 Parent Committees were surveyed. Most important factors in the review process identified by the latter were the expertise of the Committee and the need for reviewers to meet face to face and have the opportunity to ask questions of the applicants. The Parent Committees also favored having the ability to use triage in P01 review, shorter meetings, and the use of videoconferencing.

On the basis of the information collected, the P01 Working Group considered and evaluated several review formats to address the listed challenges and the issues deemed important by the Parent

Committees. As a result, the P01 Working Group recommended that: (1) the NCI adopt a cluster review format for all P01 applications (2-4 with closely related topics); (2) original and amended applications are reviewed together, with no individual site visits or teleconferences; (3) reviewers meet face to face in the Washington, DC, area or elsewhere; (4) applicants are contacted by tele- or videoconference to ask questions; (5) Parent Committee members serve on one cluster, not several individual review panels; and (6) final scoring is to be done by the Parent Committee. Dr. Bartlett noted that the cluster review format has significant advantages in that fewer reviewers are required; scoring consistency and score spread are promoted; the number of review meetings is reduced; expedited discussion and triage of poor applications is enabled; and time and cost savings are affected for NCI staff, reviewers, and applicants. Dr. Bartlett explained that the Working Group recommended a 1-year trial of cluster review beginning with the February 1, 2004, receipt date. In the meantime, plans are being developed for evaluating the impact of the process on reviewer recruitment, number of reviewers required, priority score spread, and review cost. The plan was presented to the EC on July 29, and discussed with the plenary session of the three P01 Parent Committees that evening.

Questions and Answers

From his experience as both applicant and reviewer, Dr. Norton expressed the view that face-to-face interaction at the site visit and the ability to verbally explain the project is critical to the review process. Dr. Bartlett explained how the new format incorporates those capabilities. Dr. Gray reminded the Board that this is a 1-year pilot project, and that the DEA will return to the Board within the year to present results.

X. CURRENT ISSUES IN TOBACCO CONTROL—DRS. ROBERT CROYLE, SCOTT LEISCHOW, NEIL CAPORASO, THOMAS GLYNN, AND MS. ROSEMARIE HENSON

Introduction

Dr. Robert Croyle, Director, Division of Cancer Control and Population Sciences, NCI, characterized the extent to which tobacco is a risk factor for and accounts for deaths from many types of cancer and other diseases. He noted that 10 years ago, the DCCPS gave an update to the NCAB and implemented new plans for expanding basic and applied research efforts on tobacco control. At this meeting, the presentations focused on examples of scientific advances and challenges since that time, contributions of the NCI intramural program, the federal government's efforts with state health departments to deliver tobacco control programs across the United States, and collaborations created to translate research into practice. Dr. Croyle highlighted the fact that much of the work has been done through substantial expanded collaborations with other NIH Institutes, other DHHS agencies, and private partners. He acknowledged the partnerships with CDC's Office on Smoking and Health (OSH), ACS, National Institute on Drug Abuse, Robert Wood Johnson Foundation, and American Legacy Foundation in the new and expanded program of integrative transdisciplinary research and programs.

Current NCI Activities in Tobacco Control

Dr. Scott Leischow, Chief, Tobacco Control Research Branch, NCI, called attention to the Annual *Report to the Nation on the Status of Cancer, 1975-2000,* which demonstrates that progress has been made in tobacco control and tobacco-related disease; however, much remains to be done in light of findings that cigarette smoking accounts for about 30 percent of cancer deaths in the United States and an estimated 16 percent of incident cancers worldwide. The report also emphasizes that sustained efforts will be required to reduce the percentage of adolescents who begin using tobacco and to increase the

number of adults who successfully stop. Dr. Leischow noted that his presentation would provide highlights of NCI's research in those two areas. He cited CDC data, which demonstrate that the downward trajectory started in 1964 as a result of tobacco control research and essentially plateaued for men in the 1990s (at 22.8 percent) and rose for adolescents but returned to the 1990 level (29 percent) over the same period. He stated that the NCI supports a broad spectrum of basic and applied research in the behavioral, social, and population sciences on the prevention and cessation of tobacco use among both youth and adults, and he presented examples of research with emphases on the etiology of tobacco use and addiction, adolescent prevention and cessation, adult cessation, delivery, and dissemination.

Dr. Leischow stated that research has shown that a complex interplay of genetics, family, social, and environmental factors impact the probability that adolescents will smoke. Some of the social risk factors are parents, siblings, and friends who smoke and exposure to smoking in the movies and on television. The Transdisciplinary Tobacco Use Research Centers (TTURC) RFA is exploring the nature of nicotine addiction using adolescent and adult Sprague Dolly rats. Findings suggest that the combination of nicotine and acetaldehyde (a byproduct of combustion during smoking) has a high addiction probability in the adolescent brain compared with the adult brain. There is evidence that the brains of adolescent smokers are changed even with moderate smoking and show signs of addiction before regular smoking occurs. Dr. Leischow noted that NCI-funded studies on smoking prevention and cessation include a school-based curriculum prevention study, which followed more than 8,000 third graders over 15 years. Although it was found that the experimental conditions did not prevent tobacco use, the study reinforced the CDC recommendation that tobacco use prevention programs should be comprehensive and include school, family, community, and policy interventions. The NCI also funds studies on adolescent tobacco cessation because most adults became addicted as children. One study showed that quit rates were higher in those who received behavioral intervention, but most adolescent smoking cessation studies have been ineffective, including studies on the nicotine patch.

A pharmacogenetic study of smoking cessation conducted within one TTURC grant found that smokers with a CYP2B6 polymorphism were more likely to relapse than those without the polymorphism in the placebo group. The study also found that bupropion, the intervention medication, appeared to counteract the negative effects of the polymorphism in women but not in men. Dr. Leischow noted the importance of this finding because interventions that will help women quit are essential (multiple studies have found that women, in general, are more likely than men to relapse when they try to quit smoking). Investigators in another TTURC evaluated the efficacy of selegiline as a smoking cessation medication and found the medication to be promising. Another study of an HMO cohort found that a 150 mg dose of buproprion was as effective as a 300 mg dose in combination with a moderate behavioral intervention in helping smokers quit. These results could have immediate value to health care systems that provide smoking cessation and, in effect, decrease the cost of treating tobacco dependence.

Dr. Leischow explained that the NCI is actively involved in the dissemination and delivery of information and effective interventions. The Cancer Information Service (CIS), which provides basic smoking cessation assistance and sends smoking cessation materials to those who want to quit, plays a significant role in providing the American public with access to effective smoking cessation services. The Tobacco Control Research Branch, in collaboration with the CIS, has developed a smoking cessation Web site, http://www.smokefree.gov. The site is linked to CIS' telephone service through an instant messaging system. Dr. Jon Kerner, in partnership with several organizations, has developed Cancer Control PLANET, a Web site that provides evidence-based materials and information along with links to partner organizations so that cancer control programs can be based on the best evidence and be maximally implemented. Some of the materials and resources on this site are tobacco specific. Additionally, smoking and tobacco control monographs have been a significant part of NCI's dissemination activities.

In the last 2 years, four monographs have been released, including one on light cigarettes that concluded that smokers who switch to light cigarettes cannot expect a reduction in health risk. This monograph has had huge

impact worldwide in addressing some of the advertising and other tobacco industry activities that have erroneously suggested that there is a health benefit associated with switching to light cigarettes.

Dr. Leischow concluded his remarks by emphasizing that tobacco use begins in adolescents, and new research is needed to identify effective prevention approaches. Without effective interventions, only about 5 percent of people who try to quit smoking are successful. This is a very low success rate that must be improved upon. NCI-funded research has made lasting and innovative contributions to the understanding of the etiology, prevention, and treatment of tobacco addiction. Achieving Healthy People 2010 goals will require increased emphasis on the discovery, development, and delivery of more effective prevention and treatment interventions. Before introducing Dr. Neil Caporaso, Dr. Croyle noted that the NCI has partnered with the National Institute on Alcohol Abuse and Alcoholism (NIAAA) to explore a number of different collaborations on comorbidities associated with alcohol and tobacco use. The NIAAA also has agreed to partner with the NCI on the reissuance of the TTURC RFA.

Genetic Influences on Tobacco Addiction and Tobacco-Related Carcinogenesis

Dr. Neil Caporaso, Chief, Pharmacogenetics Section, Division of Cancer Epidemiology and Genetics (DCEG), NCI, explained that there is strong evidence suggesting that inherited variation contributes to tobacco dependency and susceptibility to tobacco-related cancers. However, the specific genes are poorly understood, and large, integrated studies likely will be needed to identify and confirm those genes. DCEG's intramural program has a number of molecular epidemiology studies that are capable of addressing these questions. These are large, case-controlled studies that generally have more than 800 cases and similar numbers of controls.

Dr. Caporaso discussed the evidence for hereditary variation in cancer using lung cancer as an example. The best evidence comes from case-controlled studies that consistently show increased risks of lung cancer in the case relatives. Segregation analyses, population databases, and twin studies also suggest a hereditary influence. He briefly presented the results of one study showing that relatives of cases tend to be at greater risk for lung cancer than the relatives of controls after adjusting for a variety of other risk factors. Many independent twin studies from different countries clearly and consistently demonstrate an influence of heredity on tobacco dependency. Human genetic studies are in their infancy at present, and include a small number of linkage studies and candidate gene studies.

At least four of the major carcinogens in tobacco are under a genetic influence. Dr. Caporaso conducted a review of all of the meta-analyses he found in the literature for lung cancer and explained that for the Phase I genes (the activator genes, those that tend to put a functional group on a carcinogen and make it capable of attacking DNA), the best study involves CYP1A1. Although increased risks are observed, for risks significantly below one, the lower limit of the confidence interval generally is not far enough from one that researchers can be confident that the correct genes have been identified. For the Phase II genes (the deactivators), GSTM1 is best studied. Again, although studies consistently show risk, the lower limit of the confidence interval is very close to one. A review by Hirshhorn examined 600 reported associations; only six were consistently reproduced from among those that were studied multiple times. The investigator cited population stratification, linkage disequilibrium, failure to take gene-environment and gene-gene effects into account, and a number of minor problems (e.g., insufficient power, publication bias for study effects) as reasons. Dr. Caporaso explained that the observations are for

the best studied genes, and the evidence is short of confirmatory. Existing studies are not effective, and the situation is not unique to lung cancer.

The field needs well-designed, integrated studies that are large enough to have sufficient power and take ethnic variation into account. The capability to conduct multiple comparisons in these studies is needed as well. Additionally, an appropriate statistical framework must be in place, and researchers will need to consider gene-environment and gene-gene interactions. It is not just a single gene, as is the case in many hereditary cancer syndromes, that results in predisposition to lung cancer or smoking persistence. Colleagues in the field of genomics should be called upon to fashion a strategy, databases, and appropriate methods of genotyping to take full advantage of advanced technologies.

Dr. Caporaso highlighted some of these points in describing an NCI-funded case-controlled study being conducted in Italy that includes 2,000 cases from 13 hospitals. The study is projected to end in January 2005. A computer-administered questionnaire and a self-administered instrument are used to obtain information on lung cancer risk factors as well as nicotine dependency, depression, and alcohol use. The study also includes extensive biospecimen collection, including tissue from all of the subjects who undergo surgery. Having 2,000 cases with reasonable allele frequencies is allowing the investigators to examine gene-environment and gene-gene effects.

There are multiple points in the progression of lung cancer where genes could plausibly act (e.g., angiogenesis, alterations in immunity, disrupting the cell cycle, DNA repair genes), but virtually all work to date has focused on exposure. How do genes alter exposure? There are at least four major carcinogens that addict individuals to tobacco and that are subject to hereditary influence. Typically, studies have only looked at one of these. Therefore, it is biologically implausible that researchers will be able to discern the effects of genetics in a complex disease by looking at a single nucleotide polymorphism for only one of the genes—the entire pathway must be taken into account. The next generation of studies will need to incorporate all of these genes and incorporate a comprehensive genomic strategy that examines all of these areas in more detail.

Status of State-Level Tobacco Control and CDC/OSH Collaborations With NCI

Ms. Rosemarie Henson, Director, OSH, CDC, explained that the Office has a staff of approximately 145 individuals and a budget of $100 million. More than 30 years ago, the Office was created as the lead organization for tobacco control in the federal government to protect the public's health from harmful effect of tobacco use. Some of OSH's core activities include developing the annual *Surgeon General's Reports on Smoking and Health*; conducting ongoing surveillance of tobacco use (including national and global youth and adult tobacco surveys); operating a health communications group that supports a national clearinghouse of TV, radio, print, and other marketing resources; and directing the National Tobacco Control Program that supports state-based comprehensive tobacco control programs in 50 states, the District of Columbia, and U.S. Territories.

Tobacco use and tobacco addiction are extremely complex problems requiring a comprehensive solution involving a broad array of strategies and partners. No one agency has the resources, capacity, or mandate to solve this important public health issue. The CDC and NCI have formed a strong collaborative partnership and work very closely together on tobacco control efforts. The CDC looks to the NCI for cutting-edge research that the institute supports and conducts through its diverse extramural network of universities, hospitals, Cancer Centers, and research foundations.

One of the biggest challenges in tobacco control today is the funding crisis in the states that

threatens the sustainability of prevention programs to reduce tobacco use. Much progress has been made over the past decade in developing and implementing local and state tobacco control programs. The growth in local and state tobacco control programs has resulted from a combination of efforts, including state initiatives to increase funding for programs through higher tobacco taxes, the creation of the American Legacy Foundation (which supports a national youth media campaign), and the establishment of the Smokeless States Initiative supported by the Robert Wood Johnson Foundation. State tobacco control efforts have been highly successful, as demonstrated by declines in youth and adult smoking rates and cigarette sales in states such as California, Florida, Massachusetts, and Arizona. Perhaps the most impressive accomplishment has been the recent national decline in smoking among adolescents after nearly a decade of an epidemic of smoking among youth.

Despite these successes, state budgets have been slashed drastically because of the poor economy, and 23 states have lost substantial amounts of funding. Flagship programs such as those in California, Massachusetts, Oregon, Arizona, and Florida have suffered deep cuts in their budgets. Florida, for example, had to discontinue its highly successful program despite reducing smoking by 47 percent among middle-school students and 30 percent among high school students in just 3 years. In California, the Nation's longest running program had its budget cut by 50 percent despite the fact that it saved 33,000 lives by reducing mortality from heart disease in its first 9 years of operation. Furthermore, lung cancer rates have dropped by 14 percent in California compared with a decline of less than 5 percent for the Nation as a whole since 1988. The impact of this budget crisis has resulted in staff layoffs, the elimination of funds for essential countermarketing campaigns, and the discontinuation of quitlines and community programs. If this trend continues, the CDC will be the only source of stable funds to support tobacco control efforts in the states. The CDC spends $58 million on state tobacco control programs, and the industry spends $11 billion marketing its product.

There is a strong evidence base suggesting that tobacco prevention works. States have implemented comprehensive tobacco control programs, and significant declines in cigarette consumption, smoking prevalence, and tobacco-related diseases have been observed. To monitor and evaluate recent changes occurring in tobacco control programs across the country, the CDC, NCI, and the American Legacy Foundation have developed a plan and set aside funds to support an evaluation initiative. This project is critical for several reasons: (1) evaluating what decisions and actions that have been made by state officials will help provide timely science-based guidance to other states facing reductions in their programs; (2) it will help begin to link specific program reductions with intermediate and long-term changes in outcome measures; (3) it is essential to understand the effects of reducing or eliminating tobacco control programs on organizational capacity; and (4) a thorough evaluation of state program reductions will help to understand what happened, why it happened, and which specific tobacco control components or mix of activities are most important to sustain in states.

A second priority of high interest to the CDC and NCI is tobacco use cessation. Earlier this year, a DHHS subcommittee headed by Dr. Michael Fiore developed and addressed a plan to the Secretary with a goal of improving cessation rates nationwide. A key recommendation is to improve access to high-quality telephone quitline services. Recent evidence suggests that proactive telephone counseling is an effective form of population-based cessation services. Currently, 33 out of 50 states sponsor their own quitlines, leaving an estimated 14.5 million smokers in 17 states and the District of Columbia without quitline coverage. Most state quitlines do not have adequate resources to meet the demand for counseling from all smokers in those states. The OSH is working with the NCI to develop strategies to establish quitline services to provide coverage to those states with no existing quitlines through NCI's CIS. Additionally, the CDC will plan to provide enhancement grants to states with some level of quitline services through its National Tobacco Control Program; this plan will ensure that tobacco users have

access to high-quality, proactive quitline services.

Harm reduction, a complicated and controversial topic, likely will be the leading tobacco control issue over the next decade and is an area in which there are significant gaps in the science. The CDC, through its Division of Laboratory Sciences, and the NCI, through its extensive extramural research program, are in a strong position to help fill these gaps. There currently is insufficient science to conclude that any tobacco product is a safe alternative to cigarettes, and experience with low-tar, low-nicotine cigarettes clearly has taught experts to be much more cautious about so-called potentially safer tobacco products. Low-tar cigarettes do not provide a public health benefit, and they do not reduce lung cancer risk.

The list of alternative tobacco products is long and getting longer, with the marketing of new products such as Ariva, Eclipse, Advance, and Accord. A comprehensive, multidisciplinary approach that combines basic laboratory research, surveillance, epidemiology, and behavioral research is needed. Without such an approach, it will be impossible to assess whether or not new tobacco products increase or decrease human exposure to addictive and toxic tobacco product chemicals and to set sound public health policies. Until more definitive answers from this research are identified, the OSH will continue to communicate to the public that there is no safe form of tobacco use, and that the only sure way to minimize one's risk is to quit smoking.

Translating Research Into Practice: Establishing Criteria and Examples of NCI/ACS Collaborations

Dr. Thomas Glynn, Director of the International Cancer Programs, ACS, described the need to apply criteria to the research translation process. The tobacco area has progressed tremendously in the last 20 years, and there are a wide array of treatments and interventions available. The field is now at the point where the most important and cost-effective treatments and interventions need to be identified. Dr. Glynn explained that efforts are aimed at closing a widely acknowledged and lamented gap between development and delivery so that the return on the national investment in this area can be considerably enhanced. The challenge for tobacco control is moving treatments and interventions from development through to delivery. The first question to be asked is whether something be moved from development to delivery, not how it should be moved (i.e., the key question is not how a given area of research can be translated to practice, but rather, whether it should be). A decision analysis model can be applied to this question to maximize an intervention's or treatment's expected utility. The decision analysis model asks two primary questions: (1) What are the variables to be considered in determining first if a given area of research should be translated to practice? (2) How can the utility of the intervention or treatment derived from that research be maximized?

Dr. Glynn presented the following list of candidate variables:

- The anticipated effect: does the anticipated effect justify the translation?
- Duration of effect: is there evidence to suggest that long-lasting effects can be obtained?
- Implementation time: can the intervention or treatment be implemented in a reasonable amount of time? This is a critical question for moving from development to delivery, particularly when dealing with impatient members of Congress, patients, and the general public.
- Target population access: can the target population of the intervention or treatment be readily accessed? Does the size of the target population justify the time and cost of the intervention or treatment? Do appropriate delivery channels exist?

- Cost effectiveness: is the cost of the intervention or treatment justified in terms of the anticipated effect?
- Degree of risk: is there risk in the intervention or treatment and, if so, is it justified in terms of anticipated effect?
- Potential for institutionalization: how likely is it that the intervention or treatment can become an integral part of the intervention or treatment system for the problem or issue being considered? If there is an intervention or a treatment that appears to work in a research context, is there a way that it can be translated to the real world?
- Social acceptance: is the intervention or treatment socially acceptable?

Dr. Glynn also presented a number of questions related to the decision analysis variables (e.g., how should the candidate variables be weighted, which is more important than another, how can the candidate variables be measured, how much interaction among the variables should be expected, should there be additional/fewer candidate variables). He summarized that there is a need to be systematic when moving from development to delivery.

Dr. Glynn then discussed NCI and ACS tobacco control research translation collaborations, noting that the ACS plays a similar role as the CDC in terms of trying to translate NCI research findings to states and populations. The NCI research engine provides the discovery, the ACS and NCI can and have collaborated on development issues, and the ACS through its grassroots and field people are able to provide delivery. He briefly presented the American Stop Smoking Intervention Study as a classic example of how the ACS and NCI are able to collaborate in the development of a series of interventions that work and then deliver them to the states. Currently, the ACS is collaborating on policy economics research that the NCI has supported. The ACS, through its ability to lobby, is using this research and working with Congress to try to secure FDA regulation over tobacco and raise taxes on tobacco products.

Global tobacco issues represent an area ripe for future collaboration. Although 440,000 U.S. citizens die each year as a result of tobacco use, about 5 million people die worldwide. This number is expected to increase to approximately 10 million within about 15 years, and 7 million of these deaths will occur in developing countries. Collaborative possibilities also exist in genetics as genes and/or pathways are identified. Dr. Glynn concluded his remarks by noting that evidence-based medicine is more than simply reading the results of research and applying those results to patients. Concrete, measurable criteria are needed to move treatments and interventions from development to delivery.

Future Directions (e.g., New Products)—Dr. Scott Leischow

Dr. Leischow explained that the NCI has identified a number of priority areas that are critically important to address in the next 5-7 years, including the need to:

- Expand surveillance and epidemiology of tobacco use and tobacco-related diseases
- Increase NCI's emphasis on disparities in a number of different ways
- Continue NCI's emphasis on etiology, prevention, and treatment of tobacco use and dependence
- Investigate new tobacco products and their effects and be proactive in addressing these products; synchronize efforts with other federal agencies to address the public health impact of new tobacco products purported to reduce harm
- Sustain transdisciplinary research and network-centric approaches to science
- Continue support for assessing tobacco use in the Current Population Survey and increasing the number of non-English language translations of that survey

- Support the development of multilevel secondary analyses, analytical tools, and resources to track and evaluate progress in state tobacco control activities
- Support research to develop appropriate measures, sampling methods, and methods of data collection in small underserved and understudied populations (and expand surveys to include questions relevant to tobacco use among underserved and understudied populations)
- Initiate a prospective longitudinal cohort study on quitting and relapse to provide greater insight into how people make decisions to quit and what interventions/medications they like to use
- Implement a collaborative medication development and clinical trials network with NIDA
- Support innovative, population-based studies involving a whole genome approach to elucidate the genetics of smoking in collaboration with other NIH Institutes and Centers
- Continue supporting the TTURCs (in collaboration with NIDA and NIAAA)
- Expand the Cancer Intervention and Surveillance Modeling Network (CISNet) to develop models of tobacco use dependence, relapse, and disease development
- Accelerate the development of network-centric approaches to assure maximum linkage and collaboration across tobacco control domains.

All of these priorities intertwine, and a challenge for the NCI will be to conceptually and functionally link them. These activities will help the NCI to maximize its research and reduce the public health burden associated with smoking.

Discussion

Dr. Lander asked for some specific examples of interventions that work, and whether there is any way to capture exactly how effective they are. For example, increasing taxes and making cigarettes less affordable for young people appears to have a significant impact. Is there any way to calculate the amount of death and suffering from cancer saved per incremental increase in taxes? Dr. Lander also voiced concern that the genetic studies may invite the tobacco industry to try to convince the public that the health effects from smoking are not a problem for most people. Therefore, these genetic studies will have to be positioned carefully.

In response, Dr. Croyle explained that there have been a number of collaborative activities across the DHHS agencies on meta-analytic and evidence synthesis projects. The Guide to Community Preventive Health Services that the CDC coordinates and the Public Health Service's Blueprint on Tobacco Use Cessation have reviewed all of the evidence and ranked and rated all of the different interventions. Evidence supports the fact that increased excise taxes reduce tobacco consumption, but the political will to support these taxes is not always there. Dr. Leischow agreed that there is a need to make clear what works and what does not. He explained that a number of organizations met about 1 year ago to determine approaches for implementing effective interventions. The Subcommittee on Cessation, Chaired by Dr. Fiore, also made a number of recommendations on how to implement some of the tobacco cessation guidelines. One of the Subcommittee's recommendations was to dramatically increase the excise tax on tobacco. Dr. Leischow added that there is a great deal of resistance to these activities, not only from addicted smokers, but also from organizations and companies that receive money from the tobacco industry.

Dr. Glynn made five specific recommendations to the Board for improving smoking cessation rates in the country: (1) raise taxes at the federal, state, and/or local level; (2) reimburse physicians for treatment of tobacco control through pharmaceuticals; (3) reduce exposure to second-hand smoke (which is particularly important for decreasing youth tobacco use); (4) allow the FDA to regulate tobacco; and (5) institute a national quitline (strong data indicate that tobacco counseling over the telephone is

effective). Dr. Caporaso added that with regard to genetic studies, the current odds ratios are unsatistfying; however, when larger studies are conducted that put the genes together and that take gene-environment effects into account, more acceptable odds ratios will surface. The tools are available, they just need to be applied collaboratively in an integrated framework.

Dr. Elmer Huerta, Director, Cancer Risk Assessment and Screening Center, Washington Cancer Institute, asked the Board whether the NCAB can take any action to formally express concern about the tobacco-related issues presented at the meeting. If these issues are not addressed, NCI's 2015 goals will not be met. At the very least, he suggested that the NCAB express concern about the significant budget cuts state tobacco control programs have suffered.

Dr. von Eschenbach explained that the NCI is looking at these issues in terms of a multiple integrated strategy, with prevention as an extremely important part of the equation, along with early detection and prediction. Researchers must examine more effective interventions to eradicate disease that is established, and more effective interventions to modulate disease once it occurs. The Institute needs to be cognizant that it has to succeed at multiple places along the spectrum to meet its 2015 goals. Institute staff should take great pride in the fact that the NCI frequently is asked to provide information on high-quality, evidence-based, proven programmatic interventions that could be the basis of policy formulation. Dr. Leischow attended a meeting of all DHHS agencies to address what the President can appropriately endorse and champion regarding tobacco control enhancement. At the meeting, it was agreed that solid foundations upon which to build are quitlines with additional appropriations because the states might not be able to fund them, and a major focus should be on smoking cessation among young adults and teenagers. The NCI may play its greatest role in being able to respond to questions and problems with evidence-based data and proven, scientifically derived answers to those questions. Groups like the NCAB and ACS are critical for providing the scientific basis on which advocacy is based.

Dr. Croyle noted that NCI's tobacco control research budget (not counting lung cancer treatment or clinical trials) is approximately equivalent to what the tobacco industry spends in 3 days of tobacco marketing. To emphasize the influence and impact of the tobacco industry, Dr. Norton added that actors and actresses in Hollywood are paid large amounts of money to smoke in movies. Ms. Henson emphasized the need for a strong voice to inform the public that tobacco control is a priority public health problem in this country—this voice is disappearing, with other health issues, such as obesity, now at the forefront of the media's attention. Dr. Huerta again asked if the Board could draft a statement noting concern about the tremendous obstacles facing the tobacco control field and how these obstacles may prevent the NCI from reaching its 2015 goals. Dr. Lander agreed that this would be worthwhile, and suggested that further research be directed toward communicating tobacco control messages and educating the American public. He asked Dr. Croyle and his colleagues if it would be possible to develop four or five attention-getting public service messages, or mantras, that are backed by science and could be relayed to the public by celebrities, nonprofit organizations, and others.

Dr. von Eschenbach noted that the DCCPS also is involved in communications activities designed not just to inform people, but to persuade them. This work is becoming increasingly important as the tobacco industry continues to use and build on its effective and subtle communication strategies and techniques. He described how the protagonist in one popular television program smokes when he is celebrating, relieved, and defiant. He also noted that it is important to use all available resources. For example, the American Association of Retired Persons (AARP) is primarily made up of grandparents—there is no group more protective of young people than grandparents. Engaging AARP on these issues and finding a role for them in smoking cessation among youth and teenagers could be important. Overall, a comprehensive, integrated strategy that is attacking the problem on multiple fronts and multiple ways is

needed. Dr. Love asked whether, instead of spending a large amount of money on combating the tobacco industry's marketing strategies, the resources would be put to better use in trying to pass a law making it illegal to advertise cigarettes.

Dr. Leischow noted that the panel will develop a set of mantras, or public service messages, as suggested by Dr. Lander, and will present them to the Board. He added that tobacco companies have accepted the reality that tobacco causes disease, and that nicotine and tobacco are addictive. This has occurred as a result of tobacco control research and has forced the industry to change their operating activities. However, Dr. Love countered, there is no political pressure put on the tobacco companies to change their activities. Dr. Leischow pointed to the fact that Philip Morris has threatened to file for bankruptcy and leave the United States as an example of the impact of the science and research on the industry. Dr. Love suggested that a greater effort be made to develop more creative and persuasive advertising to counteract messages from the tobacco companies. Dr. Leischow agreed, noting that the American Legacy Foundation's TRUTH Campaign is having a positive impact on children and young adults. The challenge in these activities is to focus on areas that will have the greatest, most cost-effective impact.

Marlys Popma, an independent consultant, explained that it is much more practical to try to convince people to quit smoking than to convince Congress to place a ban on tobacco. There are many smokers across the country who would like to quit but cannot without help. Many of these individuals do not know what is effective, and one of NCI's goals should be to reach out to these individuals and help them to stop smoking. Dr. von Eschenbach emphasized the importance of a comprehensive strategy to address these issues. Addiction is an element of the equation as well, and the NCI should look to partner with other agencies that are examining addiction, whether it is associated with tobacco, drugs, or even food. Dr. Niederhuber closed the session and the public portion of the first day of the meeting by explaining that as Chair of the Board, he would enthusiastically support a public resolution or statement from NCAB in support of NCI's tobacco-related activities. He asked the panel to draft such a statement/resolution, including the four or five mantras, and submit it to the Board.

Following the presentations, the NCAB Subcommittee on Cancer Centers and *Ad Hoc* Subcommittee on Communications held their meetings. Following these meetings, the full Board reconvened for a closed session to end the day.

CLOSED SESSION

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

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

The en bloc vote for concurrence with all other IRG recommendation was affirmed by all serving Board members present. During the closed session of the meeting, a total of 2,411 applications were reviewed requesting support of $685,003,124. The subcommittee meeting adjourned at 5:30 p.m.

DAY TWO: WEDNESDAY, SEPTEMBER 10, 2003

Before the presentations began on Day 2 of the meeting, Dr. von Eschenbach clarified the role of the *Ad Hoc* Subcommittee on Biomedical Technology, which is being Chaired by Dr. Lander. That Subcommittee will commission a task force or workgroup that will bring in experts from outside the NIH and convene a series of focus groups and conduct other related activities. The task force or workgroup will be Co-Chaired by Drs. Lander and Hartwell. The overall strategy is to enable as rapidly and as effectively as possible a broad and wide cross-sectional input into the issues around technology development.

XI. NCI TRAINING COMMISSION—DR. STEPHEN HURSTING

Dr. Stephen Hursting, Deputy Director, Office of Preventive Oncology, DCP, described the NCI Training Commission, which was established this summer by Dr. von Eschenbach to help catalyze and integrate NCI training activities. The Commission is led by Dr. Carl Barrett. The Commission has as its first step, plans to inventory and promote existing training activities across the NCI. The bulk of these training efforts originate in the Cancer Training Branch, with additional programs housed in the CCR, DCG, DCB, DCTD, DCCPS, and DCP. One of the Commission's goals is to spur an increase in the training of underrepresented minority cancer researchers, drawing on lessons learned from the Comprehensive Minority Biomedical Branch (CMBB) and the Special Populations Network (SPN). For example, one of the lessons learned from the SPN is the need to establish an NCI-wide database and tracking system that can be disseminated across all of NCI's training programs. The Commission also has identified the need to develop new opportunities in translational research training. Additionally, efforts are needed to support new investigators and mentoring at the NCI.

Dr. Hursting highlighted some of the opportunities in training and career development located within the Cancer Training Branch. Approximately 1,600 positions for predoctoral and postdoctoral researchers in terms of National Research Service Awards originate from the Branch, which funded a total of 435 Career Development Awards in FY03 (including K series awards). The Branch also funded 31 education and training grants (R25T) and 70 education grants.

One area in need of enhancement and improvement is the research training opportunities for minority biomedical researchers. Dr. Hursting noted that there are some promising initiatives emerging in this area. One initiative, from the Center to Reduce Cancer Health Disparities, aims to improve research training opportunities for minority junior medical researchers and develop investigator-initiated research grant applications. Particularly impressive is the pilot program associated with this project, which included funding of 82 out of 120 pilot projects. The goal is to turn these into funded investigator-initiated awards. The CMBB also has made significant advances in these areas; the CMBB's goal is to increase the competitiveness of minority institutions.

Another initiative—Continuing Umbrella of Research Experiences (CURE)—offers training for individuals beginning at the high school level throughout their independent cancer research careers. CURE can be built on through several other training opportunities. Additionally, there is an initiative that focuses on the minority-serving institutions through partnerships between a minority institute and a Cancer Center. The goal is to increase the number of minority scientists in cancer research, and particularly increase the research competitiveness of these minority-serving institutions. The SPOREs are training programs for translational research. The SPOREs are multidisciplinary opportunities that take a team approach. There are some opportunities for funding mechanisms that will use the SPOREs as a training ground.

A New Investigators Working Group, under the direction of Dr. Brian Kimes, was formed to address concerns related to the decline in NIH funding for new investigators. The Working Group includes representation from all NCI Divisions. Its goals are to increase support for new investigators, make greater use of start-up awards, sponsor workshops for potential grantees, and work aggressively to track and monitor success rates. The group has identified the need to address reasons why there are few applications for K22 Awards, which have not been well used. Additional training issues that the group identified include: (1) consider creating a training program for masters candidates, (2) create training programs for individuals who participate in team science, (3) develop a mentoring network, and (4) establish a policy that makes the roles of Co-Principal Investigators equally responsible.

Dr. Hursting described training initiatives related to translational research, including a translational research curriculum concept designed to introduce new training modalities that bridge the basic and clinical sciences to address the need for biomedical research and engender leadership in translational science. One idea is to create a clinically augmented Ph.D. program so that a basic scientist who wants to conduct translational research may not need 4 years of medical school and the clinical training to do so, but will need a foundation in the clinical sciences. It is hoped to include a broad menu of training options, including possibly a new degree—a Doctorate of Medical Science degree—that will identify individuals who are cross-training with a strong clinical background and a focus on basic science and Ph.D. research training. A survey is being developed and will be submitted to all medical school Deans to examine current curriculum in use for translational research training and solicit ideas from Deans and their colleagues for a new training curriculum. It is hoped to hold a workshop in the spring of 2004 to bring together experts in this area to work out some of the details.

There are some translation research training opportunities that already exist at the NCI, including the "Demystifying Medicine for Ph.D.s Course," a weekly lecture series held from January to May. In the first year, 100 participants were involved, and more than 600 participants have registered for the second year. The course also is available live via webcasting. The DCP sponsors a "Summer Curriculum in Cancer Prevention," which includes courses on the principles and practices of cancer prevention, molecular prevention, and a molecular prevention laboratory course. The 6-week program, which focuses on transdisciplinary and translation research, included more than 275 participants from 22 countries this year. The DCP also sponsors a "Demystifying Medicine Course" in the winter, and a "Translational Research and Clinical Oncology Course" in the fall.

One of the final areas that the Commission is hoping to address is mentoring. Dr. Barrett brought to the Commission some of the progress that the Intramural Advisory Board is making in their Mentoring Subcommittee, which is revising the *Mentoring Handbook* for clinical and basic science researchers. The Subcommittee intends to create a computer-based training module for mentoring and develop measures of mentoring and mechanisms to reward and recognize good mentoring practices.

Questions and Answers

Dr. Niederhuber noted that the survey being distributed to medical school Deans described by Dr. Hursting is important, and asked if it would be worthwhile to send a similar survey to Cancer Center Directors, because the Cancer Centers generally are the stimulus behind the translational research education programs at academic research universities. Dr. Norton emphasized the importance of the Commission's activities, and suggested that a survey also be submitted to organizations that are dedicated to training and have training committees, such as AACR and ASCO. He also noted that to be a translational scientist, it is not enough to have a smattering of knowledge about disease or about

medicine; it requires patient contact over years to develop the skills. It may be that experts who are specially trained in the ability to integrate are needed—individuals who know enough about medicine and science but who also are trained in the ability to connect people in a new role. Dr. Hursting agreed, noting that this is a goal for this new approach to training.

Dr. Susan Love, Adjunct Professor, Department of Surgery, University of California, Irvine, School of Medicine, noted that her organization has sponsored (with support from the NCI and other organizations) a "Breast Cancer 101" conference last spring that was attended by a few hundred researchers, including clinicians and basic scientists. The conference was very well received, and another is planned for next year. Dr. Ramirez commended the Commission for including a mentoring component in its activities. Mentoring is particularly important for underrepresented population groups. She asked Dr. Hursting to consider the fact that mentors generally are overtaxed and have difficulty in mentoring more than one or two individuals. Clinicians who are interested in research are not being taught the requisite skills in medical school. As a result, when they propose pilot projects, they require a good deal of mentoring assistance. Dr. Ramirez also pointed to the critical need for increasing Hispanic representation in terms of researchers at the graduate and undergraduate levels. Dr. Hursting agreed, and Dr. Strete added that the there are some special mechanisms that allow mentors to be reimbursed.

Dr. Lester Gorelic, Program Director, Cancer Training Branch, Office of Centers, Training and Resources, NCI, explained that the NCI has supported the Clinical Oncology Training Program since 1990. The Program uses the K12 funding mechanism to help clinicians communicate with basic scientists and work with them to design and participate in clinical trials. Since 1990, more than 200 clinicians have been trained using this mechanism. Another mechanism, the R25T, is the only NIH training instrument that provides salary support for faculty to develop and implement a curriculum. This curriculum-based training grant initially was designed for cancer prevention and now is being used in other areas, such as imaging. The grant is intended to foster multidisciplinary collaborations between clinicians and basic researchers in a training environment.

Based on the large amount of interest from Board members, Dr. Niederhuber suggested that this topic be discussed again at a future NCAB meeting, with an inventory of what instruments are available, the number of participants, information on the applicant pool, and outcome data. Dr. von Eschenbach agreed, noting that this issue represents an opportunity for creative thinking and new approaches to address training-related issues at the NCI. It was agreed that at the December Board meeting, additional information on training activities currently supported by the NCI would be presented, and information from the Commission's surveys, once analyzed, would be presented at a later Board meeting.

Dr. Richard Pazdur, Director, Division of Oncology Drugs, FDA, asked about the possibility of conducting training activities at locations outside of the NIH Campus. He also suggested that training activities take advantage of technologies such as online courses. Dr. Barrett explained that the Commission is trying to work coordinately within the NCI as well as collaboratively with other Institutes and institutions to complement other activities. Dr. Pazdur noted that the FDA is interested in using NIH review staff in areas of clinical medicine. Dr. Hursting added that within DCP's Prevention Fellowship Program, the FDA has been extremely helpful in collaborating to develop a clinical track that is coming online next year.

XII. OBESITY...CANCER RISK AND PROGNOSIS—DRS. RACHEL BALLARD-BARBASH, STEPHEN HURSTING, AND JOHN MILNER

Overview of Obesity: Cancer Association, U.S. Epidemic, and Population-Level Research

Dr. Rachel Ballard-Barbash, Associate Director, Applied Research Program, DCCPS, explained that addressing and controlling the two-thirds of the U.S. population who are overweight or obese will require a major population-level campaign to improve diet and increase physical activity. In addition, because of enormous differential resistance and susceptibility to obesity, research is needed to better understand how to target treatment. In the area of obesity and cancer, there have been efforts to examine various anthropometric measures of physical activity and cancer. Currently, there is no clinical trial evidence of whether weight control or physical activity reduces cancer incidence or prognosis. There is some intervention research on weight control and physical activity related to cancer prognosis and quality-of-life. There are extensive clinical, metabolic, and basic research studies examining underlying mechanisms in both animal models and humans, and there has been extensive epidemiologic research on obesity and its association with cancer.

Dr. Ballard-Barbash brought the Board's attention to the 2002 International Agency on Research Against Cancer's report, *Weight Control, Physical Activity, and Cancer,* which summarized the literature in the area of epidemiology and basic research addressing this issue. The report found that there was substantial evidence to support an increased risk due to obesity for endometrial cancer, postmenopausal breast cancer, colon cancer, renal cell cancer of the kidney, adenocarcinoma of the esophagus, and thyroid cancer. There is a decreased risk with obesity observed for premenopausal breast cancer and for two smoking-related cancers—lung and head and neck—however, that inverse association is confounded by the fact that tobacco is associated with decreased body weight. There is insufficient evidence for a number of other cancers. There have been some interesting studies suggesting that increases in leptin—a hormone that relates to the amount of percent body fat—may be associated with increased risk for prostate cancer. Most of the studies that examined weight or body mass index (BMI) show no association with prostate cancer incidence.

An ACS paper by Gina Calle in the *New England Journal of Medicine* published this April highlighted the fact that obesity relates to cancer mortality. Being overweight is associated with an increased risk of death for men and, in fact, that study estimated that 14 percent of cancer deaths in men were associated with obesity. The researchers found even more cancers associated with obesity in women, with an estimated 20 percent of cancer deaths associated with obesity. In providing a brief history of research in the area of body size and cancer, Dr. Ballard-Barbash explained a number of recent findings, such as breast and colon studies indicating that increased calorie intake leads to increased body size, which is associated with increased organ size and the number of cells that have the potential to undergo malignant transformation. There has been little work to date on issues related to muscle mass and bone density.

Early studies examining BMI showed no association with breast cancer. More recently, however, NCI researchers have found that when stratified by menopausal status, studies uniformly tend to show strong consistency of increased risk for postmenopausal breast cancer and elevated BMIs. With regard to premenopausal breast cancer, women who are lean actually are at increased risk, and women who are obese have a decreased risk for breast cancer. It is believed that endogenous estrogens are associated with an increased risk for postmenopausal breast cancer among women who have used hormone replacement therapy, such that there are much higher levels of estrogen due to exogenous hormones, and this may overwhelm any effects associated with being overweight. Dr. Ballard-Barbash noted that thinner women

tend to take hormone replacement therapy because they are not producing estrogens in their fat mass and tend to have more symptoms as they go through menopause; these women represent an at-risk group.

One of the key issues is how to differentiate risk and determine who is at risk. The association between an increased risk for being obese or overweight is observed only among women who have either estrogen receptor or progesterone receptor positivity. In the group with both estrogen and progesterone receptor positivity, there is nearly a 2½-fold increased risk. Similarly, the same kind of relative risk differential is seen related to the risk of dying from breast cancer based on the estrogen receptor status of the tumors. In one study, women in an estrogen receptor and progesterone receptor positive group experienced a three-fold increased risk of dying from breast cancer.

Researchers have demonstrated an interaction between BMI and physical activity in colon cancer. It was found that in men who have low versus high BMI, and in a cross-section of men with high versus low physical activity, physical activity confers an approximate 50 percent protection for colon cancer risk. Furthermore, there is a suggestion of about a 3½-fold increase risk among men who have both a high level of BMI and low physical activity. A paper soon to be published in the *Journal of the American Medical Association* by Anne McTiernan from the Women's Health Study shows similar findings, with a protective effect of physical activity largely found among women who remain lean. Similar findings have been found in several other breast cancer studies.

Dr. Ballard-Barbash discussed the obesity epidemic in this country, focusing on adolescents. Data from the National Health Interview Study (NHIS) show an increase in obesity, particularly among non-Hispanic Black adolescents and Mexican-American adolescents, both for boys and girls. Increases also are seen among non-Hispanic white populations for girls in the United States. Similar patterns are seen among adult U.S. men and women. In the 1960s, only about 10 percent of the population had a BMI of more than 30 (the World Health Organization's definition of obesity). The most recent data for U.S. men indicate that almost 28 percent of men now are in this BMI category. For women, the increase was from 15 percent in the 1960s to almost 35 percent at present. Dr. Ballard-Barbash noted that almost 80 percent of U.S. African-American women are overweight or obese, based on the most recent data.

Dr. Ballard-Barbash described a study using NHIS data to measure acculturation among Hispanic populations in the United States. The primary factor that influenced acculturation in this study was use of the English language in the home. It was found that adherence to recommendations for leisure time physical activity increase with higher degrees of acculturation (e.g., approximately 41 percent of those reporting a high level of acculturation adhere to recommendations for leisure time physical activity). However, the group with the lowest degree of acculturation was found to have the highest rate of non-leisure time physical activity (e.g., approximately 80 percent of those reporting a low level of acculturation reported high levels of non-leisure time physical activity). Another study, using data from the National Health and Nutrition Examination Survey, found that the prevalence of walking was highest in people who lived in neighborhoods where homes were built before the 1940s, in contrast to homes built after an automobile economy became a major force in the United States.

Dr. Ballard-Barbash commented that the issue of obesity is much broader than the NCI, and there is an NIH Obesity Research Task Force, which was developed to define the role that NIH must play in addressing this epidemic and its serious implications for public health. This Task Force was founded by Dr. Zerhouni in April of 2003, and is Co-Chaired by representatives from the National Heart, Lung, and Blood Institute (NHLBI), and NIDDK. The Task Force has been charged with developing an NIH strategic plan for obesity-related research and identifying areas of greater scientific opportunity to

monitor what is happening in terms of that strategic plan and to provide a point of contact for discussion of obesity with research-related issues. Dr. Ballard-Barbash noted that the NCI is an active member of the Task Force. The Task Force has created a large matrix containing short- and long-term goals (e.g., evaluate the effectiveness and assure translational strategies to maintain healthy weight in children and adults through behavior change that can be applied in homes, schools or at work; use knowledge of regulation of energy store, including new therapeutic modalities to complement lifestyle interventions).

Highlights of Basic and Animal Model Research on Energy Balance and Cancer

Dr. Hursting explained that he has a joint appointment in the DCP and in the Laboratory of Biosystems in Cancer in the CCR, where he directs the Nutrition and Molecular Carcinogenesis Section. The Nutrition and Molecular Carcinogenesis Section serves as a training ground for Cancer Prevention Fellows who are interested in the basic science aspects of nutrition and cancer. The central question within the Section is whether increased cancer risk due to a genetic lesion can be offset by preventive approaches, with a focus on diet and energy balance. One of the genetic lesions being studied is p53 deficiency, and approaches to offsetting this lesion via dietary interventions are being examined.

One approach to tackling these issues is to gain a greater understanding of energy balance. Most studied regarding energy balance is the amount of calories consumed. Less studied is the types of calories being consumed, and what role that may play in terms of reducing obesity. Physical activity, growth, storage, routine metabolism, and thermoregulation also play a role in the equation. In experimental model systems, preventing adult onset obesity through calorie restriction is associated with a decrease in tumor development or growth of tumors in a variety of systems, depending on the model being used. Dr. Hursting and colleagues have tried to adopt some of the new transgenic and knockout model systems to examine these interactions. In a study of p53 knockout mice, it was found that calorie-restricted mice remained lean over a 4-week period, compared with ad lib fed mice, who underwent significant increases in adiposity and size. The calorie-restricted mice also demonstrated a longer life span, with a 50 percent delay in the development of tumor and death with a calorie-restricted diet (all mice develop tumors because of loss of p53 tumor suppressor function). The same phenomenon has been observed in wild-type mice, although much later because these mice retain the p53 gene. The researchers examined a number of
possible hormones underlying the calorie restriction effect and found that insulin-like growth factor 1 (IGF1) undergoes an almost 50 percent decrease in serum in response to calorie restriction.

Dr. Hursting explained that the calorie restriction effect is not limited only to rodent models. Across multiple species, a positive effect on lifespan is seen. In the higher species, more positive effects on cancer development are seen. Preliminary data from a National Institute of Aging study suggest that this same degree of calorie restriction is effective in extending the lifespan and decreasing tumor development in rhesus monkeys. Dr. Hursting noted that a calorie-restricted regimen can reverse somewhat the obesity state, even in middle age after a lifetime of bad eating habits, and still have positive effects. Even at the halfway point starting calorie restriction in p53-deficient mouse models, tumor development can be delayed, although the effect is not as strong.

IGF1 is a mitogenic factor for epithelial cells and also regulates apoptotic rates in these cells. High serum levels of IGF1 are significantly associated with the risk of several cancers. Immunologists probably consider IGF1 as their most promising predictor in terms of hormones or growth factors associated with cancer risk. High levels of IGF1 are associated with increased risks of prostate, breast, lung, and bladder cancers, as well as leukemia. In transgenic mouse models, calorie restriction consistently lowers plasma IGF1 levels, and in several of these models, if the IGF1 drop is reversed, so

too are many of the anticancer effects of the calorie restriction. Dr. Hursting provided an example of this using p53-deficient mice

exposed to a low-risk chronic carcinogen, further indicating that IGF1 likely is one of the mediators of the diet restriction and calorie restriction effect.

To follow up on this work, Dr. Hursting and colleagues are using gene array approaches to examine the profile of genetic changes that might underlie these observed effects. In one experiment, a number of genes were identified in mice that followed a calorie restriction dose response. Not surprisingly, the IGF1 pathway was altered. However, somewhat surprising was the degree of estrogen-metabolizing hormones that were altered. Calorie restriction appears to affect this pathway as well as the IGF1 pathway and some of the cell cycle regulatory genes. Approximately one-third of these genes were IGF-dependent, so when IGF1 was added back, the researchers were able to reverse or partially reverse many of these genetic alterations—this may be a strategy for identifying some of the underlying mechanisms outside of IGF1.

Dr. Hursting also noted that there is evidence suggesting that exercise is protective for a number of cancers. The most studied cancer in this regard is colorectal, where an inverse association between exercise and colorectal cancer has been found. Higher exercise levels also have been associated with decreased breast cancer risk, and some emerging studies suggest that similar effects are seen with prostate, endometrial, and lung cancers. The effect of exercise on cancer development in animal models has not been well studied, however. In one study, APC min mice running a treadmill experienced a modest decline in spontaneous polyp formation in the intestine. Dr. Hursting commented that exercise in combination with a reduced calorie diet likely is the most potent approach in humans.

Utilizing Nutrigenomics and Metabolomics To Unravel Obesity and Cancer

Dr. John Milner, Head, Nutrition Science Research Group, DCP, noted that many experts in the nutrition arena believe that there are some unprecedented opportunities for using foods and food components in a whole host of experiments to modify gene expression associated with obesity and other factors associated with cancer. The impact of the individual's genomic background must be considered in these efforts, because it will set the stage for what is absorbed, what is metabolized, and what reaches the target site and brings about a biological response. Bioactive food components can modify selected genes, as noted by Dr. Hursting. In addition to the nutrigenetic and nutrigenomic effects, there are effects on proteins (e.g., modifying phosphorylation or glycosylation). There are a number of stages at which nutrients can modify various signals occurring within the cells.

Using new technologies, the expression of the number of genes that are associated with lipid accumulation or with the thinning process can be modified. In fact, there likely are at least 300 genes in the worm that are associated with a decrease in caloric deposition or fat accumulation, and about 112 that are associated with obesity. Many of those have homology with what occurs in humans. Researchers most likely will be able to use some interesting new model systems and new technologies to gain a greater understanding of changes in genes and changes in diet that influence those genes. The NCI is sponsoring a number of projects that use the fruit fly to examine genes and methylation of genes. As mentioned previously, genes and lipid accumulation can be modified through caloric restriction. Simply changing the type of diet that one consumes also can accomplish this. There is clear evidence that the type of diet that one consumes can have an impact on longevity. Researchers need to consider not only the intake of nutrients, but also the site of action of those bioactive food components and the genes that modify them.

One of the nutrients that has surfaced as a modifier of obesity and of the risk of heart disease is the omega-3 fatty acid. There is evidence that the balance of lipids can be modified by the ingestion of fish and ingestion of various fatty acids, especially the omega-3 fatty acid. Omega-3 can suppress tumors, but at low concentrations some tumors tend to be inhibited while others are not. Nutrigenetics is a factor that has to be considered in the overall equation to determine the impact of the diet. Nutrigenomics, which involves a change in gene expression profile, also must be considered. Genes can be modified by changing the diet or caloric intake, but which one of these changes is most important? Not all lipid sources are identical, and there are major differences in the expression of genes. There is a growing body of evidence suggesting that a number of dietary factors can modify adiposity. One of these factors, increased calcium intake combined with a decrease in calories, yields an even greater reduction in body mass. Interestingly, supplemental calcium tablets do not appear to be as effective in this regard as dairy products. It appears that calcium is promoting a change in the expression of certain genes and is associated with increased lipolysis and decreased lipogenesis.

Caloric restriction can lead to a cascade of effects, one of which is protein-protein interaction. New technologies are needed to understand how diet modifies the protein-protein interaction and leads to a silencing of signal. Dr. Milner presented an example of changes in cell signal leading to DNA methylation in a transgenic mouse model. Future studies will need to take metabolomics—the quantity and quality of compounds where they are consumed and their overall impact—into consideration. Future work also will have to examine multiple cellular processes simultaneously and as a function of exposure and time of exposure. One recent study found that a 40 percent caloric restriction decreases mammary tumors in mice. Interestingly, when these animals were refed, the tumors started growing back, indicating that the timing response and the dose response are important considerations. Bioinformatics will be fundamental to this process, and a number of new technologies will be needed to assess what is happening inside the cell.

NCI Response to the Obesity Crisis

Dr. Ballard-Barbash emphasized that the enthusiasm for determining NCI's role in the area of obesity will not supplant its efforts related to tobacco. One critical issue is responding to lessons learned in moving forward the area of tobacco research at NCI and applying those lessons in obesity research. In November of 2002, an NCI-wide Energy Balance Working Group was created, with participation from multiple members across the Institutes, Divisions, and extramural and intramural programs. The Working Group has been debating where the NCI should proceed in this area, and it developed the Bypass Budget chapter on energy balance. Additionally, Dr. Ballard-Barbash and colleagues have been asked to provide input at a planned meeting for the National Dialogue on Cancer, which is discussing obesity at a leadership summit. As reflected in the previous presentations, work in this area focuses on intersect between diet, weight, and physical activity. This intersect is very complex, and these interactions need to be addressed. The Energy Balance Working Group's goals are to: (1) refine understanding of the relationship between energy balance and cancer; (2) define the biological, behavioral, social, and other determinates of these three important health status and health behavior issues; and (3) try to reverse adverse trends in these areas at the population level.

Compared with tobacco, obesity is in a different phase of research. More fundamental research is needed to understand and better determine how the various factors interrelate. A key issue is improving measurement methods and assessment to understand effects of behaviors and their interactions on cancer risk, and also on response to treatment and survivorship. This is an emerging area of new research. Similarly, better and more detailed research is needed to characterize determinants and physiologic

consequences and to elucidate carcinogenic mechanisms. There are key interactions between genes and health behaviors that require greater understanding. Effective interventions, both at the individual and population level, are critically needed. National surveillance efforts examining weight and diet have been critical in helping to identify where the problems exist in the population. The 2005 Bypass Budget has similar goals, one of which is to understand the causes of the adverse patterns of weight, physical activity, and diet to define their contribution to cancer and apply this knowledge to cancer prevention and control. One of the large objective areas related to this goal is in the discovery area, using both the basic science and basic models in animals and humans to discover how this interface of weight, physical activity, and diet, along with genetic and environmental factors, influence the carcinogenic process. One critical element of this objective is improving the measurement of specific bioactive food components and issues of physical activity and fitness.

Another clear objective is to improve cancer-related health outcomes, particularly in high-risk populations. Improving methods for identifying which groups are at high risk and developing effective interventions in this area are priorities. In addition, the research infrastructure must be built up, particularly in the area of training, because interdisciplinary and transdisciplinary research are badly needed. There is much to be learned from across various groups, and one challenge will be to find effective ways to bring together areas of research and investigators that traditionally have not been part of the NIH research community (e.g., urban planners, economists, and others). Dr. Ballard-Barbash concluded her remarks by noting that there is a great potential for the NCI to contribute to knowledge in this area through initiating specific research efforts.

Discussion

Dr. Love asked about secondary prevention (e.g., studies looking at weight loss and nutrition after a diagnosis of breast cancer). Dr. Ballard-Barbash noted that one of the key objectives of these activities is to understand how these factors influence response to treatment and survival. Evidence suggests that being overweight and gaining weight during the course of treatment has an adverse effect on prognosis. This is an active area of research, and gaining additional insight into differential responses and different types of dietary parameters is critical. An important question is how can obesity be controlled in these environments so that beneficial effects on cancer outcomes result? The answer may be quite different from what is seen for heart disease, diabetes, or hypertension. It cannot be assumed that approaches that have been used for the control of those outcomes will be the same in terms of cancer.

Dr. Niederhuber asked whether other NIH Institutes have similar research in terms of understanding the mechanisms of obesity. Dr. Ballard-Barbash replied that the NIDDK traditionally has been the focal point of obesity-related research at the NIH, particularly in the area of treatment. The NHLBI has a very large portfolio on the effect of obesity and comorbidities. Dr. Niederhuber surmised that obesity is a prime example of a trans-NIH activity in which the NIH is heavily involved.

In response to a question, Dr. Ballard-Barbash noted that it is hoped that different data sources become available in the future. For example, there is an effort that parallels the National Health Interview Survey, the California Health Interview Survey, which will provide much better data on many more diverse populations than were available from the National Health Interview Survey sample. Dr. Huerta noted that his patient population consists largely of low-acculturated Hispanics who tend to work very long hours. His overweight patients do not have time to exercise when they leave for work at 4:00 a.m. and return at 10:00 p.m. Dr. Ballard-Barbash noted that one significant controversy ongoing in the obesity field is whether the differential in the composition of a diet going to a low-fat diet and increasing carbohydrates may, in fact, be disregulating appetite and contributing in part to increased weight gain in

the population. Additionally, one study attributes approximately 25 percent of the increase in obesity in the U.S. population to decreases in tobacco use.

Dr. Norton noted that the data indicating that the positive effects of weight reduction and delayed carcinogenesis as well as the reversal of this phenomenon to some extent through refeeding is concordant with the concept that it is possible to live in symbiosis with a cancer. It also raises the question of whether postmenopausal obese women can have breast cancer but never manifest it. It is important to keep in mind, as the NCI strives to meet its 2015 goals, that cancer itself does not necessarily have to be eradicated. Rather, the growth and manifestation of cancer must be eradicated. Dr. Freedman asked, from a clinical perspective, how well the effects of obesity have been studied as they relate to delays in diagnoses (e.g., in breast cancer, a delay in diagnosis of intra-abdominal malignancies). Considering the fact that these people often have comorbid factors, do they receive adequate therapy? Do they get adequate surgery? From a surgical perspective, it is difficult to get adequate node staging, and many of these patients do not get the same degree of staging as non-obese patients.

Dr. von Eschenbach pointed out that much of the information presented by the panel is interwoven with many of the other themes and initiatives that have been discussed at the meeting (e.g., the opportunities associated with NCI's biotechnology initiative and how these will empower and accelerate this particular type of research). He added that a focus on understanding the macroenvironment and moving from genomics to proteomics to metabolomics, as discussed by Dr. Milner, ties closely to NCI's portfolio design. There is interesting research being conducted on lectin and some of its neurotropic mediators that interact or affect bone metabolism; as a result, the implications for bone as a site of metastases become intriguing.

XIII. CANCER TRENDS AND STATISTICS UPDATE—DR. BRENDA EDWARDS

Dr. Brenda Edwards, Associate Director for the Surveillance Research Program, DCCPS, provided highlights from the *Annual Report to the Nation on Cancer,* and explained that new data released include the 2000 cancer incidence cases from the SEER Program and from CDC's National Program of Cancer Registries. In addition, new data are becoming available on year 2000 deaths from the National Center for Health Statistics. Since the last time this topic was presented to the Board, the Census 2000 counts have been included as part of the rates that have been calculated. Dr. Edwards and colleagues also have revised populations for the 1990 decade and, more importantly, have tried to use the bridged procedure to improve estimates and to obtain more accurate estimates on racial/ethnic groups. According to the ACS, the four most prevalent cancer sites are prostate, female breast, lung, and colorectal cancer. These represent more than one-half of the cases and almost one-half of the deaths. Overall, there has been a decline in mortality associated with cancer, not only for the top four cancers, but also for many others. There has, however, been a small increase in the rate of pancreatic cancer.

After applying a delay adjustment to the rates of cancer, which takes into consideration the fact that data come in slowly and are underreported at first, there appears to be an increase in cancer incidence. This adjustment varies by cancer site and is a reflection of improvement to the database and is not reflective of any deficit in the data system itself. The new data indicate a strong increasing trend in the incidence of prostate cancer for both African-American and white men after the delay adjustment. The decline in mortality associated with prostate cancer is continuing; this decline is in part attributable to the fact that there is a decline in prostate cancer cases associated with distant disease.

As is the case with prostate cancer, data indicate that the incidence of female breast cancer is increasing. The incidence for white women is higher than for African-American women. Although the

decline in mortality associated with breast cancer is continuing, it is troubling that there is a growing disparity in the death rates due to breast cancer, with higher rates for African-American women compared with white women. The sharpest increase in incidence comes, in large part, from women aged 50 to 64 years. Most of the increase in breast cancer incidence is attributable to early stage disease, and there

continues to be an increase in regional disease. Researchers are struggling to explain why there has not been an expected decline in distant disease.

For lung cancer, the rates for men are much higher than they are for women. The incidence of lung cancer in both men and women is declining, however, and the decline begins earlier in men than in women by age. Among women, the incidence is declining in those aged 50-64 years and increasing in older aged women. In terms of lung cancer mortality, declines have been observed for women at younger ages and plateau at about age 60. There is a dramatic increase in mortality among women over 70 years of age.

Colorectal cancer incidence has declined since the mid-1980s. Mortality rates associated with colorectal cancer have undergone both increases and declines in that time. Experts are unsure what these increases and decreases are related to, although in general there have been declines in most of the stages and some increase in local disease. Overall, mortality does continue to decline for both men and women.

Dr. Edwards noted that it is difficult to provide a single picture of what is happening by various races/ethnic populations. She explained that the rate is the number of cases divided by the population at risk. The actual count from the 2000 Census was approximately 281 million; the projected count was about 275 million. As a result, there was an overall 2 percent undercount for all of the race/ethnic groups that varied substantially across the different populations. For the American Indian, African-American, and Hispanic populations, there was an overcount of individuals aged 65 years and older, which also impacted the rates. In concluding her remarks, Dr. Edwards noted that the *Report* was published in the *Journal of the National Cancer Institute* and is available online.

XIV. SUBCOMMITTEE REPORTS—DRS. JOHN NEIDERHUBER, ARTHUR NIENHUIS, JEAN deKERNION, LARRY NORTON, MOON CHEN, SUSAN LOVE, AND AMELIE RAMIREZ

Activities and Agenda

Dr. Niederhuber noted that the Activities and Agenda Committee did not meet, but it continues to work on the agenda for each NCAB meeting.

Cancer Centers

Dr. Nienhuis reported that Dr. von Eschenbach briefly commented that the NCI currently is recruiting a number of senior staff, and once those individuals are in place, the specific effort to address the several recommendations of the Working Group will begin. The Cancer Biomedical Informatics Grid, an effort led by Dr. Ken Buetow and colleagues, involves collaboration with the Cancer Centers. The goal is to develop pilot projects that can be used to begin to integrate the focus of cancer bioinformatics. Initially, this project is likely to focus on a clinical database and functional genomics. Two informational meetings related to these activities have been held for representatives from the Cancer Centers. Additionally, Dr. Buetow and colleagues have visited most of the Cancer Centers to discuss the program, learn about the expertise within the individual Cancer Centers, and begin to formulate how the pilot

projects could be selected and the grid assembly might begin. The Cancer Centers have enthusiastically responded—the vast majority participated in the informational meetings as well as in the site visits and have submitted pilot projects for consideration.

A joint effort between the NCI and National Institute on Aging to promote Cancer Center programs in aging and cancer was discussed. A workshop was held in May 2001, during which the relevant issues were identified. Subsequently, the two Institutes jointly funded an RFA for planning grants. A total of 24 applications were received, and a number of the P20 planning grants for developing programs to promote research in aging and cancer will go forward. Additionally, there have been a number of Program Announcements for R01s, which presumably will be funded through the usual mechanisms.

A number of revisions have been made to the Cancer Center Support Guidelines, most of which were minor editorial corrections. Substantive changes related to the ability to carry over funds from year to year without administrative approval also were made. Additionally, there were changes in the minimum required level of grant funding to be eligible to apply for a P30 grant. Recommendations for these revisions have been approved; however, the impact of any changes as a consequence of these recommendations will not occur until the NCI has had an opportunity to review and respond to them.

Clinical Investigations

Dr. deKernion noted that the Subcommittee on Clinical Investigations did not meet. Dr. Niederhuber added that the Subcommittee will be involved in the upcoming review of the Clinical Trials Program and its working group.

Planning and Budget

Dr. Norton highlighted major discussion points raised at the Subcommittee meeting for consideration by various advisory groups. One major issue is defining NCI's goals in terms of keeping the R01 payline at the 20th percentile for 2004 and beyond in light of limited budget growth for many scientific opportunities outside the RPG arena. Is it beneficial to increase the number of R01s without having a proportional growth in P01s, R21s, and other mechanisms? What would the budgetary implications of that be in terms of the R01 payline? Is the average cost for the grants in terms of a 15 percent policy cut rational, or should that be increased or otherwise modified? Is it wise to reduce or eliminate the future cost of living increases that currently are at the 3 percent level for nonmodular-sized grants? There was a great deal of discussion on the impact of modularity on grant size and whether it is wise or possible to find a way to reduce the number of R01 applications being submitted. Dr. Norton stated that it is unlikely that it will be possible to reduce the number of R01 applications.

Dr. Norton explained that the Subcommittee felt strongly that going below the 20th percentile in terms of the payline could have very serious psychological consequences for the scientific community, based on past experiences. For a number of other complex issues, it was felt that the Subcommittee needed another meeting to be able to formulate a rational response. It is hoped that the Subcommittee can meet again in a few weeks, so that it can provide the NCI with its input before budgetary decisions are made.

***Ad Hoc* Subcommittee on Bioinformatics and Vocabulary**

Dr. Chen noted that the *Ad Hoc* Subcommittee on Bioinformatics and Vocabulary did not meet.

Ad Hoc Subcommittee on Communications

Dr. Love noted that it had been several years since the last meeting of the *Ad Hoc* Subcommittee on Communications. One major topic discussed was the reconfiguration of the CIS and the fact that it is being recompeted. The contract period for the CIS will be October of 2004 through 2009, and under the new contract, there will be 15 regional contracts (one more than the CIS currently has) as well as four Coordinating Centers. One of the four Centers serve the Spanish-speaking population; each will have training opportunities. The Subcommittee felt that CIS' smoking line should be made available 24 hours a day, 7 days a week, and it currently is not set up to operate in this manner. It also was noted that removing the call center function from some of the Cancer Centers might have a negative impact on some of the synergistic relationships between the training partnerships and other Center activities that have been enhanced up to now by face-to-face contact. The Cancer Centers should be notified about the CIS reconfiguration so that they can anticipate and prepare for it. The Subcommittee also felt that there should be more than one Coordinating Center that can handle Spanish requests for information, and consideration should be given to using a separate telephone number for Spanish-speaking audiences. Furthermore, an intensive media campaign is needed to increase awareness of the CIS among the Hispanic population. The CIS does not have a large enough budget to support communication outreach activities at present, and it was felt that the NCAB should consider recommending additional support for these efforts if a comprehensive CIS communication plan is developed.

Ad Hoc Subcommittee on Confidentiality of Patient Data

Dr. Ramirez reminded Board members that as a result of discussions held on the previous day of the meeting, the *Ad Hoc* Subcommittee on Confidentiality of Patient Data prepared a draft letter to be sent to the DHHS sharing the Subcommittee's concerns from the public comment assessment it conducted regarding the HIPAA Privacy Rule. The draft letter was distributed to Board members, and Dr. Ramirez asked for comments on the letter. Dr. Gray noted that she and her staff will revise the draft letter, report back to the Board, and work in conjunction with NCI's Legislative Office to determine to whom the letter should be sent. This activity will occur before the next Board meeting.

Motion. A motion was made to establish the NCAB Ad Hoc Subcommittee on Biomedical Technology and approve its functional statement. The motion was seconded and passed.

XV. NCAB RETREAT REPORT AND FUTURE DIRECTIONS—DR. JOHN NIEDERHUBER

Dr. Niederhuber discussed comments related to the 1-day NCAB Retreat that was held in June of this year. At the Retreat, members agreed that the NCAB is a unique body, or Board, that has a rich history of involvement with and support of the Office of the Director and the agenda of the NCI. Based on discussions held during the Retreat, it was agreed that in addition to approving grants, the main strategic goals of the NCAB are: (1) vetting NCI's vision and plans; (2) monitoring the execution of the NCI plans and vision as well as the Director's performance in accomplishing the goals and vision articulated by the NCI; (3) asking probing questions about the plans, visions, and goals of the NCI as they evolve; and (4) enhancing communication and coordination between the NCI and the public (including the extramural scientific community) and that this was an important function of the Board. It also was noted at the Retreat that the NCAB functions effectively as a "sounding board" for the Director as issues arise that affect the public in the area of cancer.

As a result of the Retreat, a small working group was charged to examine the four items listed above and develop an implementation plan to optimize the Board's ability to address those four areas. The working group met on August 8, in Chicago. Participants included Drs. Cherie Nichols, Paulette Gray, Larry Norton, Lydia Ryan, Jim Armitage, Frank Prendergast, John Niederhuber, and Ms. Marlys Popma. The working group is developing a document that is aimed at refining NCAB's roles as recommended at the Retreat. Dr. Niederhuber will complete preparation of the document and review it with Dr. von Eschenbach before distributing it to Board members. Dr. Niederhuber also will keep NCI's EC updated on these activities and will obtain their feedback. It is hoped to circulate the document to Board members before the December meeting.

XVI. ADJOURNMENT—DR. JOHN NIEDERHUBER

Before adjourning the meeting, Dr. Gray agreed, at the request of Dr. Ramirez, to submit a list of Board members' contact information in advance of each meeting to facilitate communication activities. There being no further business, the 127th meeting of the National Cancer Advisory Board was adjourned at 11:10 a.m., on September 10, 2003.