DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL CANCER INSTITUTE
114th NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
June 13-14, 2000

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

NATIONAL CANCER ADVISORY BOARD

BETHESDA, MARYLAND

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June 13-14, 2000

The National Cancer Advisory Board (NCAB) convened for its 114th session on Tuesday, June 13, 2000, in Conference Room 10 of Building 31, National Institutes of Health (NIH), Bethesda, MD. The meeting was open to the public from 8:45 a.m. to 3:50 p.m. The meeting was closed to the public from 4:00 p.m. to 5:15 p.m. The meeting was re-opened to the public on Wednesday, June 14 at 8:45 a.m. until adjournment at 12:44 p.m. Dr. Phillip A. Sharp, Chair of the NCAB, presided during both the open and closed sessions.

NCAB Members
Dr. Phillip A. Sharp (Chairperson)
Dr. Samir Abu-Ghazaleh
Dr. James O. Armitage
Dr. Richard J. Boxer (absent)
Dr. Kay Dickersin
Mr. Stephen Duffy (absent)
Dr. Alfred L. Goldson
Dr. Ralph S. Freedman
Dr. James H. French
Dr. Elmer E. Huerta
Dr. Frederick P. Li
Dr. Susan Love
The Honorable James E. McGreevey
Dr. Sandra Millon-Underwood
Dr. Arthur W. Nienhuis
Dr. Larry Norton
Dr. Amelie G. Ramirez
Dr. Ivor Royston
Dr. Philip S. Schein
Ms. Ellen L. Stovall
Dr. Vainutis K. Vaitkevicius

President's Cancer Panel
Dr. Harold Freeman (Chairperson)
Dr. Paul Calabresi
Ms. Frances Visco (absent)

Alternate Ex Officio NCAB Members
Dr. Steven K. Akiyama, NIEHS
Dr. Peter Kirchner, DOE
Dr. Rachel Levinson, OSTP (absent)
Dr. Hugh W. McKinnon, EPA
Dr. T.G. Patel, DVA
Dr. Richard Pazdur, FDA
Dr. Eugene Schwartz, DOL, OSHA (absent)

Members, Executive Committee, National Cancer Institute, NIH
Dr. Richard Klausner, Director, National Cancer Institute

Dr. Alan Rabson, Deputy Director, National Cancer Institute
Ms. MaryAnn Guerra, Deputy Director for Management
Dr. Robert Wittes, Deputy Director for Extramural Science; Director, Division of Cancer Treatment and Diagnosis
Dr. Dinah Singer, Director, Division of Cancer Biology
Dr. Joseph Fraumeni, Director, Division of Cancer Epidemiology and Genetics
Dr. Peter Greenwald, Director, Division of Cancer Prevention
Dr. Marvin Kalt, Director, Division of Extramural Activities
Dr. Edison Liu, Director, Division of Clinical Sciences
Dr. Barbara Rimer, Director, Division of Cancer Control and Population Sciences
Dr. Carl Barrett, Director, Division of Basic Sciences
Dr. Joseph Harford, Associate Director for Special Projects
Ms. Sandy Koeneman, Executive Secretary, NCI Executive Committee

Liaison Representatives

Dr. John Currie, American Association for Cancer Education, Inc.
Dr. Ronald B. Herberman, Association of American Cancer Institutes
Ms. Barbara Duffy Stewart, Association of American Cancer Institutes
Dr. Margaret Foti, American Association for Cancer Research
Dr. Marc E. Lippmann, American Association for Cancer Research
Dr. Robert Martuza, American Association of Neurological Surgeons
Dr. Robert W. Frelick, Association of Community Cancer Centers
Ms. Kerrie B. Wilson, American Cancer Society
Dr. John Stevens, American Cancer Society
Dr. Stanley Zinberg, The American College of Obstetricians and Gynecologists
Dr. Bernard Levin, American Gastroenterological Association
Dr. Edward P. Gelmann, American Society of Clinical Oncology
Dr. Ross Abrams, American Society of Therapeutic Radiology and Oncology
Ms. Nancy Riese Daly, American Society of Therapeutic Radiology and Oncology
Ms. Ruth Hoffman, Candlelighters Childhood Cancer Foundation
Dr. Lovell A. Jones, Intercultural Cancer Council
Dr. Armin D. Weinberg, Intercultural Cancer Council
Ms. Katharine R. Boyce, Intercultural Cancer Council
Ms. Martha M. Kendrick, Intercultural Cancer Council
Ms. Jean Ard, Leukemia Society of America, Inc.
Ms. Carolyn Aldige, National Coalition for Cancer Research
Ms. Dawn Brereton, National Cancer Institute of Canada
Dr. Robert A. Phillips, National Cancer Institute of Canada
Ms. Paula Bowen, NCI Director''s Consumer Liaison Group
Dr. Eve I. Barak, National Science Foundation
Ms. Pearl Moore, Oncology Nursing Society

Ms. PaulaAnn Rieger, Oncology Nursing Society
Dr. W. Marston Linehan, The Society of Urologic Oncology

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CALL TO ORDER, OPENING REMARKS, AND CONSIDERATION OF MINUTES OF PREVIOUS MEETING -DR. PHILLIP SHARP

Dr. Phillip Sharp introduced guests representing cancer education and research associations and advocacy organizations. He welcomed members of the public and press and invited them to submit in writing, within 10 days, any comments regarding items discussed during the meeting. A motion was requested and made to approve the minutes of the February 2000, meeting. They were approved by the Board unanimously.

Dr. Sharp introduced and welcomed new appointees to the NCAB: Dr. Samir Abu-Ghazaleh, Gynecologic Oncologist, Avera Cancer Institute, Sioux Falls, South Dakota; Dr. James Armitage, Professor and Dean, College of Medicine, University of Nebraska; Mr. Stephen Duffy, Executive Vice-President, American Academy of Facial Plastic and Reconstructive Surgery & International Federation of Facial Plastic Surgery Societies (not in attendance); Dr. Ralph Freedman, Professor, Department of Gynecologic Oncology, University of Texas, M.D. Anderson Cancer Center; Dr. James French, Center for Plastic Surgery, Annandale, Virginia; and Dr. Arthur Nienhuis, Director, St. Jude Children''s Research Hospital, Memphis, Tennessee (reappointed).

FUTURE BOARD MEETING DATES -DR. PHILLIP SHARP

Dr. Sharp called Board members'' attention to future meeting dates listed in the agenda. Dates have been confirmed through 2002.

REPORT OF THE DIRECTOR, NATIONAL CANCER INSTITUTE -DR. RICHARD KLAUSNER

On behalf of the NCI, Dr. Richard Klausner, Director, welcomed the new members to the NCAB and new chair, Dr. Phillip Sharp.

Clinical Trials. Dr. Klausner called members'' attention to the President''s recent announcement of an Executive Order extending Medicare coverage to include routine clinical costs associated with participation in clinical trials. The broad announcement covers all therapeutic areas of medicine, and has the goals of removing insurance and reimbursement barriers to and increasing the level of participation in clinical trials by senior citizens and the Medicare community. Dr. Klausner hailed the announcement as an important step in reconciling government policy to reflect that the importance of high-quality clinical trials. He noted, however, that critical issues (i.e., how ""clinical trials"" and ""routine patient care costs"" will be defined and how routine patient care costs will be determined) should be addressed before the Executive Order can become workable in practice. A committee in the Department of Health and Human Services (DHHS) has been established for that purpose, with Dr. Robert Wittes, Deputy Director for Extramural Science, NCI, as the National Institutes of Health (NIH) representative. Dr. Klausner stated that the NCAB will be informed as policies emerge.

Dr. Klausner directed attention to a presentation later in the meeting by Dr. Wendy Baldwin, Deputy Director for Extramural Research, NIH, on emerging issues in the oversight of clinical research,

including the clarification of old rules and planning for, or development of, new rules across the NIH and DHHS to ensure protection for participants in human subject research. Dr. Klausner stated that Dr. Wittes would present details at a later NCAB meeting on NCI''s implementation of clinical trials oversight rules and regulations, to include information on related educational programs for NCI staff, extramural investigators and institutions, and institutional review boards (IRAS).

Reorganization of the National Clinical Trials System. Dr. Klausner stated that the NCI continues to move toward reorganizing, revamping, and reforming the national clinical trials system (electronic updates available at cancertrials.nci.nih.gov/system). Initiatives relate to broadened access by patients and physicians, generation of new ideas, education, communication, streamlined procedures, and data system automation. The twofold goals of the overall effort are to ensure that the system (1) works effectively in terms of being understood, flexible, effective and efficient; and (2) is capable of generating, and is receiving, ideas that build on scientific advances. The system should incorporate both optimized empirical approaches and movement toward more designed approaches to prevention and treatment, such as molecularly targeted interventions.

New Initiatives Released Regarding the Molecular Targets Extraordinary Opportunity. As background, Dr. Klausner noted that, although there are many possibilities for identifying, defining, and validating molecular targets, the movement from targets to effective interventions remains challenging and difficult. He presented and described his classification scheme for two groups of targets: passive (those requiring limited knowledge about biological function) and active (those requiring an understanding of the biology of the molecule). To illustrate the potential of molecular targets for improving the state of cancer prevention and treatment, he gave examples of recent research to develop interventions based on selected passive targets and the three major categories of active targets (lineage, molecular change, and conditional lethality). Dr. Klausner stated that future NCAB meetings will include presentations by intramural or extramural investigators of new and emerging approaches to developing targeted therapies, such as STR 571, a Pfizer P53 stabilization drug, and an Onyx adenoviral vector to kill cells functionally deficient in wild type P53.

Dr. Klausner then reviewed some of NCI''s new and continuing initiatives aimed at promoting and enhancing research to capture the promise of molecular targets for cancer prevention and treatment. The initiatives are outlined in the Fiscal Year (FY) 2001 Bypass Budget: (1) target identification and characterization-molecular targets drug discovery (MTDD) grants using the regular program, exploratory, and small business funding mechanisms; competing supplemental grants for credentialing and validating targets; a new mechanism called interdisciplinary research teams for molecular target assessment (IRT/MTA) to develop tools and monitoring approaches; and (2) agents/screens development-recompetition of the National Cooperative Drug Discovery Group (NCDDG) focusing largely on natural products; development of Chemistry-Biology Centers to link synthetic/biosynthetic chemists with biologists to ensure that a diversity of targets, assays, and chemicals are generated; expansion of the molecular target laboratories (MTL) initiative to develop a comprehensive program of ligand discovery for cancer-relevant targets. Dr. Klausner briefly described MTLs as having two scientific components (chemistry for the design, synthesis, and acquisition of chemically diverse libraries; biology for the development of screening assays to evaluate the probes and identified targets) and an integration component to develop high-throughput screens, databases, and analytical

tools that make the biologic and chemical resources of the MTLs accessible to the research community. Deliverables of these contract organizations in academia will be biologic assays, chemical libraries, repositories, and scientific databases. Dr. Klausner reported that a recent presolicitation meeting had elicited much interest among researchers. He emphasized the importance of forging partnerships with Federal agencies, academia, and industries. He cited the NCI-Industry Forum and Workshop on Biomedical Imaging and Oncology held the previous year in collaboration with the National Electrical Manufacturers Association, Food and Drug Administration (FDA), and Health Care Financing Administration (HCFA). Dr. Klausner noted that one outcome of the forum was the establishment of the Interagency Council on Biomedical Imaging in Oncology (with core staff from NCI, FDA and HCFA) to assist investigators and manufacturers attempting to target emerging medical imaging technologies through development and marketing. This initiative allows industry, private sector, and academia investigators to bring ideas and projects to the Council for discussion and feedback on how to move them forward. Dr. Klausner reported that a May 12 Request for Applications (RFA) resulted in 16 requests from academia and industry that span a broad range of technologies. The NCAB members will receive a report on the first meeting to be held July 20.

NCI Planning Process. Dr. Klausner reminded members that NCI''s three-pronged approach to planning includes defining extraordinary scientific opportunities in each year''s Bypass Budget, laying out specific challenges that realize the potential of those opportunities, and identifying disease-specific priorities through the Progress Review Groups (PRGs). Dr. Klausner emphasized the need to make these planning processes clear to all, and he welcomed input from all advocacy groups. In particular, he noted the increasing importance of the PRGs to NCI planning processes and directed a call through NCAB members to their communities for suggestions of possible nominees to future groups; a new PRG is formed about every 3 months.

Dr. Klausner stated that a critical issue to be addressed was developing a strategy for monitoring the long-range effectiveness of NCI implementation plans and actions in response to recommendations of the PRGs as recommended by the Cancer Leadership Council. He noted that NCI staff would continue to work with the NCAB Subcommittee on Planning and Budget on plans for extending the PRG program to include an ongoing followup review process, as well as on a strategy for communicating these processes so that the extramural cancer community clearly understands how disease-specific planning is integrated into NCI''s decisionmaking process. A progress report will be presented at the September meeting.

2002 Bypass Budget. Dr. Klausner announced that a draft of the 2002 Bypass Budget is nearing completion and would be distributed to the NCAB. He stated that two new areas of challenge are included in the section entitled NCI Challenge: Building the Capacity for the Future. The first would include quality of cancer care as a fundamental aspect of NCI priorities, with the goal of enhancing the state-of-the-science for defining, monitoring, and improving the quality of cancer care and to inform Federal-level decisionmaking on cancer care delivery, coverage, and regulation. Objectives and milestones include developing core processes and outcome measures for assessing the quality of cancer care; strengthening the methodologic and empirical foundations of quality of care assessment in cancer; enhancing the quality of cancer research within the restructured NCI clinical trials program; improving the quality of cancer care by strengthening the quality of cancer communications; and

ensuring that Federal decisionmaking is informed by the best available evidence about quality.

The goal of the second new challenge, entitled Reduce Cancer-Related Health Disparities, is to understand the causes of health disparities in cancer and develop effective interventions aimed at reducing or eliminating these disparities. Objectives and milestones are to improve capacity and accelerate knowledge through fundamental cancer control and population research; expand the ability to define and monitor cancer-related health disparities and define their causes; expand cancer control intervention and research in prevention, early detection, treatment, and communications; expand the channels for research diffusion and dissemination; strengthen training and education in health disparities research; and create within the NCI a new and comprehensive plan and structure to organize, coordinate, and monitor activities in health disparities research, education, and health services support. As a step toward addressing the latter objective, Dr. Klausner announced that Dr. Harold Freeman, President and CEO, North General Hospital, New York, NY, and Chair, President''s Cancer Panel (PCP), would be joining the NCI as Associate Director for Reducing Health Disparities and would be working over the course of the summer with the NCI and DHHS to create a new center for the study of health disparities. An update on progress in articulating the structure, resources, and processes of the new center would be presented at the September NCAB meeting.

NCI Bioinformatics Initiatives. Dr. Klausner discussed the growing body of information emerging from biomedical research in the late 20th and early 21st centuries. He described the need to be able to access, analyze, represent, interpret, and communicate that information is now a greater rate-limiting step in research. Initiatives at the NIH level included the report of the Committee for Biomedical Information Science and Technology Initiative (BISTI), a subcommittee of the Advisory Committee to the Director, NIH. The BISTI report identified the intellectual fusion of biomedicine and information technology as an overarching need as biology moves increasingly from a bench-based to a computer-based science, as models replace some experiments and complement others, and as lone researchers are supplemented by interdisciplinary teams. In response to the report, Dr. Harold Varmus, then-Director, NIH, organized the BISTI Implementation Group, chaired by Dr. Klausner and other Institute Directors. Recommendations of the Group have been announced and are being implemented include: (1) creation of planning grants for the development of National Programs of Excellence in Biomedical Computing to provide a new infrastructure in academia; (2) an NIH adaptation of NCI''s Phased Innovation Award for a series of new investigator-initiated awards in biocomputing; and (3) creation of a new office within the OD, NIH, to oversee bioengineering, bioimaging, and bioinformatics initiatives. The new office will bring together a BISTI consortium of Institute representatives to share knowledge on Institute activities in information resource support and technology as it relates to the many functions of the NIH.

Dr. Klausner observed that these global initiatives do not fully address the needs expressed often by NCI investigators. He announced that NCI, therefore, is establishing a new structure called the NCI Center for Bioinformatics with the mission of providing bioinformatics support for and integration of NCI-supported research initiatives. To make the task manageable, the decision was made to integrate the development of informatics tools within the already established NCI communities, beginning with the National Clinical Trials Program, Director''s Challenge for New Molecular

Classification Schemes for Cancer, Mouse Models for Human Cancer Consortium (MMHC), and Cancer Genome Anatomy Program (CGAP), where an interactive infrastructure exists and specific needs are known and understood. These consortia would become the alpha and beta test sites for tools that would be made widely available after development. Dr. Klausner described the Center''s model as a series of modules, each consisting of one participating NCI program or consortium (e.g., clinical trials, MMHC), around a specialized group called the NCI Central Core, which would deal with issues such as common language, principles of intraoperability, and navigation across the modules. Objectives within each module would be to establish common data elements, provide an infrastructure that allows data exchange, develop electronic data interfaces, distribute the architectural models across the activities, and provide tool chests. Module components would be operations (develop and test applications), support, research, and standards.

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exchange, develop electronic data interfaces, distribute the architectural models across the activities, and provide tool chests. Module components would be operations (develop and test applications), support, research, and standards.

NCI''s FY 2001 Budget. Dr. Klausner reported that the House and Senate Appropriations Subcommittees have completed their markups of the President''s request for FY 2001, which included a budget of $3.505B for the NCI, a $193M or 5.8 percent increase over FY 2000. The Senate mark for NIH was $20.5B, an increase of 15 percent over FY2000, with an allocation of $3.8B for NCI, also a 15 percent increase. Within their total available allocation, the House committee was able to provide a 5.8 percent increase for the NCI; however, the House committee also marked up an NIH funding level reflecting a 15 percent increase that would be provided if additional funding was available. By comparison, NCI''s final budget for FY 2000 was $3.3117B, an increase of $420M (or 14.5 %) over FY 1999 obligations. Dr. Klausner pointed out that research project grants (RPGs), which rose to more than $1.5B in FY 2000, represented the largest component of the NCI budget, and that the growth of the commitment base alone required $100M. Moreover, an increase of almost 7 percent in the number of competing R01 applications assigned to the NCI is materializing, with requested average costs 15 percent higher than FY 1999 for R01s and 50 percent higher for P01s, raising the possibility that the future commitment base could be $130M. Dr. Klausner explained how these large fluctuations in terms of the size of grant requests being received, and in the behavior of study sections, in terms of the number of highly rated grants (particularly P01s), have affected NCI''s ability to fund what had been proposed in the FY 2000 operating budget, where projections were based on previous years'' experience. With the 14.5 percent increase in the NCI budget for FY 2000, funding for RPGs within the payline was increased by 20 percent. With this increase, it was expected that about 730 R01s would be funded, for a success rate of about 30 percent, slightly lower than the 32 percent rate in FY 1999. To deal with increasing numbers and costs at the beginning of the year, average costs were limited to 10 percent increases. For P01s, costs increased from $38M in funding for 28 competing P01s in FY 1999 to $65M for about 40 P01s in FY 2000. Even with the 60 percent increase in funding, the projected payline of 162 was reduced to 159, funding was negotiated at 85 percent of recommended levels, and lengths of awards were changed on a case-by-case basis. To address these challenges in future operating budgets, Dr. Klausner requested assistance from the NCAB, Board of Scientific Counselors (BSC), and Board of Scientific Advisors (BSA). Letters will be sent to arrange for an NCAB/Executive Committee discussion on how the NCI should respond to pressures on the NCI budget created by the current rounds of grant applications. Included in the discussion will be a historical update on budgetary issues, proposed parameters for making projections, and suggestions for making decisions and communicating their underlying rationale to the entire research community

Personnel Changes. Dr. Klausner announced additional changes in NCI staff: (1) Dr. Carl Barrett, former Scientific Director, National Institute of Environmental and Health Sciences (NIEHS), is the new Director, Division of Basic Sciences (DBS); (2) Dr. Susan Sieber has been named Deputy Director for Communications, OD, NCI; and (3) Dr. Barnett Kramer, former Deputy Director, Division of Cancer Prevention, will be leaving the NCI to become the new Director, Office of Medical Applications of Research, NIH.

Recognition of Outgoing NCAB Members. Dr. Sharp presented certificates in recognition of their contributions to the work of the NCAB over the past years to retiring members Drs. Kay Dickersin, Alfred Goldson, Philip Schein, and Vainutis Vaitkevicius.

Questions and Answers

In response to a question from Dr. Sandra Millon-Underwood, Dr. Klausner stated that an update on progress in organizing the new center for the study of health disparities would be presented at a future meeting. In her position as head of the Special Populations Working Group, Dr. Millon-Underwood will participate in discussions to design the structure. Dr. Larry Norton identified a major problem in designing clinical trials as the need to integrate research developments from various sources. He asked what role the NCI could play in coordinating this effort among investigators in industry, academia, and government. Dr. Klausner explained that the Interagency Council on Biomedical Imaging in Oncology could serve as a workable model because it provides a forum to discuss overarching issues of policy and decisionmaking. Dr. Wittes further explained how the NCI is currently addressing the two kinds of barriers to integration in early stages of research, namely, intellectual property issues and fear of contamination of the toxicity database before FDA approval is achieved for at least one indication.

PRESIDENT''S CANCER PANEL -DR. HAROLD FREEMAN

Dr. Freeman summarized the results of meetings held during 1999 to review the history and current status of the National Cancer Program (NCP) as reported to the President in the document entitled The National Cancer Program: Then and Now. The National Cancer Act of 1971 created the NCP and established the NCI as an independent bureau charged to develop a comprehensive plan to coordinate and expand an aggressive program with assistance and oversight by the NCAB. The Cancer Act of 1971 instituted the Bypass Budget as an element in the budgetary process and created the PCP with the statutory responsibility of monitoring the development and execution of the NCP. Legislation since 1971 has redefined the mission, organization, and responsibilities of the NCI and its Director.

Dr. Freeman then reviewed the current status of the NCP, noting that cancer continues as a serious disease and public health problem despite the progress that has been made, with significant direct medical and indirect morbidity and mortality costs. In 1994, the NCAB Subcommittee to Evaluate the NCP (SENCAP) was congressionally mandated and produced a report that recognized the broad expanse of the NCP from basic to translational research and the need to enhance cancer care for the American public. The SENCAP report also recognized that a coordinated effort was needed involving Federal and regional government agencies, private organizations, health care providers, and all individuals. Dr. Freeman pointed out that the NCP in 2000 operates in a setting of changing demographics of the U.S. population and a changing health system, which has added the further challenges of addressing the unequal burden of cancer among differing populations in this country and eliminating disparities in access to care.

The Panel concluded after the 1999 series of meetings that despite great progress in basic science,

translational, and cancer control research, a critical disconnect exists between discovery and delivery. A modification of the SENCAP diagram for the NCP has been created by the Panel reflecting the gap between the research enterprise and delivery/care enterprise that must be bridged. Dr. Freeman then summarized Panel conclusions in this regard and presented the Panel''s recommendations:

(1) barriers that prevent the benefits of research from reaching all populations must be removed; (2) legislators and policymakers are responsible for enacting laws and policies needed to ensure access to quality cancer care for all; (3) mechanisms are needed to ensure that the public and private health care payers have access to, understand, and accept evidence for health care interventions and incorporate them into standards of care for cancer; (4) awareness of the cancer problem, as well as current knowledge about prevention and all aspects of care, must be increased through culturally appropriate public and professional education; (5) public pressure must be brought to bear in recruiting into the national cancer effort sectors that traditionally have not perceived themselves to have a role in the cancer problem; and (6) the current and future cancer workforce-researchers and care givers of all types-requires greater training and expertise in prevention, rehabilitation, cancer control, communication, the use of new technologies, end of life care, and other areas, and must become more representative of our diverse population and culturally sensitive to its needs.

In summary, Dr. Freeman underscored the Panel''s emphasis on the equal importance of the research and delivery components of the NCP and the need for concerted action by all stakeholders to overcome the divide between these components. The Panel believes that without a better connection between research and delivery enterprises, progress against cancer will continue to be slow, uneven, and incremental. In closing, Dr. Freeman noted that a series of Panel meetings has been scheduled in various regions of the country over the next 18 months to explore cancer care delivery issues faced by communities and how they are being addressed. A report to the President will be produced.

Questions and Answers

Ms. Ellen Stovall asked about the possibility of convening a PRG to look at the gap identified by the Panel. Dr. Klausner responded that it was still under discussion. He gave assurances, however, that intensive planning and priority-setting processes would be applied to organizing the new center for health disparities research, including the creation of new sorts of partnerships with other entities and agencies as a model for quality cancer care and health care delivery. Dr. Klausner pointed out that the NCI works with the DHHS to inform HCFA policies and is engaged in discussions with the American Society of Clinical Oncology about their quality care initiative. The NCAB will receive a progress report on NCI''s quality cancer care initiative.

NEW BUSINESS I -DR. PHILLIP SHARP

Dr. Sharp announced the following changes in NCAB responsibilities, concurrent with changes in membership: Dr. Norton will chair the Subcommittee on Clinical Investigation; Dr. Arthur Nienhuis will chair the Subcommittee on Cancer Centers; and Dr. Ivor Royston will succeed Dr. Schein as one of the four Board members with responsibilities for expedited concurrence of awards within paylines.

Dr. Sharp then presented a draft resolution for Board consideration. The resolution would recognize

Congressman John E. Porter for his consistently enthusiastic support of the NCI and express gratitude and best wishes of the NCAB. A motion was made to approve and forward the resolution to Congressman Porter. The motion was seconded and unanimously approved (text appended to minutes as attachment).

MINI-SYMPOSIUM: BYPASS BUDGET DIALOGUE WITH OUTSIDE ORGANIZATIONS MS. ELLEN STOVALL, MS. CHERIE NICHOLS, DR. ANNA BARKER, AND DR. LOWELL SCHNIPPER

Introduction. Ms. Stovall, Chair, Subcommittee on Planning and Budget, explained that the concept for the mini-symposium originated at a December 1999, Board retreat to discuss the NCI planning and budget processes as a whole. It was recommended that the Board engage in dialogues with key constituents of the extramural cancer community to be better prepared to provide substantive input in the Bypass Budget planning process. Ms. Cherie Nichols, Director, Office of Planning and Assessment, OD, NCI, added that every year the NCI distributes its Bypass Budget planning document between 130 and 150 organizations with a request for comments and suggestions. She recognized the valuable and extensive contributions of the American Association of Clinical Oncology (ASCO) and the American Association for Cancer Research (AACR) in responding to those requests in past years.

American Association for Cancer Research (AACR). Dr. Anna Barker, President & CEO, BIO-NOVA, Inc., and Member, Science Policy and Public Affairs Committee, AACR, commented on behalf of the AACR that the Bypass Budget has evolved in recent years to become a working document, and the planning process has become valuable to the scientific, clinical, and patient communities. The AACR recommends that the planning process be as open as possible, given the complexity of the document. The AACR recognized that the Bypass Budget has undergone a dynamic and substantive evolution over past years, including a strategic focus that is reflective of the complexity of cancer. Dr. Barker highlighted the importance of including progress and vision statements and implementation strategies in the AACR document. The AACR believes the progress statement should be compelling; tied to prior investments; related to changes in detection, prevention, and/or therapy; and focused on increased hope for the patient community by tying scientific advances to clinical advances and quality of life. The vision statement should continue to be forward-looking, bold, comprehensive and integrative, reflective of a sense of urgency, and a realistic assessment of resource requirements. Implementation strategies should take advantage of the vast array of resources represented by the total cancer community and should optimize and synergize the use of these resources. Extraordinary opportunities should be constantly revisited to ensure that they are right on the edge in terms of changing the world of treatment and early detection. Continued emphasis should be placed on infrastructure, centers and networks, as well as the creation of innovative support mechanisms (e.g., to enhance discovery by attracting young people to the field). Implementation strategies also should reflect an awareness of unique needs, such as disparity issues, that are likely to present challenges to the war on cancer.

Dr. Barker stated that the AACR hopes to see a significant focus on translational research, prevention, multidisciplinary, and integrative research in future documents, along with quantifying for

people the magnitude of the cancer problem, adopting a multiyear outlook, ensuring the required investment, and focusing on return of investment and accountability (relating investment to mortality and incidence figures).

American Society of Clinical Oncology (ASCO). Dr. Lowell Schnipper, Chief, Beth Israel Deaconess Medical Center, Division of Hematology and Oncology, Boston, MA, described ASCO as an organization, international in scope, with a membership of 14,000 that includes 9,500 cancer research physicians and clinicians in the United States. Particular emphases include education, cancer research (specifically clinical and translational), advocacy initiatives, research grants for young clinical investigators, and quality of clinical medicine as it is practiced nationwide, including the development of evidence-based practice guidelines. Dr. Schnipper then presented ASCO''s rationale for advocating strategies to enhance the Bypass Budget process to ensure the involvement of as many of NCI''s constituencies as possible. ASCO anticipates that the NCI will be asked to justify future funding requests in greater detail and that continuing to integrate ASCO and others into the Bypass Budget process will enhance the community''s ability to advocate for, and defend, spending priorities.

Dr. Schnipper stated that ASCO believes modifications to the Bypass Budget process are critical to optimizing NCI budget requests in the future. He noted that ASCO makes recommendations in response to the NCI request for comment related, in part, to how best to achieve an open and transparent budget. ASCO recommended that the NCI should continue to: (1) provide opportunities for participation early in the budget development process and extend the comment period to allow for serious analysis of the document; and (2) hold a public meeting early in the development process that would involve a broad spectrum of the cancer research and clinical community, including professional societies and advocates. In summary, Dr. Schnipper stated that the Bypass Budget is an extraordinary document, and with the power to publish this document comes special responsibilities to the community that engages in the work and supports it. ASCO believes that all would be beneficiaries of a process that involves advocates early, allows access to budget numbers with some programmatic detail, and provides a public forum to assess budget successes and failures. Dr. Schnipper cited the recent Executive Order on Medicare coverage for routine patient care costs for patients enrolled in clinical trials as a policy success based on collaborative advocacy and a model for advancing other goals of the cancer community.

Questions and Answers

Dr. Klausner pointed out that the Bypass Budget is a 2-year forward potential budget request. He also asked for suggestions on how the NCI could accommodate participation by extramural research and advocacy organizations earlier in the planning cycle, recognizing the complexity of the document and the need for processes to ensure timely completion as legislatively mandated. Dr. Barker reiterated the AACR vision that a multiyear appropriation cycle would facilitate the strategic planning process. Dr. Susan Love asked whether an evaluation of ongoing progress in programs like the Special Programs of Research Excellence (SPOREs) might be considered for this document. Dr. Klausner stated that the Bypass Budget is written, in essence, in a 3-year cycle, and calls for advice from the extramural community well in advance of drafting new challenges or extraordinary opportunities. Each annual edition within the 3-years includes modifications or clarifications based on

evaluations of the ongoing implementation processes.

COLORECTAL CANCER PROGRESS REVIEW GROUP DRS. RICHARD KLAUSNER, BERNARD LEVIN, AND RAYMOND DUBOIS

Dr. Klausner stated that PRGs are an important part of the NCI planning process. In the PRGs, the cancer community is brought together, under the guidance of external experts, to make progress against specific cancers. To present the report of the Colorectal Cancer PRG for NCAB consideration, Dr. Klausner introduced the Co-Chairs Drs. Bernard Levin, Vice President for Cancer Prevention, University of Texas-M.D. Anderson Cancer Center, and Dr. Raymond DuBois, Minna Wallace Professor of Medicine and Associate Director, Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center. He thanked PRG members and NCI staff for their contributions to the planning process, in particular Dr. Barbara Conley for her work as Executive Director of the PRG and Dr. Susan Rossi for guiding the development of the PRG process.

Dr. Levin acknowledged members'' and NCI staff contributions to the report entitled *Conquering Colorectal Cancer: A Blueprint for the Future.* He also noted the importance and relevance of early detection to survival. Dr. Levin explained that the PRG process was divided into two segments. Section I discussed the areas of biology, etiology, prevention, early detection and diagnosis, treatment and prognosis, and cancer control and survivorship. In section II, discussions consisted of genetics, environment and lifestyle, partnership platforms, imaging, and behavioral and health sciences research. The groups were asked to identify the most compelling research priorities in each area.

Biology. Recommendations were to define biological controls for the development of normal and abnormal colorectal epithelial development; and define the pathways of progression of colorectal neoplasia. **Etiology.** Recommendations were to support population-based epidemiologic studies to investigate more clearly the gene-environment interactions; validate biomarkers of exposure to environmental influences and genetic polymorphisms; sequence single nuclear polymorphism (SNP)-containing genes involved in carcinogen or hormone metabolism, DNA repair, cell growth control; and assess functional polymorphisms in molecular epidemiologic studies in diverse ethnic populations using high-throughput genotyping methods. *Prevention.* Recommendations were to define pathways that can be targets for nutritional and chemopreventive agent interventions; validate applicability to early clinical trials of surrogate endpoint biomarkers of colorectal carcinogenesis defined in preclinical models; and conduct studies of combined lifestyle and chemoprevention interventions. **Detection and Diagnosis.** Recommendations were to support research strategies for effective implementation of currently recommended methods of screening at the population level; evaluate promising available markers and modalities, especially in adenoma detection; and support developmental research into new markers and modalities. **Treatment and Prognosis.** Recommendations were to expedite new drug development by identifying innovative clinical trial endpoints; enhance local and regional therapy through improved quality control measures, and optimized radiation treatment and chemoradiation; and comprehensively characterize biological features of both host and cancer to discover new indicators of prognosis and response to chemotherapy and radiation. **Cancer Control and Survivorship.** Recommendations were to conduct studies to identify best standards of followup care after successful treatment, with attention to resectability, survival, cost, and psychosocial issues;

identify individuals at increased risk for psychological distress and investigate whether psychosocial factors affect compliance; and assess effectiveness of colorectal cancer screening, prevention, and treatment in elderly and special populations. **Genetics.** Recommendations were to identify the genes that predispose to colorectal cancer, including major and minor alleles; determine how morbidity, quality of life, and mortality are affected by genetic screening and interventions to address counseling and disclosure issues; and determine whether there are specific tumor genetic subtypes and their linkage to histologic type. **Environment and Lifestyle.** Recommendations were to integrate observational screening and interventional approaches, specifically with regard to lifestyle and environmental factors that could decrease risk of cancer or adenoma recurrence; encourage epidemiologic studies nested within cancer treatment studies; improve assessment and characterization of lifestyle and environmental factors; and enhance biological coherence of studies, looking at specific biologic mechanisms through which multiple etiologic factors operate. **Partnership Platforms.**Recommendations were to enhance interaction among NCI, NIH, FDA, pharmaceutical and biotechnology companies, physicians, and patient advocacy organizations; develop standard agreements for licensing, intellectual property rights, and data collection; develop validated markers of biologic activity to facilitate clinical trials (with emphasis on markers that would be useful to the FDA in the drug approval process); and foster partnerships among oncologists, gastroenterologists, surgeons, and radiologists to improve patient access to clinical trials. **Imaging.** Recommendations were to apply functional and molecular imaging in selection of screening, surveillance, and treatment strategies to enhance monitoring of chemopreventive and chemotherapeutic responses; further refine novel imaging technologies for screening, staging, and postoperative surveillance; and allow for rapid assessment of benefits and risks of emerging imaging technologies. **Behavioral and Health Services Research.** Recommendations were to develop conceptual models that relate to efficacy, effectiveness, and cost-effectiveness of intervention strategies in the areas of prevention, screening, diagnosis, treatment, and quality of life; characterize variations in patterns of prevention, screening, diagnosis, and treatment for different populations and medical care systems; and develop and evaluate strategies for enhancing access to screening, diagnosis, treatment, and clinical trials.

Dr. DuBois explained that the Colorectal Cancer PRG was able to discern a number of common themes and overarching issues to be addressed in the discussions of the different groups. He summarized them as follows: (1) a multidisciplinary approach to colorectal cancer, including training programs; (2) more multidisciplinary centers or SPOREs for technology development and informatics; (3) better models, both animal and cell culture; (4) linkage of genetic and biologic studies to population-based studies; (5) the role of low-penetrance genetic mutations and their interaction with diet and lifestyle factors; (6) the need for repositories of tumor tissue and blood specimens, with linkage to clinical databases; (7) assessment as to whether clinical trial results can be generalized, particularly in minority populations, the elderly, and patients with comorbidities; (8) new chemopreventive and therapeutic agents; (9) how to overcome the limited use of recommended screening and treatment procedures by the general population; (10) the need for behavioral determinants of compliance with screening and treatment; and (11) the need for multidisciplinary peer review.

Dr. DuBois noted the Colorectal Cancer PRG conclusions that indicate declines in incidence and

mortality are encouraging, that applying current knowledge about screening and early detection could substantially reduce incidence and mortality, and that development of new approaches to prevention and treatment could further substantially improve the outcome.

Questions and Answers

In response to a question from Dr. Frederick Li about developing screening tests that are less costly and invasive, Dr. Levin discussed the prospects for enhanced molecular screening of feces. He noted that the NCI is supporting molecular marker studies, for example, in the Colorectal Subgroup of the Early Detection Research Network. Asked which of the priority research areas had the greatest cost or benefit potential, Dr. DuBois stated that screening the population at large with current techniques would probably have the most impact on mortality in the clinical area, and focusing on genetics and biology in terms of the molecular pathogenesis of the disease would probably have the most impact in the research area. Dr. Levin believes that understanding why people do not get screened should be an important focus, as well as the development and use of techniques to detect the precursors of colorectal cancer. Dr. Elmer Huerta stated that the report should include a strong component related to media outreach and communication because of the need to change the public''s attitudes and behaviors toward screening. Dr. Barbara Rimer, Director, Division of Cancer Control and Prevention Sciences (DCCPS), listed a number of NCI communication and behavioral initiatives already underway in this regard andnoted that NCI staff will be making plans to respond to the recommendations in the report, with the help of behavioral investigators who are focusing on colorectal screening. Dr. Royston suggested that the report should discuss advances made in immunotherapy for treating colon cancer. In response to Dr. Sharp''s question about the next steps in the process, Dr. Klausner explained that NCI staff are mapping the recommendations against available opportunities for investment as well as against initiatives to be developed. A meeting with the Colorectal Cancer PRG will be held to review the proposals, clarify areas, and establish priorities. An implementation plan will then be developed, posted on the Web, and broadly publicized as an announcement to the community of new funding opportunities.

EMERGING ISSUES IN OVERSIGHT OF CLINICAL RESEARCH -DRS. MARVIN KALT AND WENDY BALDWIN

Dr. Marvin Kalt, Director, Division of Extramural Activities (DEA), called attention to several new DHHS initiatives revolving around the protection of human subjects in research: formation of the Office of Human Research Protections (OHRP) within the DHHS Office of the Surgeon General, structure and function of IRAS, plans to cover data safety and monitoring (DSM) in early Phase I and Phase II trials, adverse event reporting, confidentiality of data, and the need for increased education on the part of researchers who interact with human subjects. He introduced Dr. Wendy Baldwin, Deputy Director for Extramural Research, NIH, to discuss guidance documents issued for NIH-funded investigators to implement the DHHS initiatives. Dr. Baldwin noted that reviews by the Office of the Inspector General (OIG) of IRAS contributed to the urgency of recent White House and DHHS announcements about steps to strengthen human subjects protection. She then highlighted provisions in the most recent NIH guidelines requiring education on human subjects protection efforts, data and safety monitoring, and financial conflicts of interest and research objectivity.

Required Education on Human Subjects Protection. Beginning on October 1, 2000, all investigators submitting applications for grants or proposals for contracts or receiving new or noncompeting awards must demonstrate that they have had basic education in the protection of human subjects. This requirement includes key personnel on NIH-funded clinical projects. Dr. Baldwin noted that the just-in-time procedure will be used to allow extra time for the submission of compliance documentation, and NIH is preparing a Frequently Asked Questions (FAQ) document to provide additional guidance. She pointed out that the NIH does not plan to specify a particular program, but a number of curricula were already available to investigators and institutions, including an online tutorial developed for extramural staff who manage portfolios with studies involving human subjects (entitled Protection of Human Subjects: Computer-Based Training for Researchers). Dr. Baldwin called attention also to NIH program announcements (PA) for T15 awards to support short-term training in research ethics and K01 awards to support career development for individuals seeking a career in research ethics.

Data and Safety Monitoring. Building on previous requirements for a monitoring plan for all Phase III multisite trials, the new guidance specifies the establishment of monitoring plans for all trials commensurate with risks, and requires that the DSM plan be submitted to the NIH and IRB for review. Dr. Baldwin pointed out that data and safety monitoring must not duplicate project monitoring and must be independent of the principal investigator. For Phase I and Phase II trials, DSM plans that are in place must now be submitted to the NIH. Dr. Baldwin noted that these policy statements are rigorous enough to effect change but flexible enough to account for differences in research and institutions. The guidelines also augment and reinforce the oversight role played by IRBs.

Financial Conflicts of Interest and Research Objectivity. Dr. Baldwin reviewed provisions included in Public Health Service (PHS) regulations promulgated in July 1995 that require institutions to maintain a written and enforced policy on financial conflict of interest, inform research investigators of that policy and their compliance responsibilities, and report to awarding offices the existence of a conflict and assurance that the conflict has been managed, reduced, or eliminated in accordance with regulations. Dr. Baldwin noted that the current guideline was issued as a reminder of the existing policy and that it presents examples of how institutions visited by the Inspector General have used strategies developed by their IRBs. She stated also that NIH would begin to address the issue of institutional conflict of interest, noting that NIH policy at this time relates to individuals.

Questions and Answers

In response to questions from Drs. Love and Norton, Dr. Baldwin clarified that the regulation applies only to those who by NIH''s technical definition are key personnel or who have a decisionmaking responsibility in the study. She addressed questions concerning institutional conflict of interest in the changing financial environment since the Bayh-Dole legislation on patents. Dr. Schein asked whether new policies would require visits to active study sites to ensure quality of data relative to source material, adherence to protocol, or maintenance of ethical standards, which would have a budgetary impact on the cooperative group program. Dr. Wittes responded that site visit monitoring is already in place for NCI-sponsored investigational drugs and for the cooperative group program. Procedures, however, are needed and are being developed for studies supported in the RPG pool where the NCI

is not the sponsor. In response to a request for clarification from Dr. Dickersin, Dr. Baldwin stated that the guidance relates to reporting adverse events in all types of trials, not only drug trials. She noted that transfer of human subject protection efforts from the NIH Office for Protection from Research Risks (OPRR) to the new Office of Human Research Protections (OHRP) is likely to signal an increased level of clinical trials oversight and will provide an opportunity to bring classic OPRR procedures and activities of the FDA into closer alignment. She added that the NIH is also addressing topics such as the definition of an adverse event in preparation for issuing clearer and more consistent guidance. Dr. Nienhuis commented that Recombinant Advisory Committee (RAC) activities also should be brought into closer alignment with those of the FDA and OHRP, and that aggregate toxicity should be considered as well as discrete adverse events.

CLOSED SESSION

This portion of the meeting was closed to the public in accordance with the determination that it was concerned with matters exempt from mandatory disclosure under Sections 552b(c)(4) 552b(c)(6) and 552b(c)(9), Title 5 U.S. Code and 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. appendix 2).

There was a discussion of procedures and policies regarding voting and confidentiality of application materials, committee discussions and recommendations. Members absented themselves from the meeting during discussion of and voting of applications from their own institutions, or other applications in which there was potential conflict of interest, real or apparent. Members were asked to sign a statement to effect.

Application Review

During the closed session of the meeting, a total of 1,510 grant applications were reviewed requesting support of $380,066,789. Funding for those 1,510 applications was recommended at a level of $357,671,255.

TOBACCO CONTROL INITIATIVES -DRS. BARBARA RIMER, ROBERT CROYLE, JAYLAN TURKKAN, NEIL CAPORASO, AND CHERYL HEALTON

Introduction. Dr. Rimer introduced the presentation of tobacco control initiatives with a review of data from the National Health Information Survey (NHIS) to indicate the extent of the tobacco problem from the public health perspective, despite progress in understanding the scientific and many clinical aspects of the problem. To be included in this broad perspective of tobacco research are an overview of the NCI portfolio; a progress report on seven jointly funded transdisciplinary tobacco use research centers; leads to understanding both the predisposition and susceptibility to the harms of tobacco use, which were generated in the Division of Cancer Epidemiology and Genetics (DCEG); and tobacco use initiatives funded by the American Legacy Foundation.

Update on the NCI''s Tobacco Control Research Program. Dr. Robert Croyle, Associate Director for the Behavioral Research Program, DCCPS, described the role for NCI''s new activities within the context of the multiple agencies and organizations involved in tobacco control activities from

the public health perspective. He cited the favorable circumstances for this type of research, due to increasing budgets in NIH and entities like the Robert Woods Johnson Foundation (RWJF), as well as the state tobacco settlement funds. Primarily, the NCI has a research mission and its role is to fill in the knowledge gaps in public health intervention and application. Dr. Croyle stated that the guiding philosophy for NCI''s current program is to recognize the importance of basic research, applied research, and clinical or public health application; exploit new opportunities to integrate parallel scientific advances; and strengthen NCI''s scientific leadership role within the larger context of tobacco use and control research programs and policy. Important milestones in the effort to advance the science of tobacco control were the creation of DCCPS within the NCI (1997), creation of the Tobacco Control Research Branch (TCRB) (1998), development of the Tobacco Research Implementation Plan (November 1998), and designation of tobacco use and related cancers as an extraordinary opportunity in the FY 2001 Bypass Budget.

Dr. Croyle provided an update on new research initiatives resulting from requests for applications (RFAs). Twenty grants for prevention and cessation of tobacco use in youth were funded in 1997-1999 (plus 9 by other Institutes and Centers) to meet the methodological challenges of conducting high-quality adolescent use research. Seven Transdisciplinary Tobacco Use Research Centers (TTURCs) were funded in 1999 jointly with the National Institute on Drug Abuse (NIDA) and RWJF to develop new integrated conceptual models of the problem. Seven exploratory basic biobehavioral research grants funded in 1999 were considered critical to the development of more effective pharmacological interventions; therefore, the RFA has been reissued. Twelve state and community intervention research grants were funded in 2000 to exploit the unique research opportunity afforded by the many new programs funded by state settlement funds. This initiative also strongly encourages partnerships between university-based investigators and state health departments.

Dr. Croyle described selected initiatives undertaken with NIDA (cofunding of the TTURCs and other projects); National Institute of Dental and Craniofacial Research (NIDCR) (expanding initiatives through the dental profession); NIH Fogarty International Center (providing training and some assistance for investigators in the international community); RWJF (collaborating in the Smokeless States Initiative and with others groups); CDC Office on Smoking and Health (helping in the transfer of the demonstration Project ASSIST to CDC and its expansion as a national program); American Cancer Society (cosponsoring the upcoming World Congress on Tobacco and other initiatives); and AHRQ (working to support the development and utilization of evidence-based treatments of tobacco dependence in health care settings).

Dr. Croyle then presented updates on a few NCI tobacco initiatives. The Trans-NCI Tobacco Research Opportunity Team was created in 1999 to implement the extraordinary opportunity; Dr. Scott Leischow, formerly of the University of Arizona, will assume the position of Chief, Tobacco Control Research Branch (TCRB); Dr. Fran Stillman is leading the evaluation of NCI''s Project ASSIST, which is expected to be completed in the fall; and the NCI is a major cosponsor of the August 6—11 World Congress on Tobacco in Chicago, together with the American Medical Association (AMA), RWJF, and other Institutes. Dr. Croyle summarized the importance of a transdisciplinary approach, the need for rapid research synthesis and dissemination, the critical need for high-quality surveillance, and the benefits of systematic collaboration and coordination. He

announced that Dr. Jon Kerner, formerly of the Lombardi Cancer Center, has assumed the newly created DCCPS position of Assistant Deputy Director for Diffusion and Dissemination. In closing, Dr. Croyle called attention to the imminent release of a new PHS Clinical Practice Guideline entitled Treating Tobacco Use and Dependence, which has the potential to have a significant impact on payers, managed care, and coverage of services.

NIDA-NCI Collaborations in Tobacco Research. Dr. Jaylan Turkkan, Chief, Behavioral Sciences Research Branch, NIDA, reviewed the criteria for drug dependence and showed how nicotine addiction fits into normal conceptions of drug dependency. Dr. Turkkan stated that NIDA recently released a PA targeted to understanding nicotine addiction, entitled Neurobiological and Behavioral Research on Nicotine and Tobacco. She gave examples of research currently funded by NIDA and a brief review of findings: (1) functional magnetic resonance imaging (fMRI) is being used in a study to show the effects of chronic nicotine administration on cerebral blood flow; (2) genetics research in which the investigator demonstrates that gene knockout of the b2 subunit of nicotinic acetylcholine receptor prevents nicotine addiction in mice; (3) a large-scale gene mapping study, cofunded with the NCI, to identify candidate genes at risk for nicotine addiction in special populations; (4) behavioral research that indicates facial expression can be used to measure people''s emotional states when they are craving cigarettes; (5) pharmacological treatments for nicotine addiction, including nicotine replacement with bupropion; (6) research in mouse models on a vaccine that stimulates the immune system to produce antibodies that bind tightly to nicotine and result in antibody-bound nicotine so large that it cannot enter the brain; (7) research with heroin addicts in a treatment program to establish connections between nicotine and other addictions; (8) treatment grants cofunded by NIDA and NCI to assess the efficacy of ""scheduled smoking,"" the addition of Bupropion to cognitive behavioral therapy for women concerned about weight, tailoring nicotine patch dose to pretreatment nicotine intake, aerobic exercise to enhance the effects of nicotine gum in female smokers, and Web-based interventions; (9) research to assess an array of behavioral therapies; (10) school-based family and community approaches to preventing nicotine addiction, one of which demonstrated reduced use by high-risk adolescents after multicomponent intervention; (11) epidemiology studies cofunded by NIDA and NCI to survey cancer risk from marijuana (alone and combined with tobacco), and to study the epidemiology and natural history of nicotine dependence in terms of predictive behavioral, social, gender, and ethnic factors; (12) Monitoring the Future, an ongoing survey of the behaviors, attitudes, and values of secondary school and college students and young adults; (13) the seven TTURCS with themes that range from progression and etiology to relapse and tobacco exposure reduction; (14) Vectors of Vulnerability in Teen & Adult Smoking, a study that is collecting data from adolescents throughout the day using palm pilots, which is suggesting that depression and delinquency are powerful indicators of smoking behavior and urges; and (15) the NIDA Center for Genetic Studies, a repository for human genetic data and biosamples, which are made available for secondary analysis.

Genetic Epidemiology of Tobacco Use and Related Cancers. Dr. Neil Caporaso, Chief, Pharmacogenetics Section, Genetic Epidemiology Branch, DCEG, presented arguments for a central role of genetics in cancer, including the findings related to cancer families, chromosome abnormalities that characterize certain tumors, mutagens as carcinogens, and specific cancer genes that have been

identified and cloned. He noted, however, the need to consider also the role of the environment in cancer as indicated by variable international rates, findings from migration studies, changes in rates over time, knowledge of chemical carcinogenesis from animal models, and the vast body of data from analytical epidemiologic studies over the past 150 years. Dr. Caporaso briefly reviewed the results of a family-based study in his laboratory of the excretion of debrisoquine and its metabolites, which suggested that individuals who smoked and had the capacity to extensively metabolize this drug also would activate carcinogens and be at greater risk from smoking-related cancers. Another population-based study with caffeine and the acetylation phenotype showed that the portion of the population that slowly acetylates the drug also slowly eliminates aromatic amines (which also are present in tobacco smoke) and are therefore at greater risk of occupation-related bladder cancer. Dr. Caporaso cited association studies of Phase I and Phase II polymorphic genes and lung cancer and the findings from a recently published metanalysis to show that research usually focuses on single genes associated with specific exposures. He noted the many candidate gene categories in lung cancer alone that remain to be studied. Dr. Caporaso then reviewed methodologic issues in addition to gene selection to be addressed in studies of common gene variants and cancer: power and the need for study sizes in the thousands, population stratification, and study design (linkage vs. association; cohort vs. case-control; control selection; exposure issues).

Dr. Caporaso gave evidence in support of studying the genetics of smoking, including previously discussed research on the neurobiology of nicotine dependence and the body of data that suggest an inheritable component in behavioral factors in general and smoking in particular. He described an ongoing study of smokers in the Washington, DC, and Philadelphia areas, which has looked at a variety of candidate genes and has found an association with SLC6A3, the gene that controls the dopamine transporter and has some reasonable mechanistic plausibility. Dr. Caporaso described a proposed case-control study to assess the genetic contribution to lung cancer susceptibility in the presence of smoking. This Genetic Epidemiology Branch study would be carried out in an interdisciplinary setting, positioned for advanced technology, combine association/linkage approaches, provide mechanistic correlation with genetic findings, have substantial power, and coordinate with other groups such as the SPOREs.

Mission and Initiatives of the American Legacy Foundation. As background, Dr. Cheryl Healton, President and CEO, American Legacy Foundation (Legacy), stated that the Legacy was established following the Master Settlement Agreement (MSA) between the states'' attorneys general and the tobacco industry. The settlement had created a flow of funds to 46 states and 5 territories of about $25B per year for a total of $246B over the next 25 years and potentially beyond. Established by the MSA to guide use of the funds for tobacco-related projects, the current 11-member board is made up of 6 elected public officials appointed by the National Association of Attorneys General (2), National Governors Association (2), and Association of State Legislators (2), and 5 public health and medical experts. The charge to Legacy is to establish cutting-edge research, marketing, and education programs; supplement state/local tobacco programming; promote evidence-based public health education and prevention programs; and demonstrate and disseminate best practices in comprehensive tobacco control programs. Main goals are to reduce youth tobacco use, reduce exposure to second-hand smoke among all populations, increase the successful quit rate among all

ages and populations, and decrease tobacco consumption among all populations. A fifth goal has been recommended-to reduce disparities in screening and access to care for tobacco-related health sequelae. Legacy''s four sources of income are a base fund of $25M over 10 years, the Public Education Fund ($300M over 5 years), Smokeless Fund ($5M over 10 years), and income on a Reserve Fund to be available beginning in 2005. As an example of Legacy programs, Dr. Healton called attention to the new Truth campaign with a $145M annual budget, which she described as the largest counter-marketing-against-tobacco program ever launched in the United States and the largest public health adolescent campaign ever undertaken. Program development is carried out by senior staff and multifocus scientific and program advisory panels, with the help of youth advisors. Although Legacy programs (e.g., Truth) feature special populations outreach subcomponents, the main campaigns are completely multicultural, in line with the foundation''s major theme of diversity. Dr. Healton noted that Legacy, ACS, and RWJF resources have been pooled to form a $5M annual budget to provide needed training and technical assistance to states and localities that request it and to create a national training and technical assistance center. Demonstration projects include the provision of grant funding through the CDC''s 23 prevention centers nationwide for 10-12 youth and policy initiatives; a proposed tobacco and substance abuse initiative within 3 to 5 HOPE VI housing projects, being developed collaboratively with the McArthur Foundation, Housing and Urban Development (HUD), and CASA in New York; and Community Voices, a $55M Kellogg Foundation project operating in 13 of the poorest communities in the United States, to which Legacy is adding a tobacco prevention or cessation component.

In line with its major goal of reducing youth tobacco use, the Foundation funds the National Youth Tobacco Surveys, biennial school-based studies of students in grades 6-12, the first to monitor youth smoking in the earlier grades. Legacy-funded surveillance instruments for outcome data are the Legacy Media Tracking Surveys, which measure the impact of Legacy ads in media markets nationwide among 12-17 year old teens, and recently among 18-24 year old young adults. Because understanding and controlling for the effects of other tobacco influences is important to understanding the impact of Legacy initiatives, an ongoing effort has been undertaken collaboratively by Legacy, NCI, CDC and RWJF to amass data to evaluate the impact of policies. Dr. Healton noted that research gaps are beginning to be closed in areas such as price monitoring, aggregate sales data, advertising monitoring, and pro-tobacco promotions and sponsorships. In addition, Legacy has launched the American Legacy Longitudinal Tobacco Use Reduction Study (ALLTURS) in six communities to contrast changes in tobacco use over 3 years for communities with high, medium, and low exposure to Legacy''s Truth counter-marketing campaign. Finally, Dr. Healton reported that a biochemical validation study will be conducted in the fall to track the differences in self-reported and biochemical results to learn how Legacy''s Truth counter-marketing campaign impacts youth willingness to admit tobacco use and thus to close one common threat to the validity of self-report data.

Questions and Answers

Dr. Amelie Ramirez pointed out the increasing rate of tobacco use in minority populations and expressed interest in having the TCRB continually monitor for gaps in research and identify new priority areas. Dr. Rimer directed attention to a study on that phenomenon published in the *Morbidity*

and Mortality Weekly Review, which found that the use of bidis (small clove cigarettes) is not benign and that they are the preferred smoking vehicle for younger teens. Drs. Li and Huerta commended the TCRB for its success in integrating multiple disciplines, programs, and parties for the task of addressing the tobacco problem. He recommended its use as a model in other cancer efforts. Dr. Huerta also commended the choice of tobacco as one of the new areas of extraordinary opportunity. Dr. Schein asked whether the NCI counter attack was using advertising expertise of the same caliber as that employed by the tobacco industry. Dr. Rimer replied cautiously in the affirmative, noting also the difficulty of finding an ad agency that has not been a customer of the tobacco industry. Dr. Sharp asked Dr. Healton how the states were using the portion of the settlement funds that was not going to the Foundation. Dr. Healton explained that CDC has developed population-based algorithms for what the per capita expenditure ought to be in each state for each subcomponent of tobacco control and about one-third of the states meet or exceed those amounts and the rest do not.

SUBCOMMITTEE REPORTS/NEW BUSINESS II

Subcommittee on Cancer Centers. Dr. Nienhuis presented for Board consideration the written report of the Subcommittee on Cancer Centers. The committee met to consider 15 proposed revisions to the Cancer Center Support Grant (CCSG) Guidelines. Dr. Nienhuis reported that all revisions were approved by the committee after deletion of the word ""equitable"" from the revision on Developmental Funds. The Subcommittee also requested that the NCI report on how effective the revisions to the sections on Shared Resources and Required Summary Information prove to be after a period of implementation.
Subcommittee on Planning and Budget. Ms. Stovall reported that committee discussion focused on the suggestion that NCI consider including an Annual Report of achievements as a companion document to the Bypass Budget and on Ms. Nichols'' request for suggestions as to what should be included in such an appendix. In future meetings, the committee will continue the discussion on suggestions relative to planning for the Bypass Budget and will continue to focus on the budget and planning process as a whole.

***Ad Hoc* Subcommittee on Communications.** Dr. Love reported that the first meeting of the new committee focused on two presentations: one covering the mission, goals, capabilities, and future directions on the new Office of Communications by Director Dr. Susan Sieber; the other on the future of cancer communication by Mr. Bernard Glassman, Special Expert in Informatics. Dr. Love stated that her immediate charge to members was to assist in formulating a plan of action for the committee.

***Ad Hoc* Subcommittee on Confidentiality.** Dr. Li reported that the new subcommittee discussed issues raised and recommendations for practices suggested in the report entitled *Confidentiality, Data Security and Cancer Research*, which was based on a workshop sponsored by the NCI in December 1999. The workshop and report are part of a proactive effort by the NCI to develop a balanced approach to this issue and stimulate discussion of ways to ensure the protection of confidentiality without placing unnecessary restrictions on research. It was suggested that the document on Confidentiality be placed on the Internet as a ""best practices"" example.

A motion was made for *en bloc* acceptance of the written report from the June 12 meeting of the

Subcommittee on Cancer Centers and the written reports from the June 13 meetings of the Subcommittees on Budget and Planning, Confidentiality, and Communications. The motion was seconded and unanimously approved.

MINORITY BIOMEDICAL RESEARCH SUPPORT: A REASON TO CHANGE? -DRS. BRIAN KIMES AND DERRICK TABOR

As background, Dr. Brian Kimes, Director, Office of Centers, Training and Resources, NCI, explained that Minority Biomedical Research Support (MBRS) is among the oldest of NIH programs that are intended to develop and sustain research environments in minority-serving institutions. MBRS programs are cofunded by all of the Institutes, with the responsibility for NCI''s effort residing in the Comprehensive Minority Biomedical Branch.

Dr. Derrick Tabor, Program Director, Minority Biomedical Research Support Branch, National Institute of General Medical Sciences (NIGMS), discussed changes in MBRS philosophy, programs, and policies that have occurred since 1996. MBRS programs include Support for Continuous Research Excellence (SCORE), Research Initiative for Scientific Enhancement (RISE), and Initiative for Minority Student Development (IMSD). Dr. Tabor noted that the cofunding provided by NCI is used only for SCORE. Principles guiding the revisions of MBRS programs were as follows: programs should be developmental with measurable goals and objectives; programs should be institution centered, capturing the uniqueness of individual institutions; program accountability should be based on established goals and objectives and review should be provided, based on appropriate criteria; and programs should encourage broader thinking. Dr. Tabor pointed out that review criteria will now include an evaluation of the program''s contribution to the overall goals of the institution in addition to the normal grant review criteria. Another change is the emphasis on an institutional rather than departmental focus, so that programs can encompass all areas of research the NIH is currently investigating as a foundation for multi-disciplinary approaches to research. Desired outcomes of the SCORE program are meritorious and innovative research, increased research capacity and capability in minority-serving institutions, and increased numbers of competitive minority researchers and competitively trained minority students.

Dr. Tabor described the technical assistance provided through two training mechanisms to increase the capabilities of the target groups and help them meet the new standards: Promoting Effective Program Evaluation and the Grant Writing Workshop. Training in writing grants encompasses both pilot projects and full subprojects, both of which are supported under SCORE as part of the developmental focus of the program, with the goals of preparing investigators to compete at the R01 level and helping institutions develop the competitiveness of their faculty in biomedical research capabilities. In conclusion, Dr. Tabor noted that the NCI cofunds primarily those research subprojects in the MBRS portfolio that fall within the 30th percentile, and that NCI and NIGMS working together have the potential to develop the next cadre of R01 investigators by focusing on developmental research projects at minority-serving institutions.

Questions and Answers

Dr. Ramirez asked how NCI-sponsored special population networks can work with the MBRS

program to enhance their training mission. Dr. Tabor replied that the RISE mechanism provides an opportunity to explore how best the MBRS can help achieve that goal. Dr. Freeman asked whether the MBRS has a component to facilitate interactions with graduate schools, which play an important role in training. Dr. Tabor replied that the 32 institutions involved in the IMSD program are primarily graduate schools, and some of those programs involve partnerships with historically black colleges and universities and other minority-serving institutions. He suggested that graduate schools also could become involved through the NIGMS Bridges program. In response to a question from Dr. Li about evaluation metrics, Dr. Tabor noted that measurable goals and objectives for the SCORE program will be completed by year''s end, and that a progress report on definitive outcomes could be presented at a future NCAB meeting.

TARGETED IMMUNOTOXIN TREATMENT OF LEUKEMIA -DRS. IRA PASTAN AND ROBERT KREITMAN

Dr. Klausner introduced Dr. Ira Pastan, Chief, Laboratory of Molecular Biology (LMB), DBS, to make the first in a series of presentations to the NCAB on new approaches to cancer prevention and therapy based on molecular targets and understanding. As background, Dr. Pastan described the mechanisms of action of Rituxamab and Herceptin, the first molecularly targeted approaches to cancer treatment. He then described LMB''s specific approach in which protein modeling and genetic engineering are used to design and produce improved immunotoxins (molecules in which antibody is attached to a toxin to kill only cancer cells). He explained how techniques of recombinant DNA are used to change Pseudomonas exotoxin A, which is secreted by a common bacterium and which binds to, enters, and kills the first cell it encounters, so it binds only to cancer cells. Dr. Pastan noted that LMB investigators have been working with different antibodies, including one that targets colon and breast cancer, which is in early stages of testing. Another that targets ovarian cancer will soon begin testing in clinical trials. Two other molecules under investigation target antigens present on leukemias and lymphomas. One immunotoxin, named LMB-2 or anti-Tac(FV)-PE38, targets CD25, an antigen that is part of the IL2 receptor and is expressed in small amounts on normal T-cells and in high amounts on several types of T-cell-derived leukemias and lymphomas. The second immunotoxin, named BL22, targets CD22, an adhesive protein found on B-cells, which is expressed on most B-cell leukemias and lymphomas. He explained the LMB procedure for producing the highly purified recombinant immunotoxins needed to begin clinical testing. Clinical trials are carried out in the Division of Clinical Sciences, NCI, where the laboratory is set up to allow investigators to design and make the reagents, and then follow them at every stage through clinical testing. This integrated approach has produced a body of information on the molecules that has proved to be useful in managing patients. The Principal Investigator is Dr. Robert Kreitman, Chief, Clinical Immunotherapy Section, LMB.

Dr. Kreitman reported on the Phase I trial of BL22, begun in February 1999, in patients with B-cell leukemia or lymphoma who had failed standard chemotherapy, and presented evidence of CD22 positivity on the malignant cells. Eligibility criteria also included adequate hepatic, renal, and pulmonary function and no evidence of central nervous system (CNS) disease. Patients received 30-minute intravenous infusions of BL22 every other day for three doses and were retreated if neutralizing antibodies were not made or disease did not progress. A total of 28 patients were studied, 4 with non-Hodgkin''s lymphoma (NHL), 11 with chronic lymphocytic leukemia (CLL), and

13 with HCL. Dr. Kreitman reviewed the toxicity, pharmacokinetics, and immunogenicity findings in the 28 patients after a total of 90 cycles of treatment, which led to the conclusions that: (1) BL22 is an active agent in treating patients with chemotherapy-refractory B-cell leukemia, particularly HCL, where it can induce complete remissions in 80 to 90 percent of patients; and (2) BL22 may be the only agent capable of inducing complete responses in the majority of patients with either chemotherapy-resistant HCL or poor-prognosis HCL variant.

In response to questions, Dr. Kreitman: (1) presented the rationale for continuing the effort to define the MTD despite good responses seen with well-tolerated levels of BL22; (2) discussed the evidence in favor of BL22 as the better agent for patients with CD25-negative disease and the lack of evidence in patients on BL22 that there is selection for CD22-negative, even in CLL; (3) discussed the finding that the anti-inflammatory agents infliximab and rofecoxib appear to be effective in preventing inflammatory toxicity when administered with BL22; (4) noted that major responses to BL22 have not yet been seen in several patients with aggressive lymphomas who were treated at lower dose levels; and (5) discussed possible reasons why responses to BL22 treatment appear to be better in patients with HCL than in patients with CLL.

INTELLECTUAL PROPERTY ISSUES UPDATE -MS. MARYANN GUERRA AND DR. KATHLEEN SYBERT

Ms. MaryAnn Guerra, Deputy Director for Management, Office of Management, NCI, presented an overview of NCI''s technology transfer activities, the responsibility for which is located in the Technology Development and Commercialization Branch (TDCB). The Branch is the point of contact for NCI scientists reporting inventions and trademarks, a key negotiator of transactional agreements with industrial and academic collaborators, and the focal point within business operations and development for intellectual property (IP) issues related to grants and contracts. Also located in the TDCB is NCI''s Competitive Service Center for technology transfer, which serves 10 other NIH Institutes and Centers, and an active Technology Transfer Fellowship Program. Types of agreements negotiated within the Branch are cooperative research and development agreements (CRADAs), clinical trial agreements, material transfer agreements (MTAs), confidential disclosure agreements, letters of collection, screening agreements, and memoranda of understanding (MOUs). Ms. Guerra reviewed operational successes in recent years, including an increase in the number of employee invention reports, increase in royalty income at the same time as patent prosecution expenses are decreasing or staying level, creation of a Technology Review Group to advise on the filing of patents, a decrease in the number of Materials CRADAs, and an increase in income from CRADAs.

Dr. Kathleen Sybert, Chief, TDCB, NCI, gave an update of TDCB activities that have an impact on applicants and potential grantees in the extramural program, in particular, NCI efforts to implement the new NIH guidelines for the sharing of research resources. She also presented examples of negotiations conducted in accordance with the new guidelines to ensure access to research tools by NCI scientists and, by extension, to NIH-funded extramural scientists. She briefly reviewed the background of the new guidelines. Significant incidents preceding the guidelines were the Bayh-Dole Act in 1980, which allowed universities to take title to and license their inventions, and the realization by industry that biotechnology was a rich source of commercially valuable information and materials,

with the potential for commercial use considerations to restrict the sharing of research materials for academic research purposes. In 1996, the PHS put forth a policy relating to the distribution of unique resources produced with PHS funding with the requirement that results and accomplishments of funded activities be made available to the public. The PHS policy also encouraged investigators to consult with NCI in determining suitable distribution mechanisms and recognized the possibility that certain projects might require plans for the sharing of data and results. The intent of the PHS policy was to encourage commercialization through licensing while still providing access. In May 1999, the NIH published the proposed policy for comment and, in December 1999, presented the final notice of the policy entitled *NIH Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Resources*. The policy represents part of the overall implementation of the recommendations of the Advisory Committee to the Director, NIH, which are included in the Report of the NIH Working Group on Research Tools.

Dr. Sybert reviewed the Principles set forth in the NIH Guidelines: (1) ensure academic freedom in publication; (2) ensure appropriate implementation of the Bayh-Dole Act; (3) minimize administrative impediments to academic research; and (4) ensure dissemination of research resources developed with NIH funds. Dr. Sybert noted that these principles are embodied in a series of Guidelines for Implementation, which provide specific information, strategies, and model language for use in negotiations: (1) research resources that are developed with NIH funding are to be made available to the research community; (2) obligations to other sources of funding of projects in which NIH funds are comingled are to be consistent with the Bayh-Dole Act and NIH funding requirements; and (3) exclusive licenses for research tools are to be avoided. Dr. Sybert noted that agreements for importing research resources for use in NIH-funded research are expected to address the timely dissemination of research results; cannot require that title to resulting inventions be assigned to the provider; and should not restrict the recipient''s ability to promote broad dissemination of additional tools that arise from the research. The Guidelines also specify use by recipient organizations of the newly adopted simple letter agreement (SLA) for transfer of materials or a similar instrument, replacing the PHS material transfer agreement. Dr. Sybert noted that the NIH Office of Technology Transfer (OTT) will begin a survey in December 2000 to evaluate the effectiveness of the SLA in reducing administrative impediments. The NCAB members were asked to help disseminate the new NIH Principles and Guidelines within their organizations, together with the Phillips document.

Dr. Sybert concluded with examples of recent NCI and NIH negotiations with industry to emphasize the importance of the NIH Principles and Guidelines to ensure future access to research resources by NCI scientists and NIH-funded investigators: (1) the MOU concerning intellectual property which allows the NCI to purchase Affymetrix Gene Chips®® without ""reach through"" to diagnostic and therapeutic inventions and Affymetrix''s agreement to extend these principles to the academic community; (2) a Determination of Exceptional Circumstances (DEC) in setting up contracts for the Cancer Genome Anatomy Project to ensure that research materials and associated data generated in the full-length cDNA initiative are dedicated to the public domain; (3) an agreement between the NIH and I.E. DuPont that allows research use of DuPont''s proprietary OncoMouse®® transgenic animal technology and resolves issues of access by academics without ""reach through"" to intellectual property rights; (4) an agreement between NCI and Myriad Genetics, Inc., that makes the BRCA1

and BRCA2 testing package available to NIH scientists and grantees at reduced cost for research testing purposes, and at the same time, acknowledges that Myriad is the exclusive licensee of a university''s Bayh-Dole patent rights; (5) a presolicitation conference to design a DEC implementation plan that will balance the intellectual property concerns of the prospective Molecular Target Laboratories contractors and the NCI; and (6)meetings with university technology transfer offices to ensure that intellectual property rights are enhanced and not encumbered by participation in programs such as NCI''s Rapid Access to Intervention Development.

In discussion, Dr. Freeman raised the philosophical question of fairness to the American public that genes can be owned by companies and sold back to the public in general. Dr. Norton raised the issue of possibly making collaboration with the NCI less attractive to market biology firms because of the absence of ""reach through"" and the prospect of future royalties.

ADJOURNMENT -DR. PHILLIP SHARP

There being no further business, the open session of the 114th meeting of the National Cancer Advisory Board was adjourned at 12:44 p.m. on Tuesday, June 14, 2000.