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

Summary of Meeting
September 12-13, 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 115th regular meeting on Tuesday, September 12, 2000, in Conference Room 10 of Building 31, National Institutes of Health, Bethesda, MD. The meeting was open to the public from 9:00 a.m. to 3:45 p.m. The meeting was closed to the public from 4:05 p.m. to 6:00 p.m. The meeting was reopened to the public on Wednesday, September 13, at 9:00 a.m. until adjournment at 12:25 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. 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. Paul Calabresi (absent)
Mrs. Frances Visco

Alternate Ex Officio NCAB Members

Dr. Steven K. Akiyama, NIEHS (absent)
Dr. Michael A. Babich, U.S. CPSC (absent)
Dr. Peter Kirchner, DOE
Dr. Alison Martin, FDA
Dr. Hugh W. McKinnon, EPA
Dr. T.G. Patel, DVA
Dr. Eugene Schwartz, DOL, OSHA (absent)

Members, Executive Committee, National Cancer Institute, NIH

Dr. Richard Klausner, Director, National Cancer Institute
Dr. Alan Rabson, Deputy Director, National Cancer Institute
Ms. MaryAnn Guerra, Deputy Director for Management
Dr. Robert Wittes, Deputy Director for Extramural Science; Director, Division of Cancer Treatment and Diagnosis
Dr. Dinah Singer, Director, Division of Cancer Biology

Dr. Joseph Fraumeni, Director, Division of Cancer Epidemiology and Genetics
Dr. Peter Greenwald, Director, Division of Cancer Prevention
Dr. Marvin Kalt, Director, Division of Extramural Activities
Dr. Edison Liu, Director, Division of Clinical Sciences
Dr. Barbara Rimer, Director, Division of Cancer Control and Population Sciences
Dr. Carl Barrett, Director, Division of Basic Sciences
Dr. Joseph Harford, Associate Director for Special Projects
Ms. Sandy Koeneman, Executive Secretary, NCI Executive Committee

Liaison Representatives

Dr. Stanley Zinberg, American College of Obstetricians and Gynecologists
Dr. Edward P. Gelmann, American Society of Clinical Oncology
Dr. Ross Abrams, American Society of Therapeutic Radiology and Oncology
Ms. Nancy Riese Daly, American Society of Therapeutic Radiology and Oncology
Ms. Barbara Duffy Stewart, Association of American Cancer Institutes
Dr. Robert W. Frelick, Association of Community Cancer Centers
Ms. PaulaAnn Rieger, Oncology Nursing Society

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

Dr. Phillip Sharp introduced guests representing cancer education and research associations and advocacy organizations. He welcomed members of the public and press and invited them to submit in writing, within 10 days, any comments regarding items discussed during the meeting. A motion was requested and made to approve the minutes of the June 2000 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), called attention to the imminent end of fiscal year (FY) 2000 and noted that Mr. John Hartinger, Associate Director, Office of Budget and Financial Management, would be reconciling actual expenditures in all budget lines with estimates set forth in the $3.311B budget to close out the fiscal year. Dr. Klausner announced that Congressional action on the FY 2001 budget appropriations is pending and prospects for a 15 percent increase for the NIH appear favorable. Work on the FY 2002 budget is moving forward through discussions with the Office of Management and Budget (OMB) and the NIH.

Dr. Klausner presented an update on the distribution of the budget for FY 2000, reminding members that the $3.311B budget represented a 15 percent increase over FY99 or an additional $420M. Over 75 percent of that growth was allocated to grant activities, including the funding of about 1,165 competing research project grants (RPGs). About 775 R01s were funded for a dollar increase of 16 percent and an overall success rate of about 30 percent (from a total of 3,100 applications received). About 7 percent of the RPG pool was set aside for requests for applications (RFAs) and about 10 percent for grants funded as exceptions. Dr. Klausner reported that the NCI has been reviewing budget policies for RPG activities, paylines, RFA set asides, and exceptions with an *ad hoc* working group of NCAB and other NCI advisory board members. A report on the deliberations of that group will be presented at the next NCAB meeting.

Dr. Klausner called attention to four areas of particular growth in NCI's FY 2000 budget. (1) About 50 new program projects (P01s) were funded, representing about 4 percent of the total number of RPG grants and 17 percent of the dollars, a 40-50 percent increase over the FY99 figures. Average cost requests for P01s increased by about 50 percent. (2) Funding for Special Programs of Research Excellence (SPOREs) increased by about 45 percent, reflecting the disproportionate growth in translational and population-based research for the NCI. (3) The new Cancer Control and Population

Sciences Program has grown about 70 percent since its creation in 1996 (from $198M to about $375M) compared with the 47 percent growth of the NCI budget over that time. The Division of Cancer Control and Population Sciences (DCCPS), which has responsibility for the program, now administers about 600 grants, including a large grant to address issues in behavior, epidemiology, genetics, survivorship, tobacco, communications, and health disparities. In line with the increased emphasis on application of research results, Dr. Klausner announced the recruitment of Dr. Jon Kerner, former Associate Director for Prevention and Control, Lombardi Cancer Center, to the new position of Assistant Deputy Director for Research Dissemination and Diffusion, NCI. Dr. Klausner explained that the new Research Dissemination and Diffusion Program is intended to ensure that research results are not only monitored and evaluated but also incorporated into plans to change behavior, outcomes, and, ultimately, the burden of cancer. A new program Turning Results into Outcomes (TRIO) is being developed by Dr. Kerner and will be a theme to be addressed across the Institute in planning for the coming year. (4) A fourth area of growth occurred in response to NCI planning processes, which resulted in recommendations to develop and grow a new array of training programs. The career program of the NCI has grown to encompass about 400 awards, an increase of 150 grants over FY99 year and a 45 percent increase in funding.

Conversely, Dr. Klausner pointed out that the Intramural Program is the budget area of the least growth over the past 5 years. This line has decreased as a percentage of the total NCI budget from over 20 percent to about 15 percent, and is projected to continue dropping if the NIH appropriation is enacted with a 15 percent increase. Dr. Klausner stated that a restructuring and refocusing process in the Intramural Program over the past 5 years has resulted in greatly improved management and expectations about quality. For the coming year, the intramural faculty, led by the Intramural Advisory Board, has been asked to work on strategic planning for the content of the Intramural Program. They will address questions on how the Intramural Program defines itself and what the scientific content and infrastructure should be for a unique and powerful cancer center, using models from the extramural community as well as internal processes. Dr. Klausner listed changes that already have been instituted, such as the opportunity for intramural scientists to compete for and participate in major consortial initiatives with their extramural colleagues. He stated that intramural investigators and Division Directors have been challenged to become more involved in implementing the vision for the National Cancer Program outlined in the Bypass Budget, beginning with the Molecular Targets Program. Dr. Klausner reported that intramural investigators have come together to develop approaches based on particular pathways or molecular targets and clinical trials to measure and evaluate the new approaches to therapy and prevention. These activities have been based upon the extramural programs for molecular target discovery grants designed by Dr. Robert Wittes, Deputy Director for Extramural Science (ODDES), and Dr. Peter Greenwald, Director, Division of Cancer Prevention (DCP). Dr. Klausner noted that organizational meetings will be held over the next few months, and progress will be reported by the intramural Division Directors at a future NCAB meeting.

Dr. Klausner reported that a new laboratory for natural products has been established, headed by Dr. Michael Boyd, who is moving from the extramural Developmental Therapeutics Program (DTP) to the Division of Basic Sciences (DBS) in the Intramural Program. Dr. Boyd will play a leadership role in the new trans-intramural molecular targets program. Dr. Klausner stated that the NCI will also be enhancing the national natural products program to facilitate the access of investigators nationwide to NCI's natural products collections.

Communication. Dr. Klausner presented an update on the response to the recent redesign of the CancerNet Web Site. Since its launching, the site has been accessed an average of 13 million times monthly and has registered between 550,000 and 600,000 distinct user sessions, compared with 3.5 million hits and 300,000 user sessions prior to the redesign. In addition, CancerNet won the gold award in the patient education category of the World Wide Web Health Awards. The site also received special recognition for best site structure navigation and won the CIO Web Business 50-50 Award as one of the top 50 Internet sites demonstrating an ability to blend technology and design into the needs of their target audience. Dr. Klausner commended the work of Ms. Sue Hubbard, Acting Director, Office of Cancer Information, Education, and Communication, and Dr. Anne Thurn, Chief, International Cancer Research Data Bank Branch, and their colleagues in this effort.

Dr. Klausner reported on the restructuring of the Cancer Information Service (CIS), another important communication outlet for the NCI. In the past year, the CIS instituted a new contract structure, which was reconfigured with four regions for the United States and 14 regional offices, a decrease from the 19 offices in its previous configuration. In addition, new performance expectations and characteristics have been implemented in response to recommendations in the recent report of the Government Administration Office (GAO). Currently, the CIS has a total staff of about 400 located at 34 sites, including Hawaii, Puerto Rico, and the U.S. Virgin Islands. Dr. Klausner noted that no disruption in service appears to have occurred during the introduction of the new technology. Statistics for 1999 include responses to 800,000 requests, a call-answered rate of 97 percent, a 2-second average answer speed, and a busy signal rate of zero. The CIS works through partnerships with about 8,600 organizations, most of them focused on minority and underserved audiences. New partnerships have been developed with the Special Populations Networks and Intercultural Cancer Council. Efficiency and cost-effectiveness enhancements to the CIS include a pilot project for instant messaging to create a live help desk, regional computerization for the ordering of and centralized mailing of publications, a new publications locator to implement e-commerce for bulk ordering over the Internet, and a print-on-demand feature. Dr. Klausner congratulated Ms. Chris Thomsen, Chief, and the staff of the Cancer Information Service Branch for real and measurable improvements in CIS characteristics.

Early Detection. Dr. Klausner described early detection as one of the most complicated and promising areas of cancer research because of the difficulty of developing technologies that are specific, sensitive, acceptable to the patient, useable, cost-effective, and evaluable. One challenge is to find ways to introduce and evaluate new and evolving technologies in a way that does not require long-term mortality endpoint studies. Another challenge is to find methods of evaluating comparative technologies.

Dr. Klausner discussed modifications to traditional screening approaches that are being investigated to make detection screens for common cancers such as uterine, colon, and breast, more predictive and informative. The objective would be to reduce morbidity and lower the cost of followup for lesions that are found, many of which will not go on to produce cancer. Dr. Klausner cited a recent study published in the *New England Journal of Medicine* (NEJM), which demonstrated mortality reduction from fecal occult blood testing and periodic sigmoidoscopy, as well as an editorial in the same journal which likened screening for colorectal cancer with sigmoidoscopy to screening for breast cancer with unilateral mammography. Subsequent discussions with Dr. John Eisenberg, Director, Agency for Healthcare Research and Quality (AHRQ), about the lack of information about patient acceptability,

morbidity, cost, and optimal operating characteristics of colonoscopy indicated the need for a workshop to evaluate colonoscopy as a comparative technology. Dr. Klausner announced that a workshop will be held in March 2001, to evaluate a variety of sources of current data and address the question of whether the NCI should consider formulating guidance and guidelines for this important cancer, alone or in collaboration with other organizations. Dr. Klausner noted that Dr. Greenwald has been asked to lead the process, and asked for volunteers from the Board to work with representatives of extramural

organizations. The following members agreed to serve on the committee: Drs. Richard Boxer, Ralph Freedman, and Larry Norton.

Dr. Klausner described a second initiative planned to evaluate and learn more about the operating characteristics and, therefore, the potential value of digital mammography compared with plain field or screen mammography. The need for an optimal screening technique for breast cancer is based on the reality that up to 20 percent of lesions detected by physical examination are not detected by screen mammography, a high percentage of the detected lesions are false positives, and the technology has limitations in relation to interpretation of the mammograms and the nonspecific way of looking at biologically complex breast cancer cells. The potential for improved detection with digital mammography is based on the linear response over a wide range of incident radiation intensities, low system noise, and the separate processes for display and image acquisition, which allow each to be optimized through development of new analytic tools. Dr. Klausner noted that several manufacturers are developing digital devices and one has already been approved by the Food and Drug Administration (FDA) based on a trial in about 600 women in the setting of diagnostic mammography. A Department of Defense (DoD) study of under 4,000 women in a screening setting suggested that the operating characteristics for digital and screen mammography are similar but provided inconclusive evidence of the superiority of either technology. Under the leadership of Dr. Wittes, Director, Division of Cancer Treatment and Diagnosis (DCTD), and Ms. Ellen Stovall, discussions have been held with the American College of Radiology Imaging Network (ACRIN), four competing device manufacturers, the FDA Center for Devices, and the Health Care Financing Administration (HCFA) concerning the possibility of a comparative study in a screening setting with sufficient power to ask questions about primary endpoints and a series of secondary endpoints. The collaboration with the FDA and HCFA on study design issues will help to identify a pathway by which approval could be achieved for both use and reimbursement. A study in about 50,000 women has been proposed, with a 1.5-year accrual period and 1 year of followup. The study would be powered to ask questions about operating characteristics, sensitivity, specificity, receiver operating characteristics, and positive and negative predictive value. In addition, an archive would be developed to allow research on optimizing image acquisition and analysis.

Dr. Klausner presented an update on the evaluation of low-dose spiral computed tomography (CT) screening for lung cancer which was discussed during the September 1999 NCAB meeting. He stated that discussions continue on this screening technology and the NCI is working with the a consortium in New York to develop a strategy for integrating data on clinical and technologic experience across multiple institutions from a variety of clinical trial designs, including a randomized clinical trial (RCT) with mortality endpoints. The RCT was deemed necessary to assess spiral CT as a comparative technology to x-ray, sputum cytology, or the combination of both because none of these have been shown to reduce mortality in screening for lung cancer. The screening would be performed in high-risk populations (heavy present or former smokers).

Dr. Klausner turned next to a discussion of the movement toward molecular approaches to early detection, noting that the challenge in this research area is the validation of biomarkers for biologic state for drug response. Barriers include the difficulty of finding the right ones without an understanding of the disease process and the lack of a research and development (R&D) structure for developing criteria by which potential markers can be turned into robust, exportable, useable, scalable, and interpretable tests

with operating characteristics. An infrastructure for clinical and epidemiologic validation also is needed. Dr. Klausner stated that the Early Detection Research Network (EDRN or Network) was established to address the need for an R&D structure. He commended the leadership of Dr. Sudhir Srivastava, Chief, Cancer Biomarkers Research Group, DCP, in this initiative to advance translational research on cancer biomarkers. Participants in the Network spread throughout the nation, bringing together academia, industry, and government. Government agencies in addition to the NCI are the Centers for Disease Control and Prevention (CDC) and the National Institute of Standards (NIST). An associate membership process has been implemented to involve nonfunded investigators. In the initial solicitation, 18 biomarker developmental laboratories, 2 biomarker validation laboratories, 8 clinical and epidemiological centers, and 1 data management and coordinating center were funded. In addition to data management, the latter has a research component for development of new analytic tools and a component for prioritizing potential markers and for interpreting the types of studies that have been or will be done. Dr. Klausner noted that a committee has been organized to articulate standards and criteria for biomarker validation. The committee also has convened a task force for the molecular taxonomy of precancerous lesions, developed a manual of operations, and produced the first monograph on criteria and validation. Dr. Klausner announced that the first round of proposals for collaborative studies with outside investigators have been approved, and there is movement toward the first of several validation studies.

Biomarker Validation Studies. Dr. Klausner gave three examples of potential markers related to lung cancer, which is known to be an overwhelmingly environmental disease. What is not completely known is the relationship between exposure to the known carcinogens and who gets lung or another type of cancer and when. Dr. Klausner noted that the question, therefore, of whether a susceptibility component is a factor is important in terms of potential screening for both current and former smokers. The common crucible for all cancers is DNA damage that can progress to mutations because of increased impairment or decreased ability to repair. Iinvestigators have proposed that normal lymphocytes in peripheral blood can be observed through various assays to reflect the probability of DNA damage or repair. One tobacco mutagen sensitivity assay under investigation uses bleomycin, which brings iron into the nucleus and produces oxidative damage as a mechanism of mutation, and BPDE which forms covalent adducts and is a measure of nucleotide excision repair. This pathway differs from molecular pathways for oxidative damage. Preliminary laboratory studies with the bleomycin/BPDE sensitivity assay have suggested that lymphocytes show defects in the repair of these different pathways in individuals, corrected for smoking status, gender, age, and ethnicity, and especially in those individuals who show both. The odds ratio for susceptibility to lung cancer is 8.5 in these studies, making this a potentially important type of biomarker. Dr. Klausner reported that this chromosome breakage assay is one of the biomarker approaches that has been accepted by the EDRN for movement into validation studies.

Another assay was developed based on preliminary observations by a number of groups about changes in DNA that were presumed to be the result of exposure to carcinogens. The changes were caused by chemical modification (hypermethylation) of DNA, in that cytosine (one of the DNA bases) was modified by adding a methyl group, and methylation is associated with altered gene expression, depending on its location with respect to a gene. Dr. Klausner reported that various investigators conducted preliminary studies in two genes—one that acts as a tumor suppressor gene and one that is involved in DNA damage repair. They have shown with total accuracy that methylation of the promoter

region of either of these two genes can be seen in the sputum of individuals with cancer as much as 3 years before the individuals are diagnosed. These studies have involved only small numbers, and proof-of-principal studies are needed to develop robust assays. A validation study is planned.

Dr. Klausner stated that a new molecular abnormality has been observed and proposed to be associated with cancer. Investigators recently have published on the finding that specific molecular changes seem to be uniform across all of the mitochondrial DNA in cells that are cancerous or precancerous. The changes are easily detected in body fluids and are greatly amplified because of the amplification of copies of mitochondrial DNA. Dr. Klausner noted that a validation assay for this finding will be developed by the EDRN. He pointed out that EDRN has formed a series of organ sites for a variety of approaches to early detection.

Proteomics. Dr. Klausner presented an introduction to proteomics and a review of how preliminary findings in this new molecular approach to diagnosis and classification of cancer might be pursued by the EDRN. He defined proteomics as the systematic study of proteins for information about the state of the cell, a qualitatively distinct method of developing molecular fingerprints of cell states with challenges similar to those experienced in Director's Challenge genomic research approaches. Dr. Klausner explained how the protein chips in proteomic research are made using a technique called surface-enhanced laser desorption ionization (SELDI), ad how mass spectroscopy is used to measure the time-of-flight (TOF) mass of the protein as it is ionized and lysed through a tube. TOF mass spectroscopy measurement at every nanosecond produces complex patterns (fingerprints) for analysis that are reproducible, sensitive, and specific. Dr. Klausner presented preliminary results of EDRN studies, that suggest the possibility of finding new types of blood markers for human cancers. Patterns are emerging in nipple aspirate fluid, but rigorous analysis is needed to differentiate the patterns produced by normal cells, noncancerous lesions, and cancer cells. In studies of serum from individuals with localized prostate cancer, a comparison of patterns in the mass range from 5,000 daltons to 20,000 daltons shows about 15,000 signatures. Dr. Klausner emphasized that many samples must be tested to discern the potential meaning of patterns produced by serum from age-matched individuals with and without cancer. He described an early project that uses an artificial intelligence self-learning algorithm that was developed by a local company working with Dr. Lance Liotta, NCI, and Dr. Chip Petricoin, FDA. This evolutionary constrained pattern discovery process keeps learning through hundreds of thousands of iterations of the TOF patterns. A series of early studies in the serum of individuals with prostate specific antigen (PSA) levels above 10, between 4 and 10, and less than 4 are demonstrating the ability to distinguish prostate cancer from normal state. Validation attempts in small numbers of cases are showing about 96 percent sensitivity and specificity. Another study is attempting to determine whether the systematic approach can be applied to distinguish patterns in the blood of women with untreated and early phase ovarian cancer. Preliminary observations have been promising, and a large number of clinically annotated samples obtained through the EDRN infrastructure are being measured to create a robust learning set of patterns. Dr. Klausner noted that this systematic approach is being emphasized because of the public health implications of informative early detection for all cancers. Updates will be presented over coming months.

Questions and Answers

In response to a question from Dr. Peter Kirchner, Dr. Klausner explained how the 2-dimensional displays are derived from the pattern data produced by applying the self-teaching algorithms. He noted that correlations with clinical state (a clinical or biochemical parameter) will be required to assign meaning to the data. Dr. Larry Norton asked whether the proteomic and artificial intelligence approaches are moving in the same direction. Dr. Klausner replied that the objective is to support many algorithms that can be compared with each other, and that progress could depend on discovering entirely new approaches. Ms. Stovall asked how decisions will be made and resources allocated for all the promising early detection and screening studies. Dr. Klausner replied that, in determining allocation of limited funds, all proposed initiatives will be held to the standards of being valuable, compelling, doable, and able to pass multiple types of review processes. Dr. Sharp commented that help from private organizations is likely to be needed as proteomic investigators move into larger populations to achieve validation, and he asked whether private industry participation exists in an advisory or cofunding mode. Dr. Klausner stated that industry participates at the table, and some entities are funded to be part of the research, but mixing government funds with private funds is restricted by law. He agreed that early detection research, to be successful, will require much larger amounts of resources and functioning partnerships. Dr. Elmer Huerta emphasized the need to begin diffusion of information on the new research to the public. Dr. Klausner replied that the NCI is working with the National Human Genome Research Institute (NHGRI) on a major public education initiative to enhance understanding and deal with issues of acceptability of all genetics-related tests, and the situation for proteomics parallels that of genomics.

IV. NEW BUSINESS I—DR. PHILLIP SHARP

Dr. Sharp asked NCAB members to suggest issues of new business to be addressed at a future meeting. He then proposed that the Board at its next meeting consider directing a letter to the appropriate legislative committee about the management structure of the NCI and the resources committed to it. He reminded members that the NCI RMS (management) budget is now 3.3 percent of the total NCI budget, and has been declining as a percentage for the last 5 years. As a basis for consideration of this issue, the NCAB will be provided with information on the financial situation and the difficulties this level of operating funding presents to the NCI in light of increasing management and oversight responsibilities.

V. LEGISLATIVE UPDATE—MS. DOROTHY FOELLMER

Ms. Dorothy Foellmer, Director, Office of Legislation and Congressional Activities, reviewed funding levels recommended by the House and Senate Appropriation Committees in FY 2001 appropriation bills remaining to be enacted. The President's budget requested a 5.8 percent increase for the NCI. The House reported funding levels of 5.8 percent also, but included an intent-to-mark-up column in its report, with a 14.6 percent increase for the NCI if additional funds are received. The Senate mark is 15 percent. Ms. Foellmer summarized requirements or suggestions for emphasis incorporated in the House and Senate report language that accompanied the respective bills. The House report emphases were: a focus on the role of angiogenesis in bone disease; capitalizing on new technologies for detection of metastatic breast cancer; a consensus conference to be held on childhood skeletal malignancies; an interest in exploring environmental factors in the etiology of lymphoma; research into the immune systems of marine mammals to discern their mechanisms for resistance to cancer; molecular markers in head and neck cancer and multiple myeloma; coordination with other Federal agencies; a research agenda for

primary immunodeficiency diseases; development of clinical trials in prostate cancer and an accelerated pace of development for new drugs; inclusion of the rural poor in health disparities research; and attention to other urologic cancers (bladder and kidney).
Ms. Foellmer noted that the Senate report duplicated many House topic areas. Differences included: examining the impact of providing mental health services on treatment outcomes and patient survival; cancer in minorities, inclusion of Native Hawaiian populations; a complementary and alternative medicine briefing prior to next year's hearings; commendation on NCI communications efforts in cancer control expansion and biobehavioral research; the history and development of hepatocellular carcinoma in patients with hepatitis C; a leadership role in the development of new imaging systems technologies; accelerated research to identify cost-effective screening strategies and technologies for ovarian and cervical cancer; accelerated research into pancreatic cancer; and development of chemotherapeutic and hormonal agents for prostate cancer, expedited clinical trials, expanded network of researchers, and an elucidation of the role of diet in prostate cancer. Bills enacted into law during the past fiscal year include an amendment of the Radiation Exposure Compensation Act (RECA) to add uranium miners and millers to those eligible for compensation; the Semipostal Authorization Act granting the U.S. Postal Service authority to issue semipostals and extending the Breast Cancer Stamp Act for 2 years; and the Electronic Signatures Act.

Ms. Foellmer concluded with a status report on enactment of the Stem Cell Research Act, which was introduced by Senator Arlen Specter, and a brief review of guidelines issued on August 23 by the Department of Health and Human Services (DHHS) and the NIH. The DHHS/NIH guidelines outline procedures to help ensure that research utilizing human pluripotent stem cells, which are not embryos and therefore not included in the prohibited research category, goes forward in an ethical and legal manner.

In response to a request for clarification of a provision in the DHHS/NIH guidelines, Dr. Marvin Kalt, Director, Division of Extramural Activities (DEA), explained that funded investigators using pluripotent stem cells must demonstrate having obtained them from an appropriate source. A subcommittee of the Advisory Committee for the NIH Center for Scientific Review (CSR) is responsible for approving the source. The actual application of those cells to research is governed by local Institutional Review Boards (IRBs) and typical rules for human subjects research.

VI. NATIONAL CANCER POLICY BOARD UPDATE—DR. PETER M. HOWLEY

Dr. Peter Howley, Chairman, Department of Pathology, Harvard Medical School, and retiring Chair, National Cancer Policy Board (NCPB), reviewed the origins and mission of the NCPB; described its composition, operational features, and funding sources; and summarized program emphases, output, and impact. The Board was established in 1997 in response to requests from the NCI, NIH, and President's Cancer Panel (PCP) order to examine ongoing research, technology, and problems faced by all sectors engaged in the nation's battle against cancer. Core support since its launching under an NIH task order has come from a contract (recently renewed for 5 years) funded jointly by the NCI and CDC, with yearly contributions from the American Cancer Society (ACS) and AmGen, and one-time contributions or funding for specific studies from various agencies or organizations. Formal appointments to the 21-member Board are made by the National Research Council (NRC) Chair and Institute of Medicine (IOM) President. The Board meets quarterly, defining its own priorities and setting its own agenda. Long-term core funding covers 1–2 full reports per year. Activities to date have focused in the

areas of tobacco control and cancer treatment and health care. Areas of emphasis being considered for the future are cancer research and cancer prevention and control. Reports completed to date are: *State Programs Can Reduce Tobacco Use* (February 2000), *Ensuring Quality Care* (April 1999), *Sponsors of Cancer Treatment Clinical Trials and Their Approval and Monitoring Mechanisms* (February 1999); and *Taking Action to Reduce Tobacco Use* (January 1998). A letter on tobacco control was sent to the DHHS Secretary, other administration officials, and members of Congress (July 1997). Dr. Howley noted that the Board also has commissioned a number of background papers that have had impact. One report identified sources through the various sectors of funding for cancer research in the country and is being followed by a more comprehensive study. Ongoing Board studies include: *Data Systems to Improve Cancer Care*; *Interpreting the Volume Outcome Relationship in the Context of Health Care Quality*; *End-of-Life and Palliative Care*; and *Prevention Screening in Cancer Control.* A study is being considered by the Board to address management of capital-intensive research and public-private partnerships. Studies conducted under auspices of the Board include *Expanding Medicare Reimbursement in Clinical Trials* (with HCFA support) and *Technologies for Early Detection of Breast Cancer*. Dr. Howley explained that the Board has begun handing off issues such as tobacco policy and quality-of-care as other IOM or government components have taken over, and will have a followup role in the study on technologies for early detection of breast cancer. Dr. Howley assessed the Board as having had an impact in furthering the objectives of the National Cancer Program (NCP), in that the 1998 tobacco report was in the hands of Senate staff writing components of what became the McCain Bill; an Executive Order established the Quality Cancer Care Council and another Executive order initiated Medicare reimbursement for routine care costs in clinical trials following the quality-of-care report; and the 2000 tobacco control report was issued at the time state governors and legislatures were deliberating on the use of the tobacco settlement funds.

Questions and Answers

Dr. Sharp noted that the NCPB at a recent meeting also has agreed to study quality-of-life and survivorship as part of the quality care report at the urging of NCAB members. In response to a question about choice of study topics and report review, Dr. Howley explained that all reports undergo the stringent IOM review process. Rules governing the choice of issues to be studied are: the issue or problem must be an important one with policy implications; it should not duplicate an issue being addressed by another body; and there must be a receptor for the report. Dr. Howley added that the NCPB receives input in setting its agenda through workshops held for initial exploration of issues and through background papers. A public forum early in the life of the Board also helped to establish some of the priorities.

VII. NATIONAL CANCER LEGISLATION ADVISORY COMMITTEE— DR. VINCENT DEVITA

Dr. Vincent T. DeVita, Director, Yale Comprehensive Cancer Center, reported on the National Cancer Legislation Advisory Committee (NCLAC), which evolved from a national forum for cancer constituencies co-chaired by Senator Diane Feinstein and Dr. LaSalle Leffall. Co-chaired by Dr. DeVita and Dr. John Seffrin, ACS, the NCLAC was charged with developing a comprehensive "white paper" outlining policy recommendations to serve as the basis for new, expanded legislation building on the success of the National Cancer Act of 1971. Dr. DeVita related current successes in biomedical

research to the fact that more than 80 percent of the total budget allocated to the National Cancer Program since 1971 has supported basic research. He related the decline in mortality statistics to the remaining percent that went into application of the results of the basic research. Dr. DeVita pointed out, however, that many people are not benefitting from the research effort as reported in the PCP's 1999 report, and many questions remain to be addressed. The goal of the white paper will be to accelerate progress in the NCP through continued investment in research and translation and application of basic science discoveries. Dr. DeVita explained that the NCLAC evaluation process involves assimilating and summarizing the reports of the PCP, IOM, NCPB, and the March Research Task Force, as well as personal interviews with almost 100 survivors, advocates and public, private, and non-profit experts. Participants in the National Dialogue on Cancer have received summaries of materials and have provided additional feedback.

Dr. DeVita emphasized that the 26 members who make up the NCLAC were chosen for their expertise and are broadly representative of the stakeholders in the NCP. Their task will be to build on prior reports and pull together the issues that are relevant at this time. One issue to be addressed in the paper, which was raised in an interview with Dr. Klausner, was whether organizational changes could be suggested that would allow all Federal cancer research programs to be brought together to accelerate progress in the war on cancer. Dr. DeVita stated that eight round table forums have been scheduled during the period from June 28 to October 30, to amplify the expertise of the Committee. Their topics are: Cancer Clinical Investigations; Cancer Prevention and Control, Population and Behavior; Cancer in Ethnic Minorities and the Medically Underserved; Cancer in Other Special Populations; Quality of Life; Defining Quality Cancer Care; Basic Cancer Research; and Role of the Private Sector in the Conquest of Cancer. Following these, the NCLAC will work to finalize the policy recommendations received from all the sources and make them available for review by all stakeholders. In its final two meetings, the Committee will review and prioritize key issues in preparation for making recommendations to Senator Feinstein and members of Congress, which will serve as a basis for their proposals to the new President and Congress.

Questions and Answers

In response to a question from Dr. Hugh McKinnon, Dr. DeVita stated that the Committee would not poll members of Congress to discern an appropriate course for the battle against cancer. He pointed out that Congress has been very supportive of cancer research, cancer care, and translational research and appears to need only an instrument to put forward for a revitalized National Cancer Act. In response to a question from Dr. Frederick Li, Dr. DeVita explained that the ACS is the primary source of support for the NCLAC. Dr. Amelie Ramirez asked about investment in the future pipeline of researchers and training issues. Dr. DeVita replied that every workshop is addressing infrastructure. Asked to explain his conception that a critical mass had been reached in basic cancer research making possible significant gains in curing cancer, Dr. DeVita expressed the opinion that basic science research has amassed much information, for example on molecular controls for cell death and sequencing of the genome, that will produce valuable tools for understanding drug resistance, with the potential for doubling cure rates.

Dr. Klausner expressed the view that the paradigm shift in cure rates does not signal the end of the need for basic research. Dr. Devita agreed we still have a long way to go. Dr. Norton observed that in the past there usually has been a discrepancy between definition of a problem and availability of interventions, but a unique situation exists today in the availability of both improved methods of biological characterization and improved methods of intervention. In response to a question from Ms. Frances

Visco about whether a new National Cancer Act was envisioned as being more directive or less directive to the NCI, Dr. DeVita noted that the Committee report would merely amass the information for use by Congress. It would be the work of advocacy groups to convince the new President and Congress of the validity of any course of action. He gave the example of cancer clinical trials and the many opportunities to test new products that are overloading the newly restructured and effective NCI Clinical Trials Program. He suggested the need to identify other ways to obtain financing and support for clinical research. Dr. Harold Freeman framed the question to be address as whether everything that is known is being applied for benefit of the American public in an appropriate way at any given point. Dr. Sharp said the answer will lie in promoting public and private interactions, and much work will be needed to bridge the inevitable institutional and philosophical issues that will arise from these interactions.

VIII. IMPROVING THE QUALITY OF CANCER CARE: THE NCI INITIATIVE - DRS. ROBERT HIATT AND JOSEPH LIPSCOMB

Dr. Robert Hiatt, Deputy Director, DCCPS, presented an update on the status of NCI initiatives in quality cancer care, which he described as exemplifying both translational research and Federal interagency collaboration. He noted that the initiatives represent an extension of NCI's pattern of care research program and a response to recommendations on improving the quality of cancer care (QoCC) in the IOM report *Ensuring Quality Cancer Care*. Linkage of NCI research with activities of the delivery or coverage arm of the Federal government was established through the NCAB statement endorsing IOM recommendations and calling attention to "the need to define, assess, and require adherence to benchmarks that measure and monitor quality of care in the Medicare and Medicaid programs." Dr. Hiatt noted that the focus of DCCPS research in QoCC has been to define measures of structure, process, and outcome to evaluate whether health services for individuals and populations increase desired health outcomes and is consistent with current professional knowledge. The specific objective is to enhance the state of science for defining, monitoring, and improving quality of cancer care toward the ultimate goal of ensuring that all Americans receive the highest quality of cancer services across the continuum of care. Dr. Hiatt highlighted shortcomings of existing data for QoCC analysis that are being addressed in NCI initiative: lack of patient-centered endpoints; evidence that is compelling to physicians, feasible to collect, and rapidly available; absence of a national system for assessing the quality of cancer care; and a disconnect between undertaking measuring quality at a national level and providing benchmarks for researchers, policymakers, and decision makers.

Dr. Joseph Lipscomb, Chief, Outcomes Research Branch, DCCPS, presented an update on NCI's four-point research plan developed as a result of the emerging consensus on issues to be addressed if quality of care were to improve. The plan, which was presented in general form to the DHHS Secretary Donna Shalala in 1999, has the objectives of: (1) developing core process and outcome (endpoint) measures for cancer care; (2) strengthening the methods and empirical base for doing QoCC research;
(3) enhancing quality of cancer care research within the restructured NCI clinical trials program; and
(4) improving the quality of cancer communications.

Dr. Lipscomb reviewed steps for attaining each objective and progress made to date. Phase I of the first objective, which has been completed, involved reviewing the existing published literature on endpoints for measuring outcomes of importance to patients and other decision makers for each major

form of cancer. In Phase II, which will get under way in early 2001, state-of-the-art approaches of psychometrics will be applied to evaluate existing quality-of-life (QoL) instruments, including those that are cancer-site specific, cancer-specific (that is, applicable across cancer sites), and generic (that is, applicable across diseases, including cancer); develop new instruments as needed; and fill in research gaps. To move this effort forward, a Cancer Outcomes Measurement Working Group is being formed; it will begin work in early 2001 and issue its final reports to the NCI by mid-2002. The analyses and deliberations of the working group are also expected to inform NCI's plans to issue a Program Announcement (PA) to promote investigator-initiated studies in "basic" outcomes research. Regarding the development of a core set of process measures of QoCC, Dr. Lipscomb stated that NCI will lead an effort to review, synthesize, and evaluate the existing process measures for the purpose of shaping the research agenda and also informing ongoing efforts, including those in the private sector, for arriving at consensus recommendations about what constitutes "quality" cancer care.

Plans for strengthening the methodological and empirical research base for quality assessment in cancer include intensifying support for surveillance studies to determine whether existing patterns of care are consistent with current recommendations and guidelines for achieving QoCC. Dr. Lipscomb noted that NCI-supported patterns of care studies have increased in number and scope during the 1990s, and include now the Prostate Cancer Outcomes Study (PCOS) and up to 14 other major studies; support for such efforts will be intensified as part of the QoCC initiative. Other plans in support of this objective include testing the feasibility and acceptability of using the core endpoint measures developed under the first initiative; strengthening the methods basis for data collection and analysis; and working with a host of public and private entities to develop a national-level cancer care data system to monitor the impact of existing guidelines, identify disparities in access to quality care, and reassess whether existing quality benchmarks lead to improved outcomes. Dr. Lipscomb reported that the NCI Board of Scientific Advisors (BSA) at its June meeting approved the concept for a large-scale RFA-cooperative agreement called *Cancer Care Outcomes Research and Surveillance* (CanCORS). The objectives are to study the impact of targeted interventions on patient-centered outcomes, investigate dissemination of state-of-the-art therapies in the community, examine the impact of modifiable risk factors, and analyze disparities in cancer care. A national consortium will be established, consisting of research teams and statistical coordinating center, to mount large, prospective cohort studies of patients with newly identified lung and colorectal cancer (5-7 research teams and 5,000-7,000 patients for each site). The consortium will collaborate on identifying core process and outcome measures and on the design and conduct of analyses. Dr. Lipscomb noted that proposals in response to the RFA are due in January 2001 and funding is anticipated within the fiscal year. A total cost of $40M is estimated for the 5-year project period. Dr. Hiatt called attention to a complementary study launched recently by the American Society for Clinical Oncology (ASCO) and noted the agreement between NCI and ASCO for an interchange of information and sharing of instruments and progress. Additional NCI-sponsored initiatives within the current fiscal year to strengthen the empirical and methods base include: expansion of the SEER and SEER-Medicare studies to target key QoCC issues; creation of new databases linking tumor registry information with private payer claims data to study the under-65 population; and issuing new and revised PAs to support basic outcomes research methods development and additional cost-effectiveness analyses of QoCC interventions.

Initiatives to enhance QoC research in the restructured NCI clinical trials program include:

assessing the current state of the art of using QoL measures in the context of clinical trials; identifying key research questions; and developing a strategy to identify the most appropriate and efficient use of patient-centered outcomes in trials. Dr. Lipscomb noted that the NCI QoCC initiative also calls for new studies to better understand, and ultimately to improve, the rate of diffusion of important clinical trial findings into community practice.

Dr. Lipscomb stated that the QoCC initiative's fourth research aim, to improve the quality of cancer communications, draws heavily from the programs and plans proposed under the Extraordinary Opportunity in Cancer Communications, as detailed in "The Nation's Investment in Cancer Research" (the forthcoming 2002 "Bypass Budget"). These proposed efforts include gathering representative data on the current status of cancer communications, creating cancer communications Centers of Excellence, and developing new communications products and tools to facilitate informed decision-making. One project to implement the latter is the RFA initiative *Making Quality Count*, being sponsored jointly with AHRQ.

Dr. Hiatt then briefed the Board on the progress to date achieved by the Quality of Cancer Care Committee (QCCC), a trans-agency task force established following the presentation of the NCI QoCC initiative to Secretary Shalala. At that time, NCI proposed to the Secretary that cancer be made a "working model" for how to carry out research to improve the quality of health care *and* to ensure that Federal-level decision making on cancer care is informed by the best available scientific evidence. The Secretary responded by approving the formation of the QCCC, which now functions within DHHS's larger Quality Improvement Initiative. The QCCC, which is convened by NCI, includes as members those Federal agencies involved with cancer care delivery (e.g., the Health Resources and Services Administration, Centers for Disease Control and Prevention, Indian Health Service, the Department of Veterans Affairs, the Department of Defense); coverage decisions (e.g., the Health Care Financing Administration), or regulation (e.g., the Food and Drug Administration), as well as agencies or offices supporting or conducting quality of care research (e.g., the Agency for Healthcare Research and Quality, the National Center for Health Statistics) or policy formation (DHHS's Office of the Assistant Secretary for Policy Evaluation). Dr. Hiatt reported that since its first meeting in March (2000), the Committee has produced a summary of all QoCC research supported by Federal agencies and has been working to determine agency needs for evidence in this area. He noted that the process of identifying gaps in the knowledge base has led to an initial research agenda, according to which NCI will work with QCCC member agencies to provide technical and financial support for selected projects to improve the quality of cancer care. P:rojects under consideration in the FY01 budget include: (1) An extension of VA's Quality Enhancement Research Initiative (QUERI) to strengthen the evidence base and identify quality-of-care goals for at least one major cancer disease site (probably colorectal); (2) A HCFA project, with likely CDC collaboration, to enhance the effectiveness and efficiency of colorectal cancer screening among the elderly; (3) a HRSA project, with likely CDC collaboration, to improve cancer care at community-based health centers; and (4) a collaborative effort with FDA to clarify the role of quality-of-life and symptom-based measures in that agency's drug approval and marketing decision processes.
Dr. Hiatt said the QoCC initiative has benefitted significantly from the work of NCI's internal quality-of-care committee, with representatives from each Division, to identify ongoing research projects and information needs. He concluded by noting that preliminary discussions are underway with the National Quality Forum, the National Committee for Quality Assurance, and possibly other organizations about

appropriate and constructive ways the NCI initiative might serve to improve the evidence base for private-sector decision making about quality cancer care.

Questions and Answers

Dr. Patel welcomed the collaboration on a colorectal cancer project that would capitalize on the high incidence among the VA's patients and on the VA's many research scientists. Dr. Armitage commended the program and the interaction with ASCO. Dr. Ramirez praised the program and its collaboration with agencies that serve different vulnerable populations. Dr. Sharp asked about the extent to which the program is responsible for outreach to the lay community. Dr. Hiatt replied that NCI is dealing with the issue through its communications initiative. An issue to address is the connection of the QCCC, which is a Federal effort, with the private sector to achieve better two-way communication about quality cancer care.

IX. UPDATE ON THE NCI CENTER TO REDUCE CANCER HEALTH DISPARITIES—DRS. HAROLD FREEMAN AND JON KERNER

Dr. Harold Freeman, Chairman, PCP, incoming Associate Director, NCI, and Director for the NCI Center for Reducing Health Disparities, stated that the recently instituted Center would move to understand the interface and interrelationship among the complex human factors of poverty, culture, social injustice, and health disparities, and would take advantage of the opportunity to synergize the work on health disparities that is already in place across NCI Divisions. He identified challenges to be addressed by the Center: the unequal burden of disease in the United States, which presents scientific, moral, and ethical dilemmas; the disconnect between research discovery programs and delivery of the results of the findings and the need to identify barriers to access of the benefits by some populations; and the consequence of the racism inherent in racial classifications, which have been associated with fewer opportunities, greater exposure to stress and unsafe environments, and reduced access to quality health care. Dr. Freeman emphasized the need to distinguish between the effects of society's treatment of people and biological differences, and to work toward realizing the goals set forth in the DHHS report *Healthy People 2010* to increase quality-of-life and years of healthy life and eliminate health disparities.

Dr. Freeman described the preliminary structure of the Center, which will build on and elevate the work ongoing in the Office of Special Populations Research, notably the Special Population Network and the 18 grants totaling $60 million over the next 5 years to develop a cadre of minority scientists. The Center will operate out of the Office of the Director. A Deputy Director and Assistant Deputy Director for Interagency Partnerships will be named. Two major divisions of the Center will be the Special Populations Research Branch, and the Health Policy Branch. In conclusion, Dr. Freeman emphasized the importance of determining the real variables that cause disparities and when appropriate, generalizing those variables universally across all human beings, developing minority scientists, and separating social issues from scientific excellence issues. He noted that elucidating how human populations differ will require a deeper consideration of human genome findings and population genetics and a more fundamental understanding of the effect of culture and economic status.

Dr. Jon Kerner, Assistant Deputy Director for Research Dissemination and Diffusion, DCCPS, discussed the role of the Center and its relationship to the Divisions, using the example of the DCCPS interface with the Center and NCI's 5-year strategic plan to reduce cancer health disparities. The two-pronged challenge to DCCPS was to conduct epidemiological, intervention, and surveillance research and facilitate the dissemination of evidence-based interventions to help reduce health disparities.
Dr. Kerner stated that while the NIH plan has focused exclusively on disparities in the context of minorities, the NCI has developed a research framework that helps set the agenda for elucidating broad social determinants of cancer-related health disparities including, but not limited to, race/ethnicity.
Dr. Kerner explained how the DCCPS has developed a set of principles to organize health disparities (HD) research. The goals in organizing HD research are to maintain research program autonomy while at the same time, to stimulate cross-program collaborations; provide a framework for the Health Disparities Research Working Group to impact DCCPS research and training activities; and provide a formal link with the new Center. Key objectives are to review the health disparities research portfolio and develop a strategic plan for FY 2002.

Dr. Kerner presented the results of the review and preliminary analysis of the FY 1999 portfolio displaying the percentages for minority and health disparities grant dollars and the breakdown according to the cancer control continuum. He pointed out the challenges conducting this kind of analysis, which have led to the proposal to create an infrastructure within the DCCPS called the Health Disparities Research Coordinating Council (HDRCC or Council). The Council will be made up of coordinators within each DCCPS research program and from the Office of Cancer Survivorship and the DCCPS, OD. The Council will analyze each program for health disparities research and work across programs to identify and fill research gaps. Dr. Kerner discussed the DCCPS dissemination and diffusion plan under development called Translating Research into Improved Outcomes (TRIO). TRIO will model and monitor the impact of dissemination and diffusion initiatives on Year 2010 health promotion and cancer control objectives, working with the NCHS and ACS; promote adoption of evidence-based cancer control interventions by local, state, and national service organizations, in collaboration with ACS, AHRQ, CDC, HCFA, and HRSA; and place special focus on recognizing and eliminating the infrastructure barriers responsible for cancer health disparities. Dr. Kerner noted that partnerships will be developed with specific geographic sections of the United States to add financial and personnel support to integrate TRIO components with the CDC-funded comprehensive cancer control planning project being conducted by the ACS. DCCPS will work also with the District of Columbia to expand the infrastructure for delivering state-of-the-art interventions.

Questions and Answers

Dr. Ramirez suggested that the personnel in the new Center and membership of the HDRCC be recruited to represent the diversity of the populations of interest. Dr. Kerner requested that Board member nominate qualified candidates as soon as possible. Dr. Ramirez commented on the need for more research on evidence-based programs that are effective in the more vulnerable population groups. She pointed out the difficulty of transferring known interventions with the current infrastructure because of the racism that exists and suggested, as a model, CDC projects recently funded to replicate projects known to have efficacy. Dr. Li pointed out the importance at the programmatic level of having information about whether the best outcomes can be achieved through QoC, survival, and end-of-life services versus prevention and early detection. Dr. Norton suggested that guidelines for responding to questions in clinical research grants about inclusion of minorities might be a topic for consideration in the new Center. Dr. Sharp recommended that as a topic also for consideration by the NCAB Subcommittee on Clinical Investigations. As a related issue, Dr. Armitage commented on the need to address the level of antipathy that exists in some minority communities towards the American medical research establishment.

X. UPDATE ON THIRD-PARTY REIMBURSEMENT FOR CLINICAL TRIALS—DR. ROBERT WITTES

Dr. Wittes presented a brief review of actions by the NCI and other Institutes, extramural researchers, legislators, ASCO, and the advocacy community in support of reimbursement for routine medical care costs associated with participation in research studies. These initiatives preceded the announcement in June of an Executive Order that changed Medicare reimbursement policy with respect to clinical trials. Recent occurrences include HCFA's draft national coverage decision published for

public comment on the Internet, which proposed a process for adding clinical trials reimbursement to already-established categories of benefits. Dr. Wittes summarized some of the provisions expected to be included in the final version, based on the draft and discussions to date: (1) no new categories of benefits will be created, which is significant for categories not currently covered by Medicare (e.g., prevention); (2) trials to be covered must be well-supported scientifically, obey good methodology, be based on credible proposals, and conform to all standards of human subjects protection (criteria to be developed by a newly organized Federal agency committee under the leadership of AHRQ); (3) investigators will submit their own trials to be considered for this benefit, presumably with a checklist that self-certifies conformation to standards, with the probability that claims will be reviewed retrospectively as part of HCFA's audit; and (4) sponsors whose trials will be deemed as categorically included at this time are Federal agencies. Dr. Wittes noted that HCFA is developing internal systems for registration of trials and claims payment. Board discussion focused on the still unresolved questions pertaining to Phase I trials and thelack of inclusion of prevention trials.

XI. RECENT STUDIES ON GENETIC VS. ENVIRONMENTAL INFLUENCES IN CANCER—DR. JOSEPH FRAUMENI

As background, Dr. Joseph Fraumeni, Director, Division of Cancer Epidemiology and Genetics (DCEG), named the environment, inherited genes, spontaneous tumors, and interactions between genes and the environment as the four categories to which the causes of cancer in the population can be assigned. He noted that although genetic mechanisms are fundamental to the carcinogenic process, the actual contribution of genetic susceptibility and gene-environment interactions as causal factors has been difficult to assess. However, the incorporation of advances in molecular biology and genome technology into epidemiologic studies has evoked heightened interest in the interaction of genes and environment. Dr. Fraumeni summarized the findings in studies showing the international variation in cancer incidence and the relative risk by migration patterns as evidence of the importance of the environment to cancer, suggesting that environmental factors are driving the geographic and ethnic patterns. Further evidence appears in the temporal variation for certain tumors reported by NCI's Surveillance, Epidemiology, and End Results (SEER) program for the period from 1973 to 1995. Downward trends were seen for certain tumors such as the stomach and the cervix, but substantial annual average increases have been seen for a number of different cancers—melanoma, lung cancer among women, pleural mesothelioma, non-Hodgkin's lymphoma, hepatocellular carcinoma, renal adenocarcinoma, and esophageal cancer.

Dr. Fraumeni listed cancer risk factors identified in epidemiologic studies, pointing out areas where the information is incomplete or needs to be clarified: the contribution of diet and nutrition to the burden of cancer; specific causative and preventive elements in the diet; the role of metabolic and hormonal alterations; impact of chemicals from occupational exposure and environmental pollution; the role of medications and ionizing radiation; and genetic susceptibility. Dr. Fraumeni stated that the role of genetic susceptibility is the biggest uncertainty at present and that understanding its role in cancer is likely to produce much information about the environmental causes of cancer.

Dr. Fraumeni discussed findings in the Scandinavian Twin Study published in the July 13 issue of the NEJM on environmental and heritable factors in the causation of cancer. The study combined the nationwide experience of Sweden, Denmark, and Finland, all of which have population-based cancer

registries. In the total of over 44,700 pairs of twins, about 9,500 pairs had at least one cancer and the number of twins with cancer was 10,800. Dr. Fraumeni noted that the findings were remarkable in that the percent of heritability ranged from 21 percent for leukemia to 42 percent for prostate cancer, and that prostate, breast, colon, and rectal cancer figures were statistically significant in terms of heritability as a causal factor. In the same issue of the NEJM, an editorial by Dr. Robert Hoover, Director, Epidemiology and Biostatistics Program, DCEG, was published clarifying the interpretation of findings reached by the Scandinavian investigators in their article. The editorial (*Cancer—Nature, Nurture, or Both*) summarized lessons learned from the Twin Study: (1) environmental effects are in line with previous estimates; (2) heritability estimates are higher than previous studies based on family histories; and (3) the rate of concordance in monozygous twins generally was less than 15 percent. The editorial also noted that estimates were imprecise, information on screening and specific exposures was lacking, and the model assumed no interactions between genes and the environment. Dr. Fraumeni stated that publication of this paper coincided with the announcement of significant advances in deciphering the human genome, and articles in the *Washington Post* and elsewhere interpreted the study as deemphasizing the role of genes and proclaiming the predominance of environmental and behavioral factors. Press coverage of the study, in general, maintained that genes play only a limited role, raising concerns about the emphasis on the human genome project, including studies of cancer-associated genes, and ignoring the critical role of acquired genetic alterations that are due to environmental exposures and that are fundamental to the carcinogenic process.

Dr. Fraumeni explained that much of what is known so far about inherited genes comes from studies of mutations that underlie the Mendelian patterns of hereditary cancer. The gene frequency is uncommon, penetrance is high, absolute and relative risks are high, but the amount of cancer in the population due to that gene is low, and the role of environment is modest. However, attention is gradually turning to polymorphic genes, which are common gene variants that occur in over 1 percent of the population. They have low penetrance and low absolute and relative risks, but the population-attributable risks are very high, because these genes are so common and the role of environment is critical for expression. Dr. Fraumeni stated that there probably is a continuum between gene mutations and the common susceptibility genes, and that the Extraordinary Opportunity titled *Genes and the Environment* in the Bypass Budget for FY 2001 summarizes the NCI strategy for investigating the role of genes, environmental risk factors, and their interactions. Dr. Fraumeni emphasized that susceptibility genes can help detect environmental risk factors in epidemiologic studies, and he called attention to a DCEG paper on this subject that will be published soon in the online journal *Reviews in Cancer*. After briefly reviewing the various types of susceptibility genes (e.g., metabolic, cell cycle control) and their mechanisms of action, Dr. Fraumeni concluded that the environment, broadly defined, appears to drive most demographic patterns of cancer, but susceptibility genes may have a sizeable impact by modifying these risks. The search for modifying genes should help in discovering environmental factors and the mechanisms of carcinogenesis, in identifying high-risk populations and molecular targets for intervention, and in forming strategies for cancer prevention, diagnosis, and treatment.

In discussion, Dr. Fraumeni responded to questions and comments about the possibility of future studies to identify genes that decrease rather than increase the risk of environmental cancer, and whether the Scandinavian study might have significantly underestimated the contribution of genes to cancer incidence of cancer in various populations.

CLOSED SESSION

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

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

Application Review

During the closed session of the meeting, a total of 1,224 grant applications were reviewed requesting support of $355,33,108. Funding for those applications was recommended at a level of $335,652,629.

XII. SUBCOMMITTEE REPORTS/NEW BUSINESS II

Planning and Budget. Ms. Stovall presented the Subcommittee's written report for Board acceptance. The Subcommittee reviewed a plan for follow-up to Progress Review Groups (PRGs), reviewed input provided by ASCO and American Association for Cancer Research (AACR) on the effectiveness of the Bypass Budget and NCI's planning and priority setting process, and reviewed the draft NCI annual report of achievement. The Board will continue to discuss the ASCO and AACR recommendations by means of a telephone conference and will report at the December meeting. The next draft of the annual report of achievement will be distributed in time for review by the Board prior to the December meeting to facilitate a prompt release of the final document.

Communications. Dr. Susan Love presented the written report of the September 11 meeting, which focused on the recent reorganizations of the Office of Communication (OC) and the OC Web Design and Utility Branch and their planned activities, plans for observing the 30th anniversary of the National Cancer Act, and the role of the Subcommittee. The Subcommittee will dedicate its December meeting to NCI brand and marketing initiatives, following a brief presentation on the OC's recent marketing study and branding plans.

Clinical Investigations. Dr. Norton presented the written report of the September 11 meeting. He summarized the overview by Dr. Edward Korn, Biometrics Research Branch, Division of Clinical Sciences (DCS), on the role of data and safety monitoring boards (DSMBs) and the rationale behind NCI's policy regarding the release of clinical trial data by the DSMBs. The Subcommittee agreed to continue the discussion of key issues related to early release of outcome data at the next meeting. Representatives from advocacy groups, cooperative group leadership and statistical committees, and

investigators who have an interest in release of the data for planning purposes will be invited to participate. The Subcommittee also has agreed to explore the issue of developing outreach and access guidelines for engaging members of minority groups in research trials, both as volunteer subjects and investigators.

A motion was made for *en bloc* acceptance of the written reports from the September 11 meetings of the Subcommittees on Communications and Clinical Investigations, and the September 12 meeting of the Subcommittee on Planning and Budget. The motion was seconded and approved.

New Business. Dr. Love pointed out the need for more information on generic issues related to the SPOREs to be better prepared to identify potentially controversial items before voting on them. Dr. Klausner asked for suggestions as to what should trigger an NCAB discussion of a controversial decision. This topic will be explored further in closed session.

XIII. MOLECULAR TARGETS MINISYMPOSIUM

Introduction. Dr. Klausner re-emphasized the potential for molecular targets research to produce profound changes in NCI's approach to cancer because of the clear applications to molecular approaches to therapy. He noted that the task of identifying and validating molecular targets and then developing interventions promises to be long, complicated, and difficult. Recent NCI initiatives have been aimed at shifting research toward molecular targets and shifting the interface between traditional drug and biologics discovery into academia, as well as toward partnerships with industry for drug development. Dr. Klausner stated that today's minisymposium would be the first in a series of presentations on findings from the NCI-sponsored initiatives, which will be integrated to evaluate the scope and direction of molecular research programs already underway and to address potential problems.

Towards a Chemical Genetics. Dr. Stuart Schreiber, Professor of Chemistry and Co-Director of the Harvard Institute of Chemistry and Cell Biology, discussed how the infrastructure for the Harvard Institute is being built under NCI sponsorship to integrate the principles of organic chemistry and genetics for exploring both biology and medicine. He described two different approaches to using small molecules (the products of chemistry) and their mutations to explore biology. The first approach, patterned after classical genetics, involves screening small molecules for a particular phenotype of visual change that is indicative of a pathway or process of interest. The challenge then is to identify the mutation that causes the damage in a genetic screen, identify the protein to which the small molecule binds, and link that molecular target to the process of interest. The second is a reverse chemical approach in which small molecules are screened for their ability to bind to proteins, then used to modify the function of the now-known protein target. The challenge is to search broadly for the resulting phenotype. Dr. Schreiber then gave examples of high throughput screens useful in searching for phenotypes. He described research using the cytoblot assay and cytology to screen molecules in cells, which led to the discovery of a small molecule that targets the protein Eg5, as well as small molecule-induced phenotypes with unknown targets that are potential reagents for further exploration. In another example, small molecule developmental screens were devised in fertilized zebrafish embryos, which are proving to be useful tools to dissect pathways. Dr. Schreiber commented that the value of chemical genetics relative to the genetic approach

is the ability of the small molecules to instantly modulate function and to do so conditionally, which cannot be done with corresponding genetic mutations.

Dr. Schreiber described the process for synthesizing and formatting small molecules for both phenotypic and binding assays. He explained that a new kind of synthesis, diversity-oriented organic synthesis, was developed because there are no protein targets or individual molecular chemical structures in these types of experiments, which examine the whole proteome. In addition, a different kind of analysis is used which deals with building structural complexity and structural diversity in the synthetic pathways to produce an integrated analysis. He showed examples of small molecules that emerge from these pathways and presented one illustration of how his laboratory used those molecules in the context of a reverse chemical genetic experiment and was able to discover a synthetic FKBP12 ligand. Next, Dr. Schreiber described a systematic study of the entire yeast proteome to elucidate the underlying principles of small-molecule interaction with protein. The small molecules and the yeast proteins they bind to were annotated and assembled in a database for use in protein profiling. Dr. Schreiber illustrated the use of these tools to explore the pathway modulated by the small molecule rapamycin. He then outlined a recent and controversial experiment in which profiling of uretupamine, a Ure2p ligand, reveals a specific modulation of the carbon source arm of Ure2p's cellular functions.

In conclusion, Dr. Schreiber commented that microarrays have been useful for nucleic acids and protein, as well as for profiling the messenger RNAs. A new set of tools is needed to do this for protein, and small molecule microarrays and protein microarrays have potential as a similar technology. Valuable products of these studies for future research will be to continue learning how to make these reagents and make them publically available, together with their data. A way must be found to create a useful, effective public database for these kinds of experiments.

P53 and Other Targets. As background, Dr. Frank McCormick, Director, University of California at San Francisco, (USCF) Comprehensive Cancer Center, noted the underlying premise duirng the past 15 years that understanding the molecular basis of cancer should lead to new protein targets that are misregulated in cells and a search for chemical and biological means of inhibiting these pathways. Therefore, much research the past 20 years has focused biochemical means of inhibiting these pathways. Therefore, much research on elucidating pathways that play direct causal roles in cancer. Dr. McCormick listed the major pathways that cause cancer: retinoblastoma (Rb) and p53, which are altered in every cancer cell, and Ras pathway together with the tumor suppressor PTEN, which are altered in 50–100 percent of all human cancers. He presented details on how each pathway functions to explain how drug targets or other targets of intervention can be found, and gave the rationale for his laboratory's choice of the p53 pathway as the most fruitful of the three in terms of therapeutic intervention. He showed how the p53 protein acts to protect the genome when DNA in cells is damaged, by freezing the cells in the cell cycle through different mechanisms or by killing the DNA-damaged cells to prevent replication. He also demonstrated how high levels of the transcription factor E2F can induce 53 activity, noting that fundamental properties of tumor cells are high E2F activity and suppression of p53 by one way or another. The challenge then was to develop a therapeutic strategy based on loss of p53 function. Dr. McCormick stated that the strategy chosen by his laboratory was to make ONYX15 virus that replicates selectively in cells based on the loss of functional p53. The virus is made so that it replicates efficiently in cancer cells, spreading throughout the tumor from the site of inoculation until it reaches normal cells,

which induce p53 and stop the replication. Dr. McCormick stated that the virus entered Phase I clinical testing in 1996 and the Phase II results were published in *Nature Medicine* earlier this year. The virus currently is being tested in Phase III trials for head and neck cancer and in Phase I/II trials for metastatic colon cancer. In the latter, virus is infused into the hepatic artery to infect metastatic colon cancer cells that have metastasized to the liver. The virus is also being tested in pancreatic cancer, ovarian cancer, leukoplakia, and a number of other indications across the country. It has been shown to be safe, with no effect on normal tissue even in high doses.

Dr. McCormick noted that although ONYX15 is a cancer-specific agent based on these pathways, getting the virus to the tumor is a limitation to the therapy. His laboratory is working on strategies to address the clinical development issue of infusing the virus into the blood stream and getting it to the tumor before it is neutralized. Other strategies, including small molecule approaches, are in various stages of clinical testing. Dr. McCormick concluded by discussing reasons for the lack of good Ras inhibitors in the clinic today, given the fact that Ras was the first oncogene identified in tumors 20 years ago. He attributed part of the difficulty to the complex nature of the pathways turned on by Ras proteins in the process of transformation. He briefly reviewed ongoing research and expressed the view that a greater understanding of the Ras pathway will elucidate more opportunities for selective intervention in the future.

Bcr-Abl Tyrosine Kinase Inhibitors for CML. Dr. Brian Druker, Associate Professor, Oregon Health Science University (OHSsCU), briefly reviewed the public health significance of chronic myelogenous leukemia (CML). About 5,000 new cases are diagnosed per year, primarily in adults age 50 or older, and the disease progresses clinically from a stable phase of 4 to 6 years marked by massive expansion of myeloid (white) cells to an acute leukemia that is extraordinarily refractory to therapy, with a typical life expectancy of 2 to 3 months. The cure rate is 20 percent with the current therapies of allogeneic bone marrow transplant (the only curative therapy), alpha-interferon, and hydroxyurea, clearly indicating the need for new strategies. Dr. Druker then traced the scientific landmarks in understanding the molecular basis of CML from the discovery of the Philadelphia chromosome in patients in 1960, through the recognition in 1973 of the Philadelphia chromosome as a reciprocal translocation between chromosomes 9 and 22, to the validation of the resulting chimeric protein called Bcr-Abl as a therapeutic target for CML in the 1980s. Bcr-Abl was recognized as an ideal target because it is present in the majority of CML patients; the causative molecular abnormality of CML, and a constitutively activated intracellular tyrosine kinase that is required for function of the protein. Dr. Druker described the drug discovery program at CIBA-GEIGY (later Novartis) in the 1980s to identify specific tyrosine kinase inhibitors, which resulted in the identification of a number of potentially effective compounds by 1993. Dr. Druker began testing these compounds at that time and demonstrated that STI571 (formerly CGP57148) was the most potent and specific inhibitor of Bcr-Abl tyrosine kinase. In subsequent preclinical examination, STI571 was found to: (1) be a potent and selective inhibitor of the Abl and Bcr-Abl tyrosine kinases; (2) selectively kill Bcr-Abl-expressing cells *in vitro* and *in vivo*; (3) be optimal for cell killing *in vitro* at levels of 1 micromole; and (4) be highly bioavailable as an oral formulation. Phase I clinical trials of STI571 began in June 1998, at OHCU, University of California at Los Angeles, and the M.D. Anderson Cancer Center. Initial trials targeted patients in the chronic phase and were expanded as experience was gained with the toxicity profile and compound effectiveness to include patients with Bcr-Abl-positive acute leukemias. Dr. Druker summarized clinical results of the Phase I trials in chronic

phase patients: (1) STI571 has been well tolerated as an oral agent; (2) no dose-limiting toxicity has been encountered; (3) all patients treated with doses of STI571 of 300 mg or greater have had complete hematologic responses; (4) responses are sustained in 51 of 53 patients with a median duration of 310 days follow-up; (5) cytogenic responses have been observed in 53 percent of patients treated, including 31 percent major and 13 percent complete responses; (6) patients have responded to STI571 despite being refractory to other therapies; (7) inhibition of Bcr-Abl kinase activity has been documented in patients on therapy with STI571; and (8) responses have been observed at drug levels predicted to be effective from preclinical studies. Dr. Druker highlighted the findings that: (1) white counts of patients in the trial typically began to decrease within 2–3 weeks and continued through duration of therapy; (2) decreases in Philadelphia chromosome positivity were seen relatively early (by 5 months); and (3) the dose response of Bcr-Abl tyrosine kinase inhibition correlated nicely with response data. Dr. Druker reported that Phase II clinical trials have been initiated in a population of patients who failed interferon therapy. The data will be updated in December.

Dr. Druker noted that the Phase I trials were expanded to include patients with acute leukemia when doses of 300 mg were reached and the blood counts of patients in the chronic phase showed dramatic improvement. He summarized Phase I results in patients with acute leukemia: (1) STI571 has been well tolerated as an oral agent in CML blast crisis and Ph+ ALL patients; (2) responding patients have improved or maintained their performance status; (3) responses have been observed in 59 percent of myeloid blast crisis patients, with complete responses in 33 percent of patients; and (4) the response rate in lymphoid leukemias is 70 percent, with 55 percent complete responses. Enrollment has been completed for a Phase II study. Dr. Druker noted that the problem in acute leukemias has been relapses, not responses. In summarizing the clinical results, he stated that these trials indicate that Bcr-Abl kinase activity is essential to the pathogenesis of CML and that STI571 represents an example of successful drug development based on the specific molecular abnormality present in a human malignancy.

Dr. Druker discussed challenges to be addressed to use this research as a paradigm for the development of molecularly targeted agents. The first was dose selection and the fact that the maximally tolerated dose may not be an appropriate endpoint. Dr. Druker expressed the view that a molecular endpoint is needed, such as the Crkl immunoblot assay. He noted that tools are being developed to make that assay more rapid and reliable. A second area of challenge is determining why patients relapse. Dr Druker identified therapy optimization as a third area of challenge, and expressed the hope that molecular signatures of specific response patterns can be defined so the patient response to this molecularly targeted agent can be predicted. Patients could then be treated with the minimally effective treatment regimen, and new molecular targets for therapy might be identified.

Summary and Discussion. In response to Dr. Armitage's questions about the failure to respond by the two patients with chronic-phase CML, Dr. Druker explained that one patient had progressive chronic-phase disease and the other had developed blast crisis. He outlined various avenues of exploration to learn more about the mechanisms of relapse, including multidrug resistance and Bcr-Abl amplification. A range of assays are being used and microarray experiments are planned to try to identify additional targets. Dr. Norton commented that the heterogeneity that divides cancer may suggest that the next research step should be the intelligent development of drug combinations using the same type of guided targeting to properly combine novel agents that deal with multiple defects in the systems, rather

than the ultimate development of solitary agents. He pointed out that this direction would highlight the need to address proprietary issues, because the ideal reagents often are supplied by different companies.

Dr. Klausner summarized the issues that were raised in the minisymposium: (1) the need for mechanisms to support new chemistry research in academia (e.g., for validation and credentialing studies); (2) the linkage of drugs and probes in the research process; (3) the type of infrastructure support needed in academia to move the development of a chemical or target into an actual drug, and how it should be provided; (4) the need for the NCI and FDA to rethink target-based clinical trials for molecular imaging or molecular *in vivo* biochemistry; and (5) the need to raise the standards of credentialing.

XIV. PROGRESS IN CLINICAL TRIALS RESTRUCTURING—DR.. MICHAELE CHRISTIAN

As background, Dr. Michaele Christian, Associate Director, Cancer Therapy Evaluation Program (CTEP), DCTD, reminded members that the Clinical Trials Implementation Committee had been organized to respond to recommendations in the report of the Clinical Trials Program Review Group (Armitage Report). Key objectives were to promote the best science in clinical trials; increase speed of trial implementation and completion; increase accrual to and access of trials by patients and physicians; increase the efficiency and decrease complexity; create a system that is fair, functional, and fast, and offering fair compensation for work performed. The CTEP approach to achieving the objectives was to restructure elements of the clinical trials program, beginning with the development of a series of four pilot projects to demonstrate feasibility and effectiveness: State of the Science Meetings (SOTS), Concept Evaluation Panels (CEPs), Cancer Trials Support Unit (CTSU), and National Network of Treatment Trialists. The SOTS meetings were envisioned as national forums to identify new research opportunities or close research gaps in the research portfolio. Participants were to be broadly representative of the cancer research enterprise, and the goal was to hold two meetings per year in target diseases of lung and genitourinary (GU) cancers. Dr. Christian reported that four SOTS meetings have been held since September 1999, two on lung cancer topics and two on GU cancers. In addition, the cooperative group chairs have held similar meetings in acute leukemia and gastrointestinal cancers this year. Specific outcomes from the meeting on molecular targets for therapy of small cell lung cancer were the establishment of a national tumor bank as a joint effort of the NCI, lung cancer SPOREs, and Armed Forces Institute of Pathology. In addition, neuropeptide receptor antagonists were recognized as a most promising area for clinical research, and discussions are under way with two academic investigators and a drug company to move these agents into the clinic. Dr. Christian noted that the SOTS meetings afford investigators an opportunity to consider new collaborations, and the DCB has made funding available to facilitate meetings of collaborators. She emphasized that the meetings are kept fairly small but results are disseminated broadly through such media as the special Web site, direct mail, *Journal of the National Cancer Institute*, meeting exhibits, and Web-based links. Difficulties in implementing the SOTS meetings relate to finding ways to effectively integrate basic and clinical scientists; fostering productive interaction among a large number of individuals in such a short time; keeping the focus on research opportunities rather than process or administration; and the logistics of coordinating frequent large meetings.

Dr. Christian reported that the Concept Evaluation Panels, which provide broad-based disease-specific review of Phase III concept proposals, are functioning in lung and GU cancer and have reviewed

seven concepts for lung cancer research and four for GU cancers since late 1999. The CEPs meet by Internet-assisted conference calls, using a new electronic tool developed by CTEP for that purpose. Challenges to implementation of this pilot project have been the need for CEP members to gain experience in scoring and prioritizing studies and in the use of the new electronic tool. Other new undertakings to strengthen science include placing developmental funds in cooperative group awards, revising cooperative group peer review criteria, organizing interdisciplinary research teams for molecular target assessment, and adding translational research funds for correlative studies in early clinical trials in FY 2000.

Dr. Christian reported next on the Cancer Trials Support Unit (CTSU), which is operated by Westat and two subcontractors through a contract funded by the NCI. The CTSU provides a single point of access for cross-group participation in clinical trials and common simplified informatics. The CTSU opened to accept enrollment of patients onto 14 cooperative group trials in July 2000; about 300 physicians have registered and many have downloaded protocols for IRB submission. Trials in breast, lung, prostate, and GU cancers will be available for cross-group registration. The goal is to extend enrollment to non-group members and have 750 participating sites by year 3 of the pilot project. Dr. Christian noted that project management plan developed by the contractor is large and complex and NCI has organized a parallel team internally for contract management. Major accomplishments since October 1999 were: opening a functioning Clinical Trials Management Unit with 14 active Phase III trials; establishing a Web site; surveying of cooperative group regulatory, financial, data management, and educational systems and tools; and developing contract templates for delivery of accrual, leadership, technical expertise, and travel funds. In addition, CTSU systems were presented and demonstrated to each cooperative group at the annual meeting; contracts were completed to permit payments for patient enrollments; and an advertising campaign was launched to target cooperative group members and ASCO meeting attendees. Tasks to be completed before March 2001 include an in-house test of Oracle's remote data entry system, the development of Web-based and on-site educational and training materials for all CTSU protocols, and the completion of cooperative group contracts for distribution of technical expertise and leadership funds. Goals for the next year are to increase protocols on the CTSU menu to about 50; initiate the pilot remote data entry system; complete negotiation of subcontracts with individual investigators at local sites; complete the Web site for all group protocols, with referrals to specific investigators; and create a Web-based roster and IRB database for all group and non-group investigators. Challenges to implementation relate to the huge coordination effort among CTEP, the CTSU and the groups, and to integration of the numerous informatics systems involved. Dr. Christian stated that these four pilot projects will undergo a formal evaluation using a plan developed with BSA input and financed by funding received from the NIH set-aside funds for which CTEP and DCCPS successfully competed. Metrics of the evaluation will consist of both objective and subjective endpoints tracked over 4 years.

Dr. Christian described other priority initiatives in the clinical trials restructuring and reported on progress in implementing them. Following discussions with the Office of Health Research Policy (OHRP) and FDA, the NCI agreed to pilot a central IRB project and board members have been appointed. The NCI has negotiated a Cooperative Project Assurance for the central IRB; 22 academic and community IRBs in the Cancer and Leukemia Group B (CALGB) are participating in the pilot. Funding for the cooperative groups was increased by 51 percent over baseline over the past two fiscal years. In response to the recommendation to simplify the informatics and data requirements for clinical

research, CTEP initiated the Common Data Elements project, which features a common data dictionary. The expectation is that this initiative will make possible the development of common case report forms. Common data elements (CDEs) have been developed for breast, prostate, lung, and colorectal cancers for Phase III trials. CDEs are being developed for gynecologic malignancies, bladder cancer, and adult leukemia trials. The lung cancer and biomarkers chemoprevention program is nearing completion of prevention CDEs; the SPORE Pathology Committee and Intergroup Specimen Banking Committee are beginning to develop pathology CDEs; and work has begun on CDEs for eligibility criteria. Also in the data reduction initiative, a core data set has been defined for collection in disease-specific clinical trials in a collaborative effort with the FDA and industry, with provisions for collecting limited additional data specific to scientific objectives in individual trials. Peer review for cooperative groups has been modified to: (1) provide support for pilot clinical proposals and correlative studies through the Chairman's Developmental Fund; (2) lengthen period of award to 6 years for highly rated groups; (3) initiate an interim peer review for committees rated less than excellent; (4) enhance data management support in selected areas; and (5) streamline application formats. New directions for early clinical trials are increasing emphasis on treatments aimed at molecular targets of interest and on developmental phases of putative molecular targets. Applications have been received to establish interdisciplinary research teams for molecular assessment, with first awards expected in April 2001. An RFA for the Phase II clinical trials program for NCI-sponsored agents has been reissued with an emphasis on consortia and collaborative arrangements, and the investment in translational studies has been increased. Internal changes have been made to increase the speed of protocol activation. Educational and promotional efforts for new clinical trials initiatives are under way.

In discussion, Board members commended Dr. Christian and her staff for the progress made to date in restructuring the clinical trials program. Board members asked for and will receive copies of the external evaluation of the Oracle remote data entry system.

XV. RECENT TRENDS IN EXTRAMURAL GRANT SUBMISSIONS—DR. RICHARD KLAUSNER

Dr. Klausner called attention to the document prepared by Mr. Stephen Hazen, Chief, Extramural Financial Data Branch, in response to previous NCAB discussions.

XVI. HUMAN SUBJECTS POLICY UPDATE—DR. MARVIN KALT

Dr. Kalt briefly summarized the content of DHHS and NIH communications in recent weeks concerning important issues in human subjects research: (1) a requirement that all researchers receive ethics training in the use of human subjects; (2) a requirement relating to how the use of human subjects is coded and accounted for; (3) updated guidelines on the inclusion of women and minorities as subjects in clinical research; (4) further guidance on data and safety monitoring in Phase I and Phase II clinical trials; (5) the NIH policy for using human pluripotent stem cells in research; (6) the Office of Research Integrity (ORI) document *DHHS Policy on Instruction in the Responsible Conduct of Research*, which requires that all staff engaged in research or research training with PHS funds receive instruction in the responsible conduct of research; (6) the NIH Clinical Trials Database; and (7) information on the recent government-sponsored conference on conflicts of interest in research and the views of Dr. Greg Koski,

director-designate of the Office of Human Research Protection. Dr. Kalt concluded with a review of the requirements for the training of research staff included in the ORI document. He noted that the NIH is intending to develop a Web-based program that individuals could access worldwide, take the training, and receive a printed certificate that could be included with their grant applications. The NIH site is expected to be operational by late November.

XVII. ADJOURNMENT—DR. PHILLIP SHARP

There being no further business, the open session of the 115th meeting of the National Cancer Advisory Board was adjourned at 12:25 p.m. on Wednesday, September 13, 2000.