

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

**Summary of Meeting
December 5-6, 2000**

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

**NATIONAL CANCER ADVISORY BOARD
BETHESDA, MARYLAND**

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The National Cancer Advisory Board (NCAB) convened for its 116th regular meeting on Tuesday, December 5, 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 4:15 p.m. The meeting was closed to the public from 4:25 p.m. to 6:00 p.m. The meeting was reopened to the public on Wednesday, December 6, 2000, at 8:45 a.m. until adjournment at 12:05 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
Mr. Stephen C. Duffy
Dr. Ralph S. Freedman
Dr. James H. French
Dr. Elmer E. Huerta
Dr. Howard K. Koh
Dr. Frederick P. Li
Dr. Susan M. Love
The Honorable James E. McGreevey
Dr. Sandra Millon-Underwood
Dr. Arthur W. Nienhuis (absent)
Dr. Larry Norton
Dr. Amelie G. Ramirez
Dr. Ivor Royston
Ms. Ellen L. Stovall

President's Cancer Panel

Dr. Harold Freeman (Chairperson)
Dr. Dennis Slamon (absent)
Mrs. Frances Visco

Alternate Ex Officio NCAB Members

Dr. Steven K. Akiyama, NIEHS
Dr. Michael A. Babich, U.S. CPSC
Ms. Raye-Anne Dorn, DVA (for Dr. T.G. Patel)
Dr. Peter Kirchner, DOE
Dr. Alison Martin, FDA
Dr. Hugh W. McKinnon, EPA
Dr. John M. Powers, DOD, OASD, HA
Dr. George Ruby, DOL, OSHA

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

Ms. Kerrie B. Wilson, American Cancer Society
Ms. Mary Mitchell, American College of Obstetricians and Gynecologists (for Dr. Stanley Zinberg)
Dr. Edward P. Gelmann, American Society of Clinical Oncology
Ms. Kristin Simonson, American Society of Therapeutic Radiology and Oncology
(for Ms. Nancy Riese Daly)
Ms. Barbara Duffy Stewart, Association of American Cancer Institutes
Dr. Robert W. Frelick, Association of Community Cancer Centers
Ms. Paula Bowen, National Cancer Institute Director's Consumer Liaison Group
Ms. PaulaAnn Rieger, Oncology Nursing Society
Dr. W. Marston Linehan, Society of Urologic Oncology

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

Dr. Sharp welcomed guests representing cancer education and research associations and advocacy organizations. He also 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. Dr. Sharp welcomed new NCAB member Dr. Howard K. Koh, Commissioner, Massachusetts Department of Public Health. He also recognized the following new *ex officio* and alternate *ex officio* members to the NCAB: The Honorable J. Jarrett Clinton, Acting Assistant Secretary of Defense for Health Affairs (represented by Dr. John Powers); Dr. Michael A. Babich, Directorate for Health Sciences, U.S. Consumer Product Safety Commission; Dr. George Ruby, Medical Officer, Office of Occupational Medicine, Department of Labor, Occupational Safety and Health Administration; and Dr. Anita Schill, Senior Scientist, Office of the Director, National Institute for Occupational Safety and Health.

A motion was requested and made to approve the minutes of the September 2000 NCAB Meeting. They were approved by the Board unanimously.

II. 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.

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

NCI Budget Update. Dr. Richard Klausner, Director, National Cancer Institute (NCI), reported that while there is optimism for an increase of approximately 15 percent to the NCI budget for FY2001 resulting in a budget level of over \$3.8 billion, the budget increase has not yet been approved. The NCI has been operating on a continuing resolution at the same dollar level for FY2000, \$3.311 billion. The continuing resolution was to end on December 5, 2000, and it is unclear as to how long it might last, at what level, and what the resulting budget level will be when it is resolved. In light of this uncertainty, the NCI is preparing to deal with a flat budget until the FY2001 budget is resolved. The FY2001 commitment level for the grants pool alone is \$80 million, not including any new grants. Dr. Klausner described an initial set of principles and decisions that will guide the disbursement of funds in an attempt to maintain the research enterprise at the NCI. Noncompeting, or Type 5 Grants, which represent the largest single component of the NIH/NCI budget, will be frozen at last year's levels if the outyear commitment levels were greater than last year's disbursement. The Cost Management Principle, which the NIH establishes each year to provide an inflationary level of increase for continuing grants, has been suspended. The decision also was made to maintain the average cost of new and competing grants at no higher than the average cost of last year's new and competing grants. This will require cost reductions from both the requested and peer recommended levels. With the current budget restraints, it was decided to set an initial payline for the individual investigator-initiated R01 Grants at the 18th percentile. To maintain the payline at the 18th percentile, the process of accelerated executive review has been suspended.

Dr. Klausner noted that there are criteria for a reduced level of dollars for exceptions funding, with an emphasis on Type 2 Grants that successfully recompute. To ensure that as much of this ongoing research continues, these ongoing grants will be funded at up to last year's payline on an interim basis through April 1, 2001, by which time a resolution to the FY2001 budget is expected. If the budget remains unchanged throughout FY2001—Dr. Klausner stated that he does not expect this to happen—it is projected that 620 new and competing R01 Grants will be funded within the payline, compared with 720 last year at a success rate of 23 percent compared with a 30 percent success rate last year. In terms of P01 Grants, paylines have not been established—the Executive Committee will consider and evaluate all of them. The dollars that are set aside for P01s will remain at approximately 20 percent of Research Project Grant (RPG) dollars, the same level as last year. Dr. Klausner said the situation is helped by the fact that there has been a slight drop in the number of P01 applications—89 this year compared with 110 last year. The set-asides for published RPG requests for applications (RFAs) will be honored, but no new RFAs will be released until the FY2001 budget situation clarifies. All other mechanisms, including Centers, Specialized Programs of Research Excellence (SPORES), training, Cooperative Groups, intramural research, and internal activities are frozen at no more than last year's level. Dr. Klausner said that legal mandatory cost-of-living increases will not be suspended.

Dr. Klausner said that immediate action will be taken to amend these budgets once the FY2001 budget is finalized, and Board members will be kept up to date on these decisions. If/when the payline is set higher, all grants that were within the new payline automatically will be funded. He emphasized that all of this information has been posted on NCI's Web site and distributed by listserv to all grantees.

Congressional Activities. Dr. Klausner described three bills representing loan repayment programs that Congress has passed and the President has signed. The first bill, the Minority Health and Health Disparities Act of 2000, establishes a National Center of Minority Health and Health Disparities at the NIH, to be headed by Dr. John Ruffin. This Center will work closely with NCI's new Center for Reducing Health Disparities. This bill also provides loan repayment for health professionals engaged in health disparities research. The second bill, the Public Health Improvement Act, is aimed at assisting loan repayments for individuals who are engaged or who will be engaged in clinical research. The third bill, the Children's Health Act, allows the Secretary, Department of Health and Human Services (DHHS) in consultation with the NIH to establish a pediatric loan repayment plan. Dr. Klausner said that NCAB members would be briefed in the future on the many details of these three bills. Another bill that recently was passed, the Technology Transfer Commercialization Act, gives legality to the document used by the NIH on sharing research resources, *Research Tools Principles and Guidelines*. There had been some question as to whether these guidelines were supported by legal authorization. The language of this new Act reads, "To ensure that inventions made by nonprofit organizations or small business firms are used and are managed to promote free competition enterprise without unduly encumbering future research and discovery." This applies not only to the NIH, but across all of the government. The Act also changes how royalty funds can be used—they now can be used over 3 fiscal years, or over 2 additional fiscal years after the year they were received, resulting in 2 extra years of flexibility. Previously, after royalties that reached 5 percent of a laboratory's budget were collected, any additional royalties were distributed so that 75 percent went to the U.S. Treasury, and the remaining 25 percent went to the laboratory. As a result of this Act, however, the 5 percent level that must be reached is 5 percent of the total agency's budget, not of the individual laboratory's budget.

Resources. Dr. Klausner discussed several resources at the NCI. One of them, referred to as the “Cancer Rolodex,” lists available resources for the community on a variety of cancer topics, including genomics, the Cancer Genome Anatomy Project (CGAP), clones, clinical trials issues, cancer communications resources, and software packages for epidemiology. Another resource is a new initiative, the Tissue Array Research Program, headed by Ms. Susan Waldrop. This initiative is a collaboration between the NCI and the National Human Genome Research Institute (NHGRI) to develop and provide researchers with tissue microarrays—microscope slides that contain up to 1,000 tissue samples that are annotated and organized. It is anticipated that these microarrays will be widely used tools by investigators at the NCI and elsewhere. These microarrays provide high-resolution viewing and allow investigators to look at more than one sample at a time. It is anticipated that as this technology is further developed, a complete pathology archive will be available on one microscope slide. The NCI will be working with the Cooperative Groups and other entities to develop specialized microarrays and provide education and training on how to use this new technology. Dr. Klausner stated that the 1998 data from the Surveillance Epidemiology and End Results (SEER) Program are being analyzed and evaluated. The NCI, in collaboration with the Centers for Disease Control and Prevention (CDC), National Center for Health Statistics, and American Cancer Society will release its annual report in the spring, providing an update of the analysis of the latest statistics and trends. The report’s theme this year is on cancers whose incidence or mortality rates are rising.

NCI Web Site. Dr. Klausner reported that the new NCI Web site will be launched in early 2001, with the URL cancer.gov. The NCI also is launching a new Web site called usability.gov, which is intended to provide information to individuals who are developing or refining health-related Web sites.

RAID Program. Dr. Klausner described the Rapid Access to Intervention Development (RAID) Program, which has been ongoing for 2 years. The RAID program acts as a virtual drug company linking the academic community, the laboratory, and clinical trials. It provides a preclinical contract research resource to the academic and small business communities. One unique aspect of the RAID Program is that reviews are conducted within 2 months of the applications’ receipt, and it is conducted by peers in early drug development. The investigators are not employed by the NCI, and their institutions hold all intellectual property rights resulting from the research. Dr. Klausner said the RAID Program is not a pipeline for NCI investigational new drugs, nor is it an assistant mechanism for big pharmaceutical companies. The contract dollars are assigned not to the investigator, but to the compound, and the dollars follow the compound wherever it is studied. There is a Web-based project tracker for the RAID Program that is available to the public and to industry. One of the goals of the RAID Program is for industry to observe this process, determine if they have an interest in any of these compounds as work on them progresses, and then contact the investigators and/or the NCI to move the compound out of the RAID Program and into an industrial development partnership. Progress is tracked via RAID rounds—to date there have been five RAID rounds. Between 30 and 40 applications are received during each cycle, and approximately 30 percent of them are approved. Dr. Klausner said that as a result of the RAID Program, there now are between 50 and 70 novel compounds entering the pipeline.

Philosophy. Dr. Klausner said that as the application of science is being discussed more frequently, he is concerned that some may question the need for basic research and science. The NCI is committed to the diffusion, dissemination, application, and methods of monitoring and assuring that what is known is applied, but Dr. Klausner voiced concern that it continue to be recognized within those institutions that are fundamentally about discovery how much more needs to be discovered. He noted that

a constant tension remains between medical public health needs and scientific opportunity. Dr. Klausner described the NCI's planning process in terms of a Jeffersonian approach to science. He explained that a Jeffersonian model requires that it be clearly articulated that: (1) all the knowledge and tools necessary to reduce the burden of cancer currently are lacking; (2) cancer remains an unsolved puzzle; (3) this puzzle can only be solved through scientific discovery, gaining knowledge, and addressing the areas of ignorance; and (4) the nature of discovery entails both uncertainty and surprise. Dr. Klausner said that given the premise of a Jeffersonian approach to science, attention must be given to the exploration of processes that allow for discovery. He related two components of the Jeffersonian model—the exploration vehicle and the exploration domain—in describing the philosophical basis for the Bypass Budget, in terms of determining research needs and setting research priorities. To link the principles of Jeffersonian science to how the NCI and its planning process function, NCI leadership must: (1) articulate the societal need as a challenge requiring new knowledge; (2) articulate science as the discovery process capable of creating that need of knowledge; (3) articulate the connection between discovery and the application of discovery to societal need; (4) establish criteria and processes for determining the vehicles, domains, and the support needed for the exploratory activities that are needed for discovery, and (5) address with some realism timelines, milestones, and expectations, along with an awareness of the uncertainties of both timelines and plans that are fundamentally dependant upon discoveries not yet made.

Dr. Klausner described the three components of NCI's planning process: (1) the NCI Challenge, which is organized to address the vehicles of exploration; (2) the Extraordinary Opportunities for Investment section, which is aimed at describing new and promising domains of exploration; and (3) the disease-specific Progress Review Groups (PRGs), which develop reports to the NCI that formulate and prioritize what knowledge is needed and outline a framework to accomplish goals. The NCI Challenge and Extraordinary Opportunities components make up NCI's Bypass Budget. Dr. Klausner described how these planning processes relate to Jeffersonian science in terms of mapping the recommendations driven by medical or public health needs against the plans, programs, and priorities established through a scientific opportunity-based planning process in the Bypass Budget. He pointed to the fact that 80 to 85 percent of the recommendations from PRGs map to vehicles and domains that were established by addressing scientific opportunity, which reinforces the essential role of discovery activities in making progress against particular cancers. He said that it is important that federal agencies that cut across all of the science enterprises learn from each other and work to evaluate how the tensions between societal needs that motivate public investment and the conduct of science are addressed, and how to best formulate a Jeffersonian model that can have resonance with the public, with politicians, and with the scientific community.

Questions and Answers

Dr. Susan Love recommended including the topic of the Jeffersonian view of science as a topic to be discussed during a dinner at the next NCAB meeting.

IV. OFFICE OF MANAGEMENT UPDATE—MS. MARYANN GUERRA

Ms. MaryAnn Guerra, Deputy Director for Management, Office of Management (OM), NCI, briefly updated the reorganization of the OM, noting some recent hires within OM—Dr. Jed Rifkin, Associate Director for Information Systems and Computer Sciences; Ms. Janis Mullaney, Associate

Director for Administrative Operations; Ms. Pat Abel, Associate Director for Innovation and Evaluation; and Mr. Arturo Giron, Associate Director for Space and Facilities Management. Ms. Guerra said that all OM activities have been consolidated under the Associate Directors, who have full authority to support the goals of simplifying, delegating, and centralizing the OM. She stated that the theme of the OM during the past year has been to connect planning, implementation, and evaluation within the OM. The Office has been taking the necessary steps to ensure that resources devoted to OM business infrastructure are committed to NCI's mission-critical activities. To achieve this mission-critical focus, all ongoing OM activities were presented to the OM's management group to identify priorities, the relationship to other functions within the NCI, and any overlaps. It was found that OM staff and NCI staff need to be better trained in project management. The OM also connects scientific planning to business planning, implementation, and evaluation by assigning OM team members to map their activities to the Bypass Budget. Among the implementation needs that were identified were informatics infrastructure requirements, recruitment support, administrative support, space requirements, technology transfer needs, and the development of novel mechanisms for partnering and communications tools.

Ms. Guerra described accomplishments over the last year. In terms of recruitment and equal opportunity employment and the NCI's diversity program, Ms. Guerra said the OM is doing quite well—40 percent of new hires in the past year were minorities. Furthermore, less than 1 percent of employees filed formal or informal complaints. The NCI was recognized for its commitment to diversity at the NIH Gay and Lesbian Employees Forum. The NCI also received the NIH award for work life quality, and Ms. Christine Bruce, Director of the Office of Diversity and Employment Programs (ODEP), NCI, received the NIH Director's Award for outstanding recruitment and retention activities. OM staff tested more than 3,000 computers for Y2K compliance and surveyed more than 1,200 pieces of laboratory and biomedical equipment during the Y2K process, which Ms. Guerra characterized as an easy, seamless transition. The OM also provided security and performance enhancements for NCI Web sites and network operations. With increased activity using core services, calls to the OM's help desk increased dramatically, up from 3,700 calls in 1998 to 8,500 in 2000. More than 15 percent of calls to the help desk have been due to a lack of knowledge on how to use NCI's Enterprise software. To help reduce this burden of calls to the help desk, an Enterprise Technology Training Initiative was introduced. This initiative includes four components: (1) new employee training, (2) core competency training, (3) continuing education, and (4) lead user programs. The OM also has expanded the Intramall, NIH's desktop shopping mall, to fit into the NIH-wide Enterprise resource system that is being built, and it is hoped that the Intramall will be the first module to be launched utilizing the new Enterprise software. The Intramall has been recognized with the Vice President's Hammer Award, the E-Government 2000 Trailblazer Award, the Center for Excellence and Information Technology Best Practice Award, the Association of Government Accountants Best Practice Award, and the Government Executive Magazine Government Technology Leadership Award.

Ms. Guerra described a new Web-based resume system that allows hiring officials to view and download resumes at their local PC. This system simplifies the complex Title V government scale hiring system by automating the process of writing and classifying position descriptions, developing standards, and staffing and recruitment documentation. It also has reduced the timeframe for recruiting and appointing these individuals by at least 28 days. By reducing the man hours related to this process, it is estimated that the NCI's annual cost has been reduced by approximately \$430,000 this year. This system can be used to hire more than 1,000 scientific staff at the NCI and allows for more compensation flexibility. To integrate and assimilate new staff into the NCI once they are hired, an orientation program

has been established that will be launched at the beginning of 2001. It will be a full-day session for full-time and part-time employees—fellows will be oriented for the first time. The orientation program will describe NCI's mission and provide hands-on information technology (IT) desktop training to maximize the use of core services, NCI's intranet, essential scientific and administrative resources, and new online training systems. To house new employees, the OM has renovated approximately 87,000 square feet of space. The OM also has entered into an agreement with the Maryland Economic Development Corporation to explore the possibility of partnering with them and creating an off-campus NCI research park.

Ms. Guerra said that the Grants Administration Branch (GAB), Division of Extramural Activities (DEA), has developed and launched the Expedited Board Concurrence and Early Award Initiative. For both the January/February and May/June board rounds, the GAB sent the intent-to-pay letters on the same day the grant was posted with NCAB and program approval. The GAB also is spearheading an NIH Institutional Funding Agreement, whereby the NIH and participating grantees will enter into a renewable agreement covering specified grants for the upcoming year, pending a 2001 budget. It will reduce the workload of both grantees and budget staff by electronically processing Type 5 Grants and will streamline up to 3,000 grant actions, reducing paperwork and mail handling costs. The OM also implemented the Broad Agency Announcement, a procurement and acquisition mechanism that allows researchers to develop their own statements of work to provide for unique deliverables and technology platforms that might not be identifiable under traditional requests for proposals. She said this mechanism encourages collaborations between diverse disciplines. In terms of future activities of the OM, Ms. Guerra said that the OM has partnered with the Honorable Maurice Metigue, former New Zealand cabinet member and a world leader in results-based management, to develop mission-critical goals for the OM. The Office also has partnered with Denali Associates to help train staff in writing effective performance measures. The OM also is finalizing external review guidelines and having them reviewed and commented upon by the John F. Kennedy School of Government at Harvard University, the National Academy of Public Administration's Center for Improving Government Performance, and the Council for Excellence in Government.

V. REPORT OF THE PRESIDENT'S CANCER PANEL—DR. HAROLD FREEMAN

Dr. Harold Freeman, Chairman, President's Cancer Panel (PCP), summarized the 1999 PCP Report to the President and other PCP progress for Board members. The report stressed that the equal importance of the research and delivery components of the National Cancer Program and the disconnect between these components must be recognized. If these research and delivery enterprises are not better connected, then progress against cancer will continue to be slow, uneven, and incremental. Dr. Freeman said there are populations in the United States that do not receive the benefits of scientific discoveries with respect to cancer—this is not only a scientific and medical issue, it is a moral and ethical challenge to the Nation. To achieve improved cancer care for all, he said that there must be better connections between basic research, translational research, applied research, and delivery—applying and providing scientific advances to all members of the population. Overcoming the divide between the research and delivery components of the cancer effort requires concerted action by all stakeholders. The following recommendations were included in the report to the President:

- Barriers must be identified and removed. This will require legislative and policy action, payer acceptance of new interventions, and professional education.

- Public pressure is needed to change counterproductive activities by some sectors.
- The cancer workforce requires greater training, diversity, and sensitivity. Numerous studies have shown that health care providers do not necessarily treat people from different ethnic backgrounds in the same manner.

Dr. Freeman also updated Board members on regional meetings of the PCP intended to solicit feedback from individuals in diverse communities who have had problems in obtaining health care, as well as from health care providers who have had problems administering health care, education, and treatment to these populations. These meetings also are intended to result in recommendations for resolving the disconnect between scientific discovery and delivery. Regional meetings already have been held in Omaha, NB; Burlington, VT; Billings, MT; and Nashville, TN. Future meetings will be held in Los Angeles, CA; Albuquerque, NM; and Bethesda, MD. Dr. Freeman said the essence of what was found from these meetings so far has been anecdotal information in the following emerging areas: financial issues, information/knowledge, cultural issues, physical access, and system issues.

Financial Issues. Dr. Freeman said that financial issues (including lack of insurance and underinsurance) are driving much of the disparities between discovery and delivery. The United States has a market-based health care system, but no provision for universal access. During these regional meetings, PCP staff heard testimony from individuals who have been put into debt or bankrupted because of their cancer-related medical bills. Many of these individuals have incomes too high to qualify for Medicaid, but not enough income to pay their medical bills. Many of these people also lost their jobs because of their cancer care. Dr. Freeman also noted that geography was identified as a barrier to care—one person reported having to drive more than 300 miles to receive chemotherapy treatment. Other identified barriers to care related to finances include a fear of debt leading to avoidance of care, families being forced to put basic needs ahead of cancer care, a lack of funds for treatment after an abnormal screen, and the fact that reimbursement policies are very complex in this country.

Information/Knowledge. Dr. Freeman reported that at these regional meetings, testimony was heard from individuals who stated that health care providers do not believe that younger patients can have cancer. Another problem is that very few health care providers have research concerns and backgrounds and, therefore, are not enrolling their patients in clinical trials for cancer care. Testimony was heard from patients indicating that a lack of access to information, poor understanding of information, language/literacy issues, and poor information-seeking patterns all are barriers to receiving cancer care. In some remote states, thousands of Americans have no telephone, no internet, no access to libraries. Barriers identified by providers included misdiagnosis of young patients, a lack on information on current treatments, and insufficient knowledge about end-of-life issues.

Cultural Issues. Some of the cultural issues identified include a lack of trusting relationships between patients and health care providers, a prohibition on discussing cancer among some cultures, cultural taboos and modesty, and the incompatibility of the health care system with patient traditions and wishes at the end of life. Dr. Freeman reported that the issue of trust between the patient and the health care provider was particularly important in Native American communities. In some cases, PCP staff heard from patients who had a sense of secrecy about their cancer—some patients reported feelings of guilt and were concerned about what their cancer diagnosis meant for their children. Dr. Freeman noted

that some cultures feel that cancer is communicable. He also said that some patients object to being examined by an opposite-sex physician and/or one that is not a member of their culture or ethnic group.

Physical Access. Many cancer patients reside in remote or rural areas, where there is a lack of health care providers, and where transportation and weather can be a much larger issue than it is in urban areas. Dr. Freeman said that about 25 percent of the U.S. population lives in what are considered remote or rural areas. For example, one-half of the counties in Montana, which has a population of 800,000, are considered “frontier” counties, with three or fewer people living per square mile.

System Issues. System issues identified include the need to focus on acute care, the fact that regulations controlling how health care providers work are developed by nonproviders, and the fact that sparsely populated states may have less power in government to spearhead political change.

Dr. Freeman said the next steps for the PCP are to complete the regional review and analysis of the United States and its territories, which will continue through June 2001. A report summarizing the findings of these meetings will be delivered to the President in December 2001. Dr. Freeman concluded his presentation by showing a 6-minute video containing patient and health care provider testimony from these various regional meetings.

Questions and Answers

Dr. Klausner asked whether the PCP has considered collecting some of the testimony and stories from these regional meetings and partnering them with the media to have more of an effect than a single report that may or may not be seen by the President. Dr. Freeman responded that this type of creativity is needed. He also noted that testimony from these individuals could be used to influence policymakers. Dr. Armitage asked how some of these issues will be resolved if much of the medical establishment in the United States opposes the idea of universal access to health care. Dr. Freeman responded that the medical community alone cannot be the driving force behind this. He suggested the answer will come from the public putting pressure on policymakers.

VI. REPORT ON TRENDS IN RMS MANAGEMENT FUNDS—DR. RICHARD KLAUSNER

Dr. Klausner reported that the current budget for Research Management Support (RMS) is \$120 million, or 3.6 percent of the FY2000 budget. RMS funds support the infrastructure that in turn supports the extramural research initiatives, similar to indirect costs for other organizations. RMS does not, however, include running the intramural program and certain aspects of running cancer control and in-house activities. Dr. Klausner explained that RMS funds are distributed so that about one-third is dedicated to the extramural program management, one-third is for business management, including information technology and telecommunications, 17 percent is for grant contract review and approval, and 18 percent leaves the NCI for use by either the NIH or DHHS. Dr. Klausner explained that RMS growth has been severely limited while the overall NCI program has expanded. Today it represents 3.6 of the NCI budget, while in 1995 it represented 5 percent of the NCI budget. RMS components are almost exclusively driven by new and expanding NCI program initiatives. Dr. Klausner expressed concern that the overall health of the cancer research enterprise in terms of public trust and the NCI’s overseers’ trust may suffer if RMS funds are inadequate. He also said he is concerned with the strain of an increasing

workload on some NCI staff. For example, from 1995 to 2000 in the GAB, there was an increase from 4,500 grants funded to 6,600 grants funded with only a small increase in the number of staff. There now is an annual turnover rate for these employees of over 25 percent—more than one-half of grant specialists have fewer than 2 years of experience. When these employees leave, they cite workload, the inability to pay overtime because it comes out of RMS funds, and the lack of support as reasons for their departure. Dr. Klausner noted that in other areas of the NCI not under this RMS constraint, the turnover rate is about 12 percent per year. He said that an additional \$27 million in funds to pay for reasonable workloads and the amount of time to do the work, as well as an additional \$29 million for IT infrastructure needs should be added to the \$120 million set aside as RMS funds for this year. He said that the RMS needs for this year actually are \$176,610,000, or 5 percent of the NCI budget. Dr. Klausner said he is worried about the consequences of this inadequate expenditure, and whether the NCI can satisfy customer needs and fulfill oversight needs, particularly in areas of human subjects research. For whatever projected growth rate there is for the NCI, it is felt that an RMS funding level of 5 percent of the NCI's budget is appropriate.

Questions and Answers

The Honorable James E. McGreevey, Mayor of Woodbridge Township, NJ, asked Dr. Klausner if he wanted a statement of support from the Board advocating an increased RMS funding level. Dr. Klausner responded that he wanted Board members to understand the RMS dilemma and to speak up in its capacity about the need for adequate support for management and running the Institute. Dr. Richard Boxer, Professor of Family and Community Medicine, Medical College of Wisconsin, asked how the 3.6 percent level of RMS funding compares with other institutions. Dr. Klausner said that the RMS funding level is approximately 7.8 percent at the National Science Foundation, and comparable entities generally have an RMS level of greater than 10 percent. He said the NCI can directly calculate what its needs are, what its shortfall is, and what is happening to its staff. He also noted that it is difficult to set a benchmark for RMS funds because of the differences between the NCI and other organizations and institutions. Dr. Klausner said he did not know if the FY2001 budget could be impacted, and he recommended addressing the RMS issue in the FY2002 budget. Dr. Ivor Royston, President and CEO, Sidney Kimmel Cancer Center, asked whether the RMS budget was dictated by the Secretary, DHHS, or whether it is congressionally mandated. Dr. Klausner responded that the RMS budget has been defined by the appropriators in the last few years. Dr. Sharp asked Board members if there was consensus to pass a resolution requesting the RMS budget to be increased to 5 percent. Board members voiced support of such a resolution, which was drafted and approved.

VII. NCI PROGRAM UPDATE

DBS Vision Statement. Dr. Carl Barrett, Director, Division of Basic Sciences (DBS), stated that the mission of the DBS is to: (1) be at the forefront of cutting-edge basic science research; (2) provide a rich training environment for the future generation of cancer researchers; and (3) translate the research findings to achieve the mission of the NCI. The DBS is the largest of NCI's Divisions, with 225 Principal Investigators covering a wide range of disciplines and research efforts. The DBS focuses on the training and research environment, translation of research findings, and developing high-quality research programs that will reduce the burden of cancer. Investigator-initiated research is a strong component of the DBS, and a strong peer review system is critical. Dr. Barrett noted that the ability to conduct independent research conflicts with the goal of translating these research findings, so tools are needed to enable investigators to make important discoveries. Improvement also needs to be made in providing

training and research opportunities for young investigators at the DBS. Dr. Barrett said that mechanisms to facilitate the contribution of basic scientists to the NCI's mission include:

- Investigator-initiated research—Dr. Barrett said that the best ideas and discoveries will come from individuals who are in a creative environment and who have the necessary freedom.
- Laboratory-based infrastructure and scientific initiatives.
- Intramural-wide core facilities and infrastructure, including: (1) cDNA microarrays, which will have a major impact across all NCI Divisions; (2) animal resources, including rodents and primates; (3) imaging technology, such as microscopic confocal imaging; (4) proteomics, which Dr. Barrett termed a “major new frontier;” and (5) mouse molecular pathology, in efforts to compare and contrast murine model results with those of humans.
- Training programs, including those at the NCI Training Office, the DBS Trainees Assembly and Retreat, the Molecular Epidemiology Training Program, the Interdisciplinary Training Program in Chemistry, and the Molecular Pathology Training Program.
- Research programs, including the HIV Drug Resistance Program, the Mouse Genetics Program, and the Structured Biology Program.
- Joint appointments in the DBS and Division of Clinical Research, which has helped to facilitate a number of transdivisional activities.
- NCI Extraordinary Opportunities, such as the Mouse Models of Human Cancers Consortium, the Molecular Signatures Extraordinary Opportunity, and the Genes and the Environment Extraordinary Opportunity.

Questions and Answers

Dr. Larry Norton, Director, Medical Breast Oncology, Evelyn H. Lauder Breast Center, Memorial Sloan-Kettering Cancer Center, commended Dr. Barrett on the development of the Extraordinary Opportunities Program as well as its availability and accessibility to extramural investigators, calling it a role model for the interplay between the intramural and extramural program. Dr. Barrett commented that the involvement in these larger extramural activities of the NCI has been equally rewarding for intramural scientists. Dr. Sharp asked Dr. Barrett to identify the largest problem facing the DBS. Dr. Barrett responded that time and space are the largest problems.

P53 and Apoptosis. Dr. Karen Vousden, Chief, Regulation of Cell Growth Laboratory, DBS, NCI, explained that the tumor suppressor p53 has been dubbed “the molecular policeman” because of the ability of the protein that it encodes to recognize oncogenic abnormalities in cells and eliminate those cells by either killing them or by stopping them from growing. While p53 is critical in the prevention of tumor development, it is not necessary for normal growth and development. P53 is activated in response to many types of stress, including DNA damage as a result of carcinogen exposure, oncogene activation, and abnormal cell proliferation. In cases where there is mutant p53 or no p53 function at all, the cells responding to stress continue to grow, which has led researchers to conclude that loss of p53 is an

important contributor to the development of many types of human cancers. Dr. Vousden said that roughly 50 percent of malignancies in common cancers like those of the lung, colon, breast, and stomach show evidence for mutation of the p53 gene leading to a loss of its function. Those cancers that do retain wild-type p53 genes still are defective in the ability to mount a p53 response, and they have mutations or aberrations in the pathways that allow activation of p53.

Dr. Vousden described approaches to treating tumors that retain wild-type p53 but have a defect in the ability to activate p53, with the endpoint being activation of this endogenous p53 in the cancer cells. Experiments with normal mouse embryo fibroblasts treated with activated p53 showed that the cells stopped growing; but it was a reversible arrest, and the cells did not die. Conducting this same experiment with mouse embryo fibroblasts that have been transformed with an oncogene showed that the sensitivity of these cells to dying increased dramatically. It is hoped that tumor-selective killing can be achieved through the activation of p53 in cancers that retain wild-type p53 while minimally affecting normal surrounding cells. The protein MDM2 is one of the principal regulators of p53; it binds to p53 and degrades it. Dr. Vousden explained that MDM2 is expressed in response to p53, so there is a feedback loop in normal cells where p53 levels can never get very high because as soon as p53 levels increase, MDM2 levels increase, thereby decreasing the amount of p53. MDM2 functions as an enzyme that can conjugate ubiquitin to p53 and also to itself. It also allows the nuclear export of p53. Dr. Vousden showed a slide of the gel-based assay used to measure the ubiquitin ligase activity of MDM2. She hypothesized that under normal circumstances, MDM2 ubiquitinates p53 and that ubiquitination is important for export to the cytoplasm and for degradation of the p53 protein. In response to stress, however, p53 is stabilized because MDM2 is inhibited from targeting p53 for degradation. Expression of another protein, ARF, inhibits MDM2 function in response to abnormal proliferation. ARF inhibits MDM2 E3 ligase activity and allows the relocation of MDM2 to the nucleolus, so it is in a different part of the nucleus than p53.

Dr. Vousden said it is believed that ARF is one of the key points at which a cell can monitor whether there are abnormal proliferative signals. In response to abnormal proliferative signals, ARF is activated, which in turn activates p53, which stops the cells from growing. Experiments have demonstrated that in tumors containing wild-type p53 that are introduced to ARF, the endogenous p53 is activated and the tumor stops growing. Dr. Vousden and her group have screened about 5,000 compounds obtained from the Developmental Therapeutics Branch. She presented some preliminary data suggesting that this approach might be useful in identifying lead compounds to use in experiments to inhibit MDM2. Some of these inhibitors appear to be able to partially enter cells and stabilize p53 and MDM2. She also presented preliminary data on one compound that has the ability to kill transformed cells in a p53-dependant manner. She concluded her presentation by recognizing her collaborators.

Questions and Answers

Dr. Klausner asked whether compounds being developed inhibit ARF and MDM2. Dr. Vousden replied that it is not known whether they inhibit ARF and MDM2; these studies have not yet been conducted. Dr. Sharp asked if these inhibitors have been tested against p53-negative cells. Dr. Vousden said that these studies are just underway. Dr. Klausner asked what is planned for these lead compounds and screens. Dr. Vousden replied that it is hoped to develop the assay to a high throughput screen. Her group is in discussion with a company about the development of the assay to allow high throughput

screening. They are actively seeking other people or investigators outside the NCI/NIH to assist them with these endeavors.

Molecular Signals for T-Cell Development. Dr. Alfred Singer, Chief, Experimental Immunology Branch, DBS, NCI, presented a new perspective on how developing T cells determine their appropriate cell fate. He began by with an overview of how the immune system eliminates invading molecules and distinguishes them from the body's own normal molecules and cells, and the roles T lymphocytes play in this process. He described the roles of the two distinct subclasses of T lymphocytes: CD4 T cells and CD8 T cells. For a competent immune system, T lymphocytes must express the correct matching set of coreceptor and T-cell receptors—for a CD8 T cell to be functional, it must express a receptor that is capable of recognizing the class I major histocompatibility (MHC) molecule. Conversely, for a CD4 T cell to be functional, it must express a T-cell receptor that is able to see the class II MHC molecule. Dr. Singer said this process occurs during the development of a mature T cell. Stem cells enter the thymus and develop to a stage where they express both CD4 and CD8 coreceptor molecules—these cells are called double-positive thymocytes, and they have the ability to become either CD4 or CD8 T cells. Double-positive thymocytes use the MHC molecules that are expressed on epithelial cells in the thymus to determine the specificity of their T-cell receptors. If a double-positive thymocyte expresses the T-cell receptor that is capable of binding to MHC class I molecules, it does so by pre-engaging the molecule with the CD8 coreceptor. The CD4 molecule is not coengaged. Dr. Singer explained that this coengagement signals a double-positive thymocyte, and it is presumed that this signal shuts off expression of a gene that encodes the wrong coreceptor; in this case it shuts off the CD4 gene so the cell becomes a CD8 T cell with the appropriate T-cell receptor.

Dr. Singer said it was hypothesized that double-positive thymocytes have two different ways of responding to a signal, either by shutting off CD4 or by shutting off CD8. An experimental system to test this model was developed, and researchers unexpectedly found that regardless of the signal that the double-positive thymocytes received in the thymus, they only did one thing—they shut off CD8 and only became CD4 T cells. Dr. Singer explained that CD8 T cells then are created when the newly arising CD4 T cells respond to a growth factor present in the thymus, called interleukin-7 (IL-7), by expression of a specific receptor on the surface. During a process termed “coreceptor reversal,” newly arising CD4 T cells have shut off the CD8 gene, but in the presence of IL-7 within a few hours, these cells then turn off the CD4 gene that they have been expressing, and they turn the CD8 gene that they had stopped expressing back on. As a result, investigators have been attempting to determine how both CD8 and CD4 T cells are produced and understand what prevents cells from undergoing coreceptor reversal so that they become CD4 T cells. Dr. Singer explained that the ability to signal through the IL-7 receptor is self-regulated through signals from the T-cell antigen receptor. Persistent signals to the T-cell antigen receptor results in IL-7 receptor desensitization, and the T-cell receptor signal blocks the coreceptor reversal that would have been induced by the IL-7 receptor. This is the pathway by which cells prevent coreceptor reversal and become CD4 T cells. He said that in this model, the double-positive thymocyte receives a differentiation signal, and it responds in a preprogrammed way to turning off one of those two cell fates. It becomes a CD4 T cell and turns off the CD8 gene, thereby becoming an intermediary cell. At this point the cell determines whether it made the right choice by whether the signal persists. If this initial signal persists, the cell becomes a CD4 T cell; however, if the initial signal is lost, then the cell needs the CD8 gene to be expressed to sustain this signal, and the cell undergoes coreceptor reversal to become a CD8 T cell. Dr. Singer said it is thought that this model is relevant not only for the immune

system, but also for many other biological systems in which a bipotential precursor cell has to choose one of two alternative cell fates.

Questions and Answers

Dr. Klausner asked what prevents developed cells from re-engaging their receptors and becoming double-negative. In other words, why don't these cells "recycle?" Dr. Singer said there are two reasons. First, this ability to undergo coreceptor reversal is limited to a very brief developmental timeframe, so there is a narrow window during which the cell's fate is determined. Once this window closes, cells cannot change their fate. The second reason is that most of the MHC molecules are expressed in the part of the thymus where they contact the double-positive thymocytes that are just starting to make up their mind. Once these double-positive thymocytes move from that area of the thymus, they probably do not encounter MHC under the right circumstances to change their mind again.

A New Approach to Cloning Genes Involved in Cancer Progression. Dr. Barrett described the efforts of his laboratory in trying to identify the genes involved in suppressing metastases. There is clear evidence that there are genes that negatively suppress the metastatic phenotype and genes that are involved in the regulation of cellular life span—normal cells have a finite life span, and there are genes that must be lost for cells to acquire indefinite growth potential. It also is known that activation of telomerase is a key step in this process, but the genes that negatively regulate telomerase are poorly understood. Furthermore, there are genes involved in the finite life span of cells that are not involved in the telomerase pathway that also are not well known. Dr. Barrett reported that there has been great success in cloning genes involved in genetic predisposition using positional cloning technologies. He then described a new approach—a combination of functional and positional technologies. Using this technique, called chromosome-mediated transfer, Dr. Barrett's laboratory has engineered copies of each of the human chromosomes into a panel of mouse cells and introduced selectable markers into these chromosomes. These chromosomes then are removed into microcells, which can be introduced into cells of interest. As a result, intact copies of human chromosomes can be transferred and individual chromosomes can be studied to determine whether they affect metastases, growth, development, differentiation, metabolism, and so on. He and his colleagues have been able to narrow down the genes on chromosome 1 involved in cellular senescence down to a region of one megabase.

The technology used to narrow down and clone genes based on identification of their function is called transformation associated recombination (TAR) cloning. Dr. Barrett described TAR cloning as a good example of how fundamental research in basic science can ultimately be applied to solving important problems in the cancer arena. He explained the process of TAR cloning, which involves isolating human DNA and incorporating it into the yeast *Saccharomyces*. Dr. Barrett said the advantages of this approach is that it does not yield any chimeric molecules, it can isolate entire genes, and the process is rapid—a gene can be isolated using TAR cloning in 1 to 2 weeks. One use of TAR cloning is to make chromosome-specific or subchromosomal-specific libraries, which have been utilized by the NHGRI. Other uses of TAR cloning include cloning specific chromosome regions for closing gaps on physical maps, cloning unclonable regions, and cloning specific individual genes. Dr. Barrett noted that this technology has been modified so that different sizes of genes can be isolated, a process called radial TAR cloning. Dr. Barrett described how yeast artificial chromosomes are transferred into bacterial artificial chromosomes, which then are transferred into human cells at efficiencies approaching those associated with plasmid transformations. An added benefit of this technology, he said, is that it offers the

chance to examine the function of the gene with its natural promoter intact. It also can be used to clone genes that cannot be cloned using other technologies—human centromeric DNA, for example. In addition, Dr. Barrett said that application of this technology can lead to the development of a human artificial chromosome, and in addition to cloning the genes involved in cellular senescence, work is ongoing to study the genes involved in suppressing metastases. Dr. Barrett concluded his remarks by stating that TAR cloning will be useful for studying the function of genes and for identifying new genes.

VIII. MOUSE MODEL CONSORTIUM—DRS. DINAH SINGER AND JEFFREY GREEN

Dr. Dinah Singer, Director, Division of Cancer Biology (DCB), NCI, said that the objective of the Mouse Models of Human Cancers Consortium (MMHCC) is to develop and validate mouse models, using information on cancer genes, with heritable malignancies that parallel human disease. The Consortium aims to make these models available to the cancer research community so they can be exploited in the development of new approaches to the screening, detection, and treatment of cancer. The Consortium is developing an infrastructure to support the: (1) validation of mouse models of cancer; (2) application of models to preclinical trials; (3) innovation of new technologies to further validate the models; (4) integration of information about the models and their relevance to cancer; and (5) dissemination of information and resources to the broader cancer research community. Dr. Singer said that at the core of the MMHCC's infrastructure is a set of U01 Grants—two Principal Investigators from each U01 Grant form the Consortium's Steering Committee. The Consortium has agreed to collaborate and make any of the resources they develop generally available. MMHCC researchers participate in an outreach program composed of a variety of researchers and think tanks, among other individuals, to share information and resources. The first RFA associated with the Consortium was released in July 1998. It was awarded in September 1999. At the time the RFA was issued, the NCI anticipated funding 6 U01 applications and 1 intramural project; however, 31 applications were received and of them, 19 U01 Grants and 1 intramural project were awarded. Dr. Singer noted that the intramural project was reviewed using the same criteria as those used to review the U01 Grants, and the intramural project received one of the highest scores.

The first meeting of the MMHCC's Steering Committee was held approximately 1 year ago. At that meeting, the priorities of the Committee and the Consortium were established. Dr. Singer said that one of the questions guiding progress of the MMHCC is establishing the criteria by which a model is judged to be valid. The following Organ Site Committees were established: Breast, Central Nervous System, Gastrointestinal, Hematopoietic, Lung, Ovarian, Prostate, and Skin. Progress in validating mouse models includes: (1) comparative histopathology workshops sponsored by each of the Organ Site Committees; (2) acquisition of cDNA arrays for gene expression profiling; (3) training and distribution of cDNA arrays; and (4) the Hematopoietic Malignancies Lexicon Project to develop a common vocabulary. To integrate knowledge, the MMHCC has started to build and populate the following three databases: (1) Mouse Phenotype Database; (2) Tool Mouse Database, which contains information on different kinds of genetic approaches; and (3) Resource Database, that will list available resources (e.g., antibodies against cancer). For application in preclinical trials, the MMHCC has held roundtable meetings with biotechnology/pharmaceutical companies to bring members of the MMHCC together with the private sector. The MMHCC also is collaborating with the Developmental Therapeutics Program to initiate prevention and drug testing trials. In terms of innovation, the MMHCC is testing bacterial artificial chromosome arrays for comparative genome hybridization and investigating novel gene modification/disruption strategies. Dr. Singer said that in terms of dissemination of information and

resources to the cancer research community, the Consortium has established or developed: (1) a mouse models repository in Frederick, MD; (2) Web sites for the rapid dissemination of information protocols—these Web sites currently are only available to MMHCC members, but it is hoped that they soon will be made available to the public; (3) Mouse Engineering Workshop; and (4) Mouse Model Symposium.

The MMHCC Implementation Group is comprised of 16 NCI extramural scientist staff members who also are members of the MMHCC's Steering Committee. Dr. Singer said the goals of the Implementation Group are to: (1) serve as a scientific resource for MMHCC activities; (2) assess the needs of the broader cancer research community and ensure that they are addressed by the MMHCC; (3) ensure integration of MMHCC goals and activities with other NCI programs; (4) participate in formulating and implementing new MMHCC initiatives; and (5) provide continuity for the MMHCC, and expect the infrastructure to last beyond the life of the U01 Grants. The goals of the MMHCC Forum Program are to: (1) establish a dissemination program to inform the cancer research community about MMHCC activities and available resources; (2) receive feedback from the cancer research community; (3) identify the needs of the cancer research community beyond those identified by the MMHCC; (4) provide guidance to the NCI for new MMHCC initiatives; and (5) serve as a vehicle for communication within the broader cancer research community. MMHCC forums include: Leukemia and Lymphoma Models Focus Group, Ovarian Cancer Models Think Tank, Neuro-Oncology Models Forum, Colon Cancer Forum, Prostate Cancer Models Focus Group, Complex Traits and Genetic Modifiers Forum, Cutaneous Malignancies Models Think Tank, Pancreatic Cancer Models Think Tank, Prevention Models Focus Group, and Small Animals Imaging Interest Group.

Dr. Jeffrey E. Green, Principal Investigator and Staff Scientist, Laboratory of Cell Regulation and Carcinogenesis, DBS, NCI, discussed some of the progress over the last year in support of the MMHCC from an intramural perspective. Progress included developing a Web site, establishing a repository, developing new informatics tools, and developing the ability to share reagents across numerous organizations. Dr. Green said their community is composed of 25 Principal Investigators, mostly from within NCI, but also from other parts of the NIH. As an intramural group, he said the first goal is to develop a comprehensive system to validate the genetically altered mice as models for human breast cancer. Dr. Green noted that there now are more than 100 different transgenic models that have a phenotype in the mammary glands, making it the organ system furthest developed in animal models, as well as the most difficult to try to bring together in terms of informatics. The second goal is to develop an extensive and comprehensive dataset that will include gene expression profiles, genomic information, and the descriptive pathology and natural history to compare what happens in the mouse model with what is known about human breast cancer. The third goal is to develop new models that can be used to study the biology, tease out new molecular pathways, and then apply this knowledge to develop chemoprevention methods and use of these models in preclinical trials. Dr. Green briefly described the Annapolis Workshop of Comparative Pathology Between Mouse and Human Cancers, which brought together human pathologists, veterinary pathologists, and mouse modelers to: (1) discuss and redefine the histopathology classification system to allow clinicians to understand which histopathology of a particular mouse model might best relate to human breast cancer; and (2) assist mouse modelers in better understanding what is essential for developing a model that mimics more closely the human disease. Dr. Green said the Workshop was very successful, noting that it has resulted in a landmark publication in the field. Some experimental advances made by the group include: (1) the development of new models by knocking out the BRCA-1 gene in mice—these mice develop a phenotype that is very similar to the BRCA-1 type phenotype of human breast cancer; (2) continuing to cross mice with multiple genetic

abnormalities to try to understand genetic interactions and how these manifest themselves in the development of cancer; (3) developing better technologies to inducibly alter the genome in an adult mouse; (4) trying to identify genes that modify cancer; and (5) performing preclinical testing with some of the mouse models.

Dr. Green described efforts to apply the microarray approach to information associated with the CGAP to help discover new genes and understand genes that already are known to play a role in the process of cancer progression. His group has started to apply this technology in an attempt to analyze multiple mammary tumor types. He noted that this and other work has led to the identification of genetic signatures for various kinds of tumors, and it is hoped that it will lead to the identification of new cancer markers in the mouse and in the human datasets, allowing researchers to follow cancer progression in a noninvasive way. It ultimately is hoped that new therapeutic approaches will uncover new therapeutic targets that will serve as a means for trying to prevent and/or treat cancer in new and novel ways. Dr. Green concluded his remarks by stating that the group is an integral component of the MMHCC, and it is believed that the cutting-edge technologies discussed here will provide critical new insights into mammary cancer biology, and finally, that the next generation of mouse models will be even better and more important for preclinical therapeutic testing.

Questions and Answers

Dr. Sharp commented that a great deal of attention needs to be given to open dissemination of information resulting from the work of the MMHCC, noting that the support for this endeavor from the scientific community would be negatively impacted if one group of investigators is perceived to have more or better access to developing technologies and study results than other groups. Dr. Singer responded that the MMHCC is attempting to disseminate as much information as is possible and to make all the resources publicly available. The MMHCC also is discussing strategies for forming more formal links with the outside community.

Dr. Norton stated that competition between the extramural and intramural components of the MMHCC could be problematic, particularly in light of the fact that there may be a difference in terms of their abilities to pursue various avenues of research. Dr. Singer explained that there is no competition for research dollars between the intramural and extramural components.

Dr. Klausner noted that the MMHCC is set up so that the entire Consortium has access to all the infrastructures, informatics, and technology. Dr. Singer noted that the MMHCC is having a Steering Committee meeting in January, and one of the items on the agenda is the issue of dissemination to the community. Dr. Norton asked whether there have been any collaborative efforts between the MMHCC and the SPORES Program, noting that there are large segments of the cancer research population that are not communicating. He added that the output variables for human therapeutic trials are fairly primitive, while output variables on the mouse models side can be very sophisticated. He also said that conducting more directed therapeutic trials on the basis of the mouse genome is a critical feature of the Consortium that needs to be expanded. Dr. Singer stated that the preclinical trials group of the MMHCC is addressing this issue by organizing workshops to educate mouse modelers in the design of preclinical and clinical trials.

IX. PROGRESS REVIEW GROUP REPORT: BRAIN TUMORS—DRS. DAVID LOUIS AND RICHARD KLAUSNER

Introduction. Dr. Klausner stated that the report of the Brain Tumors PRG is a result of collaboration between the NCI and the National Institute of Neurological Disorders and Stroke (NINDS). He recognized the efforts of the Brain Tumor PRG leadership—Dr. David Louis, Associate Professor at the Kubik Laboratory for Neuropathology, Massachusetts General Hospital; Dr. Jerry Posner, Member, Department of Neurology, Memorial Sloan-Kettering Cancer Center; Dr. Rick Kaplan, Executive Director, Brain Tumor PRG; and Dr. Tom Jacobs, Executive Director, Brain Tumor PRG. Dr. Klausner said that bringing together neuroscience with molecular oncology has resulted in an intriguing and interesting dynamic. He reminded Board members that the report of the Brain Tumors PRG has been received by the NCAB and has been posted on the Web.

Report of the Brain Tumor PRG. Dr. Louis apologized on behalf of his copresenter, Dr. Posner, who was unable to attend the meeting. He also thanked the NCI and NINDS for cosponsoring this PRG. Dr. Louis provided background information on brain tumors, which are moderately common, particularly among children—brain tumors constitute the most common solid tumor of childhood and are second only to leukemias in terms of overall tumor incidence in the pediatric age group. Brain tumors rank among the 10 most common tumors among adults, and there are approximately 17,000 new cases of primary brain tumors diagnosed in this country each year. He noted that brain tumors are among the most devastating human neoplasms because they affect the brain, resulting in very difficult questions surrounding treatment options and quality-of-life issues. The Brain Tumor PRG had its first meeting in March, and a roundtable meeting attended by 120-130 patient advocates, industry representatives, clinicians, and basic scientists from around the country in July. In late summer and early fall of this year, the report of the Brain Tumor PRG was written. Hard copies of the report will be available by January, and a meeting with the directors of the NCI and the NINDS in response to this report is set for early March of 2001. Dr. Louis listed problems associated with brain tumors, including: (1) they affect the brain, impacting cognition and the ability to interact with the environment; (2) there are many varieties of brain tumor types—at the recent World Health Organization Classification Meeting, 126 variants of brain tumors were identified; and (3) these tumors affect children as well as adults, so pediatric issues need to be addressed. He said two environmental issues that offer particular challenges in brain tumors are the blood-brain barrier and the immune privilege of the central nervous system. Also, conventional cancer therapies are, in general, mostly ineffective in the treatment of brain tumors—surgery, a mainstay of treatment for other types of cancers, cannot be accomplished to the same degree in the brain because if the tumor involves some vital portion of the brain, it cannot be resected. Similarly, chemotherapeutic agents usually are ineffective either because they do not have effect on the tumor, or because they have problems with delivery through the blood-brain barrier into the central nervous system.

Dr. Louis then described the Brain Tumor PRG's report, which was divided into two sections: hypothesis-driven "scientific priorities," and hypothesis-generating "resource priorities." Dr. Louis said there were six distinct areas of scientific priorities: basic biology, epidemiology, detection and diagnosis, treatment, outcomes, and the issue of specific tumor types. He noted the similarities and differences between these areas in terms of brain cancer and in terms of other types of cancers. Some of the brain tumor-specific scientific priorities include: (1) characterizing the interactions of brain tumor cells with the normal brain; (2) providing a detailed molecular classification of the cells of origin in defining how these cells of origin arise, differentiate, and assume their unique cell fates; (3) gaining a better

understanding of the immune system within the brain as well as the blood-brain barrier; (4) linking existing databases to allow larger numbers of cases to be analyzed; (5) expanding existing databases to include all primary brain and spinal cord tumors, both for malignant and nonmalignant tumors in adults and children; and (6) obtaining better epidemiological data on tumors that biologically are not malignant but act in a highly aggressive manner. Additional scientific priorities identified in the Brain Tumor PRG Report include enhancing the therapeutic ratios for new agents as well as for radiation therapy; developing better outcome measures; studying the long-term outcomes of pediatric brain tumor cases; and focusing on low-grade gliomas, nervous system lymphomas, extra-axial brain tumors, and metastatic brain tumors. Dr. Louis reported that some members of the Brain Tumor PRG made the recommendation that the NCI consider a specific PRG devoted to metastatic brain tumors. Resource priorities identified in the report include: (1) advancing the field of animal models for brain cancer; (2) improving and linking tissue banks and databases; (3) following predisposed populations, such as those with neurofibromatosis Type 2; and (4) improving high throughput technologies for understanding gene function, identifying targets and pathways critical to brain tumor biology, as well as genes and genetic variations that underlie tumor resistance to chemotherapy, radiation therapy, and so on.

Dr. Louis said that the Brain Tumor PRG is planning to establish a set of interactive meetings involving scientists from different biological disciplines to encourage collaborative interdisciplinary grant applications in brain tumor biology. In its report, the Brain Tumor PRG also emphasized the importance of continuing the ongoing process of collaboration between the NCI and the NINDS, the importance of encouraging advocacy groups, and the need to address the relative paucity of investigators that are trained in both clinical and basic research aspects of brain tumors. He concluded his remarks by describing three results of the Brain Tumor PRG to date: (1) the brain tumor community in general has been very excited about the process, and it is felt that the priorities laid out by the Brain Tumor PRG are a blueprint for how brain tumor research should proceed during the next 5 to 10 years; (2) the introduction of neuroscientists to cancer biologists was a major accomplishment that hopefully will lead to interesting meetings and collaborations in the future; and (3) the enhanced collaboration between the NCI and the NINDS, which has led to discussions on setting up a working group between the two Institutes to begin to set common goals for brain tumors.

Questions and Answers

Dr. Koh asked Dr. Louis to expand on the epidemiology and what is known about specific tumor types that are increasing in incidence. Dr. Louis stated that the primary brain tumor type that is increasing in incidence is central nervous system lymphoma—some of that is due to the AIDS population, but there also appears to be an increase in non-AIDS related primary central nervous system lymphomas. There is no evidence of a specific etiology related to these.

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)(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 review of intramural site visits and tenured appointments, committee discussions, and recommendations. There was also a discussion of personnel and proprietary issues. Members absented

themselves from the meeting during discussion for which there was potential conflict of interest, real or apparent. Members were asked to sign a statement to that effect.

X. DCS UPDATE AND CLINICAL CENTER PLANS—DR. EDISON LIU

Dr. Edison Liu, Director, Division of Clinical Sciences (DCS), NCI, updated Board members on the activities of the DCS. He explained that the DCS is one of the three intramural Divisions at the NCI, with a mandate to be the clinical investigation arm of the intramural program of the NCI. The DCS consists of 16 branches, departments and laboratories, with approximately 1,100 employees, including almost 100 Principal Investigators and approximately 400 trainees. He said the DCS functions as a miniature school of medicine with training and research in pathology medicine, radiation oncology, pediatric oncology, pediatrics, surgery, urology, neurooncology, and dermatology, along with other more modality- and topically specific branches. The mission statement of the DCS is to work at the interface between science and patients to find a cure and prevention of cancer. Part of the DCS' mandate also is to concentrate on the concept of translational science, which Dr. Liu defined as the movement of ideas or technologies from one discipline to another with the ultimate goal of understanding and treating human disease, in this case human cancer.

XI. NEW STRATEGIES IN HEMATOPOIETIC STEM CELL TRANSPLANTATION--DR. RONALD GRESS

Dr. Ronald Gress, Chair, Department of Experimental Transplantation and Immunology, Experimental Immunology Branch, DCS, NCI, overviewed the DCS' efforts with respect to allogeneic bone marrow transplantation. He said there are four major barriers to allogeneic bone marrow transplantation: (1) graft rejection, which might be viewed as a host-versus-graft response; (2) graft-versus-host disease (GVHD); (3) relapse despite the powerful curative potential of graft-versus-leukemia (GVL) or graft-versus-tumor (GVT) activity, which is mediated by cells in the peripheral blood stem cell or marrow graft; and (4) immune incompetence following the engraftment. Dr. Gress said these four barriers are interlinked, and researchers believe there is currently an opportunity to approach these barriers, beginning with a focus on graft rejection, then pursuing strategies in GVHD control, optimization of GVL, and finally, strategies of immune reconstitution. Dr. Gress noted that as strategies to overcome graft rejection are initiated, GVHD is increased; as strategies to decrease GVHD are initiated, the beneficial effect of GVL are decreased; and as the T cells involved in all three of these interactions are manipulated, immune reconstitution is compromised. Dr. Gress said the DCS has dedicated efforts assigned to these obstacles in allogeneic bone marrow transplantation. DCS researchers have expertise in T-cell immunology to address issues and new strategies in graft rejection, expertise in cytokine biology to address issues in GVHD, strategies of enhancing GVL, and expertise in T-cell regeneration to address the problem of immunoincompetence after transplant.

Dr. Gress explained that to overcome the barrier of graft rejection, efforts are being focused on optimizing fludarabine as an immunoablative agent. It currently is being used as an antineoplastic agent for the treatment of chronic lymphocytic leukemia (CLL), and Dr. Gress said there are ways to improve its utilization in the transplant setting as an immunoablative agent. DCS researchers have found that simultaneously administering fludarabine with agents such as cytoxan in mice reduces CD4 cells and CD8 cells to levels below that which are obtained by lethal total body irradiation while maintaining hematopoiesis. This strategy has been translated into the clinic, and after 15 transplants, preliminary results indicate that full-donor chimerism is being observed at 14 days after transplant, not 2 to 3 months,

as is commonly observed with “mini-transplants” or nonmyeloablative transplants. As expected, however, there has been an increased incidence of GVHD among these patients. Fortunately, Dr. Gress said, there has not been an observed increase in the severity of the GVHD among these patients. It was hypothesized that Type 2 T cells (as defined by cytokine phenotype) placed into the donor inoculum may prevent GVHD because Type 2 T cells regulate those cytokines responsible for mediating the GVHD. Murine experiments conducted during the past several years have demonstrated that this is the case. Dr. Gress said these experiments also have been translated into a clinical protocol combining fludarabine with cytoxan. It is anticipated that as GVHD is decreased among these patients, relapse will increase. To combat this problem, researchers have focused on the Tc2 CD8^{positive} cell, which elaborates cytokines that do not mediate GVHD; these cells mediate an antitumor response through their cytotoxicity without mediating a GVHD through cytokines. This work has resulted in a clinical protocol that currently is undergoing approval. To address the problem of disease relapse after transplant, researchers are also working on vaccine strategies in which the donor is immunized, so that immunized antitumor T cells are included in the donor inoculum that is infused into the host. Dr. Gress said that DCS researchers also are working on a novel antiangiogenesis factor as an additional strategy to enhance anti-tumor responses in the post-transplant period and so decrease tumor relapse. Dr. Gress described the lack of immune reconstitution with respect to CD4 T cells and described a pilot trial in which DCS investigators harvested T cells prior to chemotherapy under the hypothesis that chemotherapy damages T cells and limits their ability to contribute to immune reconstitution in autologous marrow transplantation. These cells were harvested and frozen as they would be for stem cell transplant, and reinfused as a T-cell transplant after all chemotherapy was over, under the coverage of cytokine. Dr. Gress said that preliminary results indicate a statistically significant increase in CD4 T-cell immune reconstitution of these patients if they received both the T-cell infusion and coverage with IL-2.

Questions and Answers

Dr. James Armitage, Professor and Dean, College of Medicine, University of Nebraska, asked if this renewed reconstitution pattern applied to individuals who did not have significant GVHD. Dr. Gress stated that was the case, noting that the modeling intentionally was done in the absence of GVHD to see what happens without GVHD before the issue is addressed with GVHD. Dr. Klausner asked Dr. Gress to comment on the infrastructure that has been set up and what the obstacles to progress are. Dr. Gress stated that it is difficult to simultaneously maintain basic scientific investigations and clinical investigations, and that it also is difficult to translate ideas from the laboratory to the clinic. To address this, the DCS has established a team approach combining efforts of individuals who are primarily laboratory-based and individuals who are primarily clinic-based. In addition, DCS has established an infrastructure component called the Preclinical Support Service, which is charged with assisting investigators in taking ideas from the laboratory to clinical application.

XII. THE IL-15/IL-15 RECEPTOR SYSTEM: RELEVANCE TO LEUKEMIA PATHOGENESIS AND THE IMMUNOTHERAPY OF CANCER—DR. THOMAS WALDMANN

Dr. Thomas Waldmann, Chief, Metabolism Branch, DCS, NCI, stated that cancer research has not yet taken full advantage of enormous specificity of the immune system in recognizing the differences between normal cells and cancer cells for effective prevention and care. However, there are two encouraging areas of scientific discovery: monoclonal antibodies and cytokines. Advances in monoclonal

antibodies have led to the definition of new targets of action, including growth factor and cytokines, and to the approval of a variety of new agents. He said that the rationale for IL-2 receptor-directed therapy is based on the fact that resting cells in the body do not display the receptors either for IL-2 or IL-15, nor do they make the cytokines. Rather, when an antigen appropriately processed with costimulatory signals sees its receptor on T cells, this stimulates these cells to make IL-2, and the IL-2 receptor and the cell become activated. Dr. Waldmann described how the IL-15/IL-15 receptor system was discovered. He explained that IL-2 and IL-15 share an array of functions, including T-cell proliferation, B-cell activation, and NK-cell development; however, they are quite different when it comes to the two other goals of immune system. IL-2 is pivotally involved in activation-induced cell death and peripheral tolerance. IL-15 completely inhibits this process. IL-15 stimulates the persistence of memory cells, while IL-2 has the opposite effect. Stimulating the persistence of memory cells provides the opportunity for long-term response to infectious agents. He said that in terms of therapeutic implications, anything that interrupts T-cell receptor signaling or IL-2 from seeing its receptor prevents the generation of tolerance. Therefore, treatments used to maintain tolerance—for example, in an organ transplant—will not do so if these systems are inhibited. Dr. Waldmann said that anti-CD40 ligand can be given to a monkey or a human and put in a kidney, and it will stay for the long term—2 or 3 years with only early therapy due to this nonresponsiveness to foreign antigens. However, if the generation of both IL-2 and the IL-2 receptors is interrupted, this tolerance is lost and as soon as treatment with anti-CD40 ligand is stopped, the organ is rejected. Dr. Waldmann said that IL-15 does not have this effect; it inhibits organ rejection by different mechanisms and does not abrogate tolerance. So, for example, making islet cell transplants using the anti-IL-2 receptor antibody could be better accomplished using an antibody directed toward IL-15 or its receptor. He noted that IL-15, with its role in memory cells and its role in preventing T-cell suicide, may be very valuable in tumor systems—it is therapeutically beneficial to not have tumors that are recognized as self, and it is advantageous to not have a T-cell response to a tumor lost by self-induced cell death. Dr. Waldmann described ongoing efforts testing these concepts.

Dr. Waldmann said that it is planned to: (1) evaluate IL-15 as a therapeutic agent in the treatment of diseases now being treated in part with IL-2, in an effort to take advantage of maintaining a memory response and avoiding activation-induced cell death; (2) inhibit IL-15 in autoimmune diseases and in leukemias that have an autocrine IL-15/IL-15 receptor pathway; and (3) develop small molecule inhibitors to Jak3, which is constitutively active in leukemias, and which is used by all the cytokines to activate T cells. Dr. Waldmann characterized IL-15 as a 14 to 5 kilodalton, 4-alpha helix member of the cytokine family that is critically involved in T- and NK-cell function, especially in memory CD8 cells and NK cells. He said that in light of the opposing actions between IL-15 and IL-2, IL-15 may be superior to IL-2 in the treatment of cancer and as a component of vaccines for cancer, AIDS, and other diseases. Dr. Waldmann noted that abnormalities of the IL-15 system have been noted in patients with an array of autoimmune diseases as well as all diseases caused by HTLV-1, suggesting this cytokine may contribute to the pathogenesis and the maintenance of these diseases. Finally, he said that immunosuppressive agents are being developed to IL-15's receptor and to its signaling pathway for use in the therapy of autoimmune diseases and autocrine T-cell leukemias involving IL-15 and its receptors.

Questions and Answers

Dr. Boxer asked if any studies have demonstrated that blocking IL-15 helps treat inflammatory bowel or rheumatoid arthritis diseases. Dr. Waldmann replied that IL-15 can be blocked in multiple ways, but to date, none have been applied to human beings. He said that he foresees these disorders being some of the first applications of IL-15 receptor-directed therapy.

XIII. DEFINING NEW CANCER TYPES BY GENE EXPRESSION PROFILING—DR. LOUIS STAUDT

Dr. Louis Staudt, Senior Investigator, Metabolism Branch, DCS, NCI, described a new method of defining diseases with gene expression profiling using DNA microarrays. He said the basic idea is to examine, using molecular means, whether the fact that cancer is more than one disease has a bearing on a patient's clinical course. He noted that the microarrays have tens of thousands of genes on them, many of known function, and provide insight into the signaling pathways in individual genes that could be pathogenically involved in malignancy. Dr. Staudt said that these studies are conducted in the context of clinical trials in which molecular diseases are defined by gene expression profiling to determine whether they have any relation to the resistance or response of that patient to chemotherapy and that patient's ultimate outcome. The array used in these studies, the lymphochip, contains 18,500 genes and is enriched for genes that are expressed in lymphocytes or malignant lymphocytes or are known to be functionally important in them. The lymphochip contains 3,500 genes that have a known biological function and 15,000 genes whose function are not known but are differentially expressed among malignancies in normal lymphocytes. Dr. Staudt described how the lymphochip is used in experiments to compare the relative levels of RNA expression for tens of thousands of genes at a time in two different cell types. These experiments compare every pair of genes from these cells to see which have the most related expression pattern. He then presented slides from a diffuse lymphoma trial that demonstrated how this technology identified a subtype of this cancer. He also described how this technology, gene expression profiling, is starting to be applied to the study of diffuse large B-cell lymphoma and CLL, the most common leukemia found in humans. Dr. Staudt explained that diffuse large B-cell lymphoma, the most common non-Hodgkin's lymphoma, is a major clinical problem—it is increasing in incidence by 5 percent every year. Combination chemotherapy can cure only 40 percent of these patients, suggesting that there might be an underlying molecular heterogeneity in this disease. In fact, two groups of patients subdivided by their expression of a group of genes that are characteristic of the germinal center B cell were identified—those patients with germinal center-like diffuse lymphomas had a much better prognosis than those who did not, leading investigators to conclude that this disease is at least two diseases. This work is being pushed forward under the auspices of the Lymphoma/Leukemia Molecular Profiling Project.

Dr. Staudt said other studies utilizing lymphochip technology have helped determine that CLL is one disease that can be subdivided into two prominent and important clinical variants by gene expression profiling. One variant of CLL has unmutated immunoglobulin genes, and the other variant has mutated immunoglobulin genes. He said that those patients that with unmutated immunoglobulin genes seem to have a much more progressive course, requiring earlier treatment, compared with those who have mutated immunoglobulin genes. In a study of 35 patients, investigators used lymphochip technology to examine immunoglobulin sequences. A common CLL-specific gene expression signature was found to be shared by both subtypes, as were genes that distinguish these two subtypes. These genes were used to build an extremely accurate predictor of the CLL subtype. He said the genes involved are ones that are turned on when a B cell is being signaled through its B-cell receptor. Most of those genes that are high in unmutated

CLL are turned on during B-cell receptor signaling, while those that are low in unmutated CLL and high in mutated CLL are turned off during B-cell receptor signaling. Dr. Staudt concluded his presentation by acknowledging his collaborators.

XIV. ADVANCES IN THE TREATMENT OF HIV-ASSOCIATED LYMPHOMAS—DR. WYNDHAM WILSON

Dr. Wyndham Wilson, Staff Scientist, Department of Experimental Transplantation and Immunology, DCS, NCI, presented an update on advances in the treatment of AIDS-related lymphoma (ARL). The incidence of Non-Hodgkin's lymphoma is increased in patients with HIV by 100-fold, and is the cause of death in 16 percent of these patients. Highly active antiretroviral therapy (HAART), which is combination antiretroviral therapy, has had no effect on the overall incidence of systemic lymphomas. Furthermore, lymphomas have increased from 3.6 percent to 4.9 percent of AIDS cases between 1994 and 1997. Doxorubicin-based (CHOP) regimens are the standard of lymphoma treatment, associated with 40 to 60 percent complete remission rates and a median survival period of 9 to 18 months. Dr. Wilson noted that HAART has had no demonstrated effect on lymphoma remission rates or on overall survival among lymphoma patients. Based on the hypothesis that drug schedule and dose rate can impact drug resistance, investigators developed the infusional (EPOCH) chemotherapy regimen. This strategy requires incremental changes in dose and an optimization of treatment components, including drug selection, drug schedule and pharmacokinetics, and modulators of drug resistance. EPOCH involves administering etoposide, vincristine, and doxorubicin as continuous infusions over 96 hours; cyclophosphamide as a bolus on day 5, and steroids administered orally on days 1 through 5. This regimen is given over 6 to 8 cycles every 21 days. Dr. Wilson described a Phase II study to examine the effect of EPOCH in patients with untreated non-HIV large B-cell lymphomas. The study objectives were to determine efficacy and toxicity endpoints, examine pharmacokinetics, and establish a tissue bank for collaborative studies. Researchers adopted a dose-adjusted schedule of etoposide, doxorubicin, vincristine, and cyclophosphamide. The study enrolled 53 patients with large B-cell lymphomas confirmed by histology. Thirty patients had a low to low-intermediate prognosis based on the International Prognostic Index, and the remaining 22 patients had a high-intermediate to high prognosis. For the 51 evaluable patients, investigators found a 90 percent complete remission (CR) rate—a 93 percent CR rate among low-risk patients and an 86 percent CR rate among high-risk patients. With a median followup of 4 years, progression-free survival for all patients is 71 percent and overall survival is 81 percent. Dr. Wilson said these results demonstrate that EPOCH is effective in treating aggressive B-cell lymphomas and suggest that it may be effective in treating ARL.

Dr. Wilson explained that ARL presents unique therapeutic challenges, including the need to: (1) balance the effects of chemotherapy on immune suppression with an effective dose intensity; (2) balance the benefits of HAART on HIV control with the potential adverse effects of HAART on chemotherapy toxicity and pharmacokinetics; and (3) develop more effective treatment approaches. In adopting the EPOCH regimen to ARL treatment, the dose of cyclophosphamide is adjusted to minimize CD4 cell loss, and HAART is suspended during chemotherapy. This is a controversial step because the HIV is uncontrolled when HAART is stopped. However, Dr. Wilson explained that this approach offers the advantages of eliminating pharmacological interactions and overlapping toxicities, increased dose intensity, and a potential reduction in the emergence of HIV resistance. A Phase II study of EPOCH in untreated ARL was conducted to assess the activity and toxicity of this regimen as well as to establish a tissue bank for collaborative studies. The study focused on the effects of withholding HAART to

measure the effects of EPOCH on CD4 populations, the effects of EPOCH on viral control, and changes in viral resistance mutations. The study enrolled 33 patients: 23 with large B-cell lymphoma, 5 with Burkitt's lymphoma, 4 with intermediate effusion, and 1 with primary effusion. Sixteen patients had a low to intermediate-low prognosis, and the remaining 17 had a high-intermediate to high prognostic index. Full doses of etoposide, doxorubicin, and vincristine were administered. Cyclophosphamide was administered at 55 percent the normal dose. Seventy-nine percent of patients achieved CR—67 percent of those with CD4 counts less than 100, and 86 percent of those with CD4 counts higher than 100. Investigators found 100 percent disease-free survival among patients who went into CR. Dr. Wilson said this study indicates that: (1) EPOCH in the absence of HAART is highly effective in treating HIV-associated lymphomas; (2) cyclophosphamide dose adjustment may minimize CD4 cell loss and reduce overall toxicity while maintaining full dose intensity of infused agents; and (3) CD4 recovery and viral control occurs following EPOCH. Dr. Wilson noted that the high disease-free survival rate suggests that this strategy may provide a unique mechanism of lymphoma control.

Questions and Answers

In response to one question, Dr. Wilson explained that quality-of-life measurements for patients treated with EPOCH in the ARL study returned to baseline levels or were higher than baseline levels within several months of finishing chemotherapy. Dr. Wilson noted that antiretroviral therapy was stopped for the 4- to-5-month duration of chemotherapy among patients in the ARL study. Dr. Klausner asked if any Phase III trials of EPOCH are planned. Dr. Wilson said that his group has been in discussion with the AIDS Malignancy Consortium to study the effect of EPOCH in AIDS.

XV. NONMYELOABLATIVE STEM CELL TRANSPLANTATION AS ALLOGENEIC IMMUNOTHERAPY FOR TREATMENT OF REFRACTORY RENAL CELL CARCINOMA—DR. RICHARD CHILDS

Dr. Richard Childs, Hematology Branch, National Heart, Lung and Blood Institute, began his presentation by providing a background on allogeneic transplantation, which has been used successfully for more than 30 years to treat patients with hematological malignancies that would otherwise be fatal. There are two components that contribute to the potential curative effects of allotransplantation: (1) dose intensification during these regimens with the intent to completely eradicate all malignant cells; and (2) the immune effect that occurs post-transplantation mediated for immunocompetent donor lymphocytes, known as GVL or GVT, hopefully eradicating any micrometastatic or minimal residual disease. There now is compelling evidence that dose-intensive therapy in the majority of cases does not completely eradicate all of the malignant cells. Dr. Childs said that based on an increasing knowledge of the immune effects that occur after allogeneic transplantation, researchers have begun to explore whether the GVT or GVL effect alone would be sufficient to eradicate malignancies in patients with hematologic malignancies that are potentially curable with standard transplants. He noted that the best evidence to support GVL alone as being potentially curative comes from data in patients with chronic myelogenous leukemia relapsing post-allotransplant that are induced back into remission simply by infusing lymphocytes from the original stem cell donor. Some of these patients now are 10 years post-treatment and are most likely cured because of a lymphocyte infusion given in the relapse setting. However, for more aggressive relapsing leukemias like acute myelogenous lymphoma, the success rate of this approach is much lower and there is a more limited efficacy. The goal of this approach is to dose deintensify the conditioning regimen to try to select a regimen that will be safe but immunosuppressive enough to allow

for the engraftment of the donor immune system and then rely on the immune effects that occur afterwards in the hopes that GVL alone will be sufficient to eradicate malignancy.

With this safer method of delivering an alloimmune system, researchers over the last 3 years have been exploring ways to generate a GVT effect against solid tumors. A study of this approach in renal cell carcinoma patients included a series of patients with a median age of 49 years. All patients had metastatic renal cell carcinoma that was radiographically progressive and confirmed by biopsy. Dr. Childs described the results of the first 33 patients treated using this approach. The median time from diagnosis of metastatic disease to treatment was 10 months. Ninety-one percent of the patients were male, 94 percent had more than one metastatic focus—a negative prognostic indicator for long-term survival, and all had failed prior therapy. All patients became neutropenic; the median time to neutrophil recovery was 10 days. All patients also developed febrile neutropenia, treated successfully with empiric antibiotics. At day 14, all patients had evidence of donor engraftment. Dr. Childs said that most patients tolerated the conditioning regimen extremely well. The major toxicity of the regimen was acute GVHD. Fifty-one percent of the patients developed acute GVHD, 12 patients had Grade 2 GVHD, and 5 had Grade 3 or 4, potentially life-threatening GVHD. Four patients developed chronic GVHD. None of the patients rejected the allograft, and all patients achieved 100 percent donor T-cell chimerism, with the exception of one patient who died from disease progression early in the study. Sixteen of these 33 patients had disease response, either a partial response or complete response. Four patients so far have achieved a complete response, all of them remaining disease-free. The first patient treated now is 33 months post-transplant. Dr. Childs said these results are encouraging in that responses are being observed, but these responses are taking a significant period of time before they occur, limiting this approach to patients who have expected survival times that are sufficient for an antitumor effect to occur. Dr. Childs said that future efforts need to be undertaken to determine why some patients respond and others do not. It is hoped that an adoptive targeted immunotherapy approach can be developed in the future to expand efficacy and decrease the period of time required to get a response.

XVI. SUBCOMMITTEE REPORTS/NEW BUSINESS

Clinical Investigations. Dr. Norton presented the Clinical Investigations Subcommittee's written report for Board acceptance. A major focus of the Subcommittee's meeting was the issue of access by individuals who have to plan Cooperative Group trials and other trials to data that are being guarded by data and safety monitoring boards (DSMBs). More information is needed about the function of DSMBs, and one potential next step is conducting a formal study of providing education on the issue of access to data. Dr. Norton said that further discussion is needed about what information should be collected, and how to most efficiently collect that information. He said the Subcommittee will report back to the Board on this issue.

Planning and Budget. Ms. Ellen Stovall, Executive Director, National Coalition for Cancer Survivorship, presented the Planning and Budget Subcommittee's written report for Board acceptance. She said that much time was spent reviewing the role of the public in having input into the Bypass Budget, and how to best realize that opportunity without encumbering the role that NCI management and executive staff have in allocating funds. The Subcommittee also spent time responding to the presentations given to the Board last meeting by the American Society of Clinical Oncology and the American Association for Cancer Research on the effectiveness of the Bypass Budget. The Subcommittee also discussed the benefits of the information resulting from PRG reports.

Communications. Dr. Elmer Huerta, Director, Cancer Risk Assessment and Screening Center, Washington Cancer Institute, Washington Hospital Center, presented the Communications Subcommittee's written report on behalf of Dr. Susan Love. The Subcommittee discussed NCI's image and its identity in the eyes of the American public. He said that the public does not have a good understanding of what the NCI is or what it does. Dr. Huerta discussed the development of a marketing effort for the NCI and the results of a survey that found the public wants the NCI to be the gold standard for cancer information, the place to go to for critical cancer information, and an organization that is concerned about the American public. Dr. Huerta noted that the survey found that the CDC and the American Cancer Society are more recognized by the American public than is the NCI. As part of this marketing effort, the Board will be presented with an identity strategy prepared by a contractor. It is hoped that this identity strategy will reach out to the American public as a majority but also to minorities and the medically underserved.

A motion was made for *en bloc* acceptance of the written reports from the meetings of the Subcommittees on Clinical Investigations, Planning and Budget, and Communications. The motion was seconded and approved.

New Business. Dr. Sharp described a revised resolution to increase the RMS budget of the NCI to 5 percent of the annual budget. Board members asked for clarification on what specific dollar amounts would be allocated to the RMS budget—Dr. Sharp clarified the ambiguity regarding these dollar amounts. A motion to adopt the revised resolution was made seconded, and approved. Dr. Sharp discussed the status of the FY2000 annual report and emphasized the need to distribute it as soon as possible. He asked for a resolution to accept the report and to recommend that the NCI publish it in addition to posting it on the Internet. Dr. Klausner suggested distributing the report electronically because of convenience and cost issues. Dr. Marvin Kalt, Executive Secretary, NCAB, recommended distributing it via e-mail and including a message asking for comments on the report in the e-mail message. A motion was made to distribute the FY2000 report via e-mail. The motion was seconded and approved.

XVIII. ADJOURNMENT—DR. PHILLIP SHARP

There being no further business, the open session of the 116th meeting of the National Cancer Advisory Board was adjourned at 12:05 p.m. on Wednesday, December 6, 2000.

2-7-01

Date



Phillip A. Sharp, Chairperson

2-7-01

Date

Marvin R. Kalt, Executive Secretary