NATIONAL CANCER ADVISORY BOARD

convened on September 23-24, 1999, at the:
National Institutes of Health
Building 31-C, Conference Room 10
Bethesda, Maryland 20892

ATTENDEES

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The National Cancer Advisory Board (NCAB) convened for its 111th regular meeting at 9:00 a.m., September 23, 1999, in Conference Room 10, C Wing, Building 31, National Institutes of Health.

NCAB Members
Dr. J. Michael Bishop (Chairperson) (absent)
Dr. Richard J. Boxer
Dr. Kay Dickersin
Dr. Alfred L. Goldson

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

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
Dr. Larry Norton
Dr. Amelie G. Ramirez (absent)
Dr. Ivor Royston
Dr. Philip S. Schein
Dr. Phillip A. Sharp
Ms. Ellen L. Stovall (absent)
Dr. Vainutis K. Vaitkevicius

Alternate Ex Officio NCAB Members
Dr. Steven K. Akiyama, NIEHS
Col. Louis F. Diehl, DoD (absent)
Dr. Michael Hodgson, NIOSH
Dr. Peter Kirchner, DOE
Ms. Rachel Levinson, OSTP (absent)
Dr. Hugh McKinnon, EPA
Dr. Lakshmi C. Mishra, CPSC (absent)
Dr. T. G. Patel, DVA
Dr. Eugene Schwartz, DOL (absent)
Dr. B.A. Schwetz, FDA

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. George Vande Woude, Director, Division of Basic Sciences
Dr. Joseph Harford, Associate Director for Special Projects
Dr. Susan Sieber, Associate Director for Special Projects
Ms. Sandy Koeneman, Executive Secretary, NCI Executive Committee

Liaison Representatives
Dr. John Currie, American Association for Cancer Education, Inc.
Dr. Edwin A. Mirand, Association of American Cancer Institutes
Dr. Margaret Foti, American Association for Cancer Research
Dr. Marc E. Lippman, American Association for Cancer Research
Dr. Robert Martuza, American Association of Neurological Surgeons
Dr. Robert W. Frelick, Association of Community Cancer Centers
Ms. Kerrie B. Wilson, American Cancer Society
Dr. John Stevens, American Cancer Society
Dr. Stanley Zinberg, American College of Obstetricians and Gynecologists
Dr. Bernard Levin, American Gastroenterological Association
Dr. Edward P. Gelmann, American Society of Clinical Oncology, Inc.
Dr. Roth Abrams, American Society of Therapeutic Radiologists
Ms. Nancy Riese Daly, American Society of Therapeutic Radiologists
Ms. Carolyn Corry, Candlelighters Childhood Cancer Foundation

Dr. Lovell A. Jones, Intercultural Cancer Council
Dr. Armin D. Weinberg, Intercultural Cancer Council
Ms. Katharine R. Boyce, Intercultural Cancer Council
Ms. Martha M. Kendrick, Intercultural Cancer Council
Ms. Jean Ard, Leukemia Society of America
Ms. Carolyn Aldige, National Coalition for Cancer Research
Ms. Dorothy J. Lamont, National Cancer Institute of Canada
Dr. Robert A. Phillips, National Cancer Institute of Canada
Ms. Paula Bowen, NCI Director's Consumer Liaison Group
Dr. Eve I. Barak, National Science Foundation
Ms. Pearl Moore, Oncology Nursing Society
Dr. Marston Linehan, Society of Urologic Oncology

CALL TO ORDER, OPENING REMARKS, AND CONSIDERATION OF MINUTES OF PREVIOUS MEETINGS
Dr. Phillip Sharp

Dr. Phillip Sharp, acting for Chair Dr. J. Michael Bishop, called to order the 111th meeting of the National Cancer Advisory Board (NCAB), and introduced guests representing cancer education and research associations and advocacy organizations. He welcomed members of the public and the 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 1999 meeting. They were approved by the Board unanimously.

FUTURE BOARD MEETING DATES
Dr. Phillip Sharp

Dr. Sharp called Board members' attention to the meeting dates listed in the agenda. Dates have been confirmed through 2001.

REPORT OF THE DIRECTOR, NATIONAL CANCER INSTITUTE
Dr. Richard Klausner

NCI Budget Update. Dr. Richard Klausner reviewed the NCI's distribution of the FY 1999 budget, which included a 14.3 percent increase over the previous year or $366M in new dollars. Eighty percent of the 366M new dollars was allocated to grant activities, half of which went into the Research Project Grant (RPG) pool to bring the RPG total to $1.375B or 47 percent of the total NCI budget. About $80M additional was required for an increased commitment base, and about $60M was allocated for competing awards, representing a 20 percent growth. The NCI was able to fund approximately 900 competing awards (R01s) in FY 1999 compared with 707 in FY 1998, maintaining the payline at the 24th percentile despite a 23 percent increase in applications. Dr. Klausner noted that the NCI also sets aside 15 percent of the competing RPG pool for a variety of

exceptions-funding mechanisms. Through the Accelerated Executive Review (AER) mechanism, basic and patient-oriented research grants that fall within the 30th percentile for the former and 35th for the latter receive an Executive Committee (EC) review, then rapid funding if the applicants respond successfully to scientific issues raised by the EC. Exception dollars also are used to fund Program Announcements (PAs) tied to initiatives identified by the Progress Review Groups (PRGs) (e.g., Breast and Cancer PRGs), which are part of the NCI's new approach to planning for disease-based research.

Next, Dr. Klausner reviewed funding and current activities in special and prominent NCI programs. Cancer center funding increased from approximately $134M in FY 1998 to about $152M in FY 1999. Over the past 4 years, the revised cancer center guidelines have been implemented; seven academic centers have become NCI-designated cancer centers; and five institutions now have cancer center planning grants. The P50 Special Program of Research Excellence (SPORE) mechanism was evaluated conceptually by the NCI extramural program's Board of Scientific Advisers (BSA). As a result of the positive and enthusiastic evaluation, a 5-year plan has been proposed that will expand the SPORE program from the current 15 awards to about 33 awards over the next 5 years. Toward that end, a series of specific Request for Application (RFA) set-asides for ovarian SPOREs have been issued to move toward more of a standing, investigator-initiated process. The projected growth of the program will encompass new organ sites and a wider range of diseases. Currently, the overall budget for the SPORE program is about $33M, including funding for two new ovarian SPOREs.

Individual SPOREs have been encouraged to work together as consortia within and across disease groups and report to the NCI on critical issues related to translational research. In FY 1999, the NCI awarded about $25M for research that could be addressed with one-time funding to avoid increasing the grant commitment base without the certainty that future budgets would include increases of the magnitude of the FY 1999 budget. Much of this additional one-time funding was applied to bring SPOREs together: (1) to work on projects needing a critical mass of investigators provided by multiple institutions, (2) to serve as test sites for the development of multi-institute translational consortia, and (3) to devise mechanisms for the transfer of information on research funded in the SPOREs to the larger community. Examples of projects funded with one-time supplements are: (1) a biomarkers and chemoprevention consortium formed from the lung cancer SPOREs, which is planning an Internet-accessible database for studying early detection and intervention, standardized forms for registering chemoprevention trial participants, standardized genetic epidemiology questionnaires, and tissue banking for premalignant lesions; (2) an intra-SPORE technology group to develop core facilities that provide access to high-throughput technology; and (3) a clinical trials group developed by the prostate cancer SPOREs to identify priorities and accelerate the process of patient accrual to Phase I/II clinical trials, and link those efforts to new funding mechanisms such as Rapid Access to Intervention Development (RAID) and QuickTrials.

Dr. Klausner stated that clinical cooperative groups received a 30 percent increase in funding during FY 1999 or about $20M for a variety of new initiatives: (1) for increasing per-patient funding as part of the NCI approach to increasing clinical and correlative

trials accrual; (2) for developing and disseminating informatics; (3) for the integration efforts of the pediatric oncology groups; and (4) for a variety of outcome studies. Dr. Klausner noted that, through these new approaches, the NCI has gained experience in linking independent researchers with the cooperative groups for collaborative correlation studies. Funding is provided through R01 and R21 grants, which are applied for independently after the collaborations have been established. These applications are reviewed by a new Special Emphasis Panel (SEP) for clinical oncology in the Center for Scientific Review (CSR). The 35 applications received for this initiative in the past year will be monitored carefully.

Dr. Klausner reported that, in the area of manpower and training, increases have been seen in the use of the NCI's new transition awards such as the Howard Temin award. In addition, the K23 grant for career development in cancer patient-oriented research and K24 grant for mid-career clinical investigators have been awarded to 21 individuals in the first year of the new transition awards program. A 21 percent increase in the R25 cancer education program is supporting training in cancer prevention, end-of-life care, education, outreach activities, and a variety of oncology curricula proposals in medical schools and schools of nursing and public health. There was a 21 percent increase in the National Research Service Award (NRSA) pool to fund a 25 percent increase in stipend levels and an increase in the total number of trainees to more than 1,700 in FY 1999.

NCI Role in Department of Health and Human Services (DHHS) Efforts Regarding Quality Cancer Care. As a preface to this topic, Dr. Klausner noted that the NCI has been working to restructure its research base across the entire continuum of the cancer research program and now, through the Bypass Budget, has an integrated set of approaches to capturing new science that will rapidly transform the experience of cancer. He acknowledged, however, that reduction in incidence and mortality will happen only as progress in research is translated to all communities in a move toward evidence-based care. The Institute of Medicine (IOM)/National Cancer Policy Board (NCPB) independently approached the broad policy issues related to quality of cancer care. In a series of meetings in 1998, the President's Cancer Panel found gaps in knowledge about the quality of cancer care and identified major problems to be addressed. The Panel also highlighted the unique role of the federal government in ensuring quality care, through the research it supports and application of that research, e.g., the significant impact made by the DHHS through policies in the Health Care Financing Administration (HCFA). Dr. Klausner reminded the Board that NCI's long-standing commitment to deal with outcome issues was significantly expanded through the newly organized Division of Cancer Control and Population Sciences (DCCPS). NCI outcomes research initiatives have included: research into patterns of care, treatment approaches and their outcome, access to care and disparities; longitudinal studies of outcomes among cancer survivors; linkages of national utilization databases such as Medicare with registered cancer patients; studies of the practice and quality of cancer screening; the collection of data on cancer risk factors and behaviors in the National Health Interview Survey (NHIS); and economic studies on the cost of cancer clinical trials and treatment.

Recognizing that achieving a robust research approach to quality cancer care will continue to require integration across multiple federal agencies and in response to the NCPB recommendations in its report entitled Ensuring Cancer Quality Care (which has been endorsed with enthusiasm in a resolution adopted by the NCAB), the NCI has proposed a major new quality care initiative within the DHHS, for which the NCI would assume a leadership role. The proposed initiative, which had been presented the previous week to the Secretary, DHHS, and representatives of all DHHS agencies, would be a working model for research, decisionmaking, and application of the principles of evidence-based quality cancer care. As proposed, a trans-Departmental working group would be established, which would work through two subcommittees: one to develop and implement an integrated and expansive research program on quality care and one to evaluate the needs for policy-makers (e.g., HCFA and Health Research Services Administration [HRSA]) in terms of structural and delivery issues. The latter also would provide a mechanism by which federal policy-setting related to delivery of care and services would be integrated with and informed by the research and generation of evidence related to these issues. Dr. Klausner stated that the proposal was enthusiastically received by all and the NCI is proceeding to establish the necessary structure. Details will be reported to the NCAB over the coming year. The emphasis will be on making this a federal process with linkage to other stakeholders in achieving the goal of improving the quality of cancer care and reducing the burden of disease.

Dr. Klausner noted that the IOM in its report defined quality of care as the degree to which health services for individuals and populations increased the likelihood of desired health outcomes and are consistent with current professional knowledge. He pointed out that much is yet to be learned about quality of care, and gaining that knowledge will require measures to address issues of infrastructure, methodology, and funding as well as outcomes. Five research recommendations in the IOM report were: (1) develop and use core sets of quality measures; (2) invest in clinical trials that deal with patient-centered questions; (3) develop a cancer system to provide benchmarks for quality of care; (4) support patterns-of-care studies in new cancer patients; and (5) support studies of appropriate care in specific segments of the population. The objective for this research initiative is to enhance the state-of-the-science for defining, monitoring, and improving the quality of cancer care. Dr. Klausner briefly described the process for implementing NCI's quality of care research plan, which will use cancer as a model for addressing broad quality initiatives in conjunction with the President's Cancer Panel, President's Quality Initiative, and the DHHS Secretary's Quality Improvement Initiative. Objectives will be to develop a core set of outcome measures for cancer care; strengthen the methodologic and empirical research base for quality assessment in cancer; restructure the NCI clinical trials program to provide better access and understanding of costs; and improve the quality of cancer communications. Dr. Klausner outlined specific research and initiatives needed to achieve these objectives. For example, a memorandum of agreement is being formalized between the Centers for Disease Control and Prevention (CDC) and the NCI to link the national program of cancer registries with NCI's Surveillance, Epidemiology, and End Results (SEER) program as one initiative in the development of a methodologic and empirical research base. Toward the end of improving cancer communications, new centers of communications excellence are

envisioned in the new Bypass Budget and new communications products and tools will be developed under the leadership of the new Outcomes Research Section in DCCPS. Dr. Klausner emphasized the need also to begin to create the infrastructure within the DHHS to link research in quality cancer care and outcomes to the policies that profoundly affect the actual experience of patients, particularly through Medicare. The standing task force envisioned in the proposal would facilitate two-way communication between the research community and Medicare and other third-party payers.

National Imaging Forum. Dr. Robert Wittes, Deputy Director for Extramural Science, presented information on a recent national forum held at the NIH, in which the NCI was instrumental in bringing to the table representatives from different federal agencies with scientific, medical, and industrial representatives from the private sector to address issues related to technology research and development. The initiative was undertaken to capitalize on the opportunity represented by imaging for the development of target- and molecularly-specific tools for cancer treatment and prevention. Impetus for the meeting was the recognition that industry participation was necessary for the making, testing, and marketing of imageable probes for biological processes and that one barrier was how to promote industry understanding of biomedical needs. Dr. Wittes stated that the decision to sponsor a national forum for addressing the entire spectrum of issues—scientific, medical, industrial, regulatory, and reimbursement—was an initial implementation of the NCI's expressed intent to involve the device industry in activities with respect to the development of imaging technologies. Assistance in planning this first forum was obtained from the Board of the National Electrical Manufacturers Association (NEMA) and representatives from industry, the Food and Drug Administration (FDA), and HCFA. Dr. Wittes reported enthusiastic participation in all aspects of the forum by the approximately 250 persons who accepted NCI's invitation. The attendees included chief executive officers, marketing personnel, and business people of all types. Physicians and scientists making the presentations focused on actual unsolved problems, such as those in prostate cancer; round-table discussions of the issues following the presentations formed the basis for further action. Dr. Wittes noted that the task ahead is to put in place programs and processes for identifying crucial technologies and approaches for which industry cooperation is needed, as well as for lowering the activation energy required for the various steps, e.g., working with the FDA and HCFA to make regulatory and reimbursement steps more defined, predictable, and publically known. Dr. Klausner commended Dr. Wittes and his staff for their role in organizing the event. He added that NCI plans include setting up a standing infrastructure for round-table consideration by the NCI, government, academia, and industry of a series of explicit issues.

NCI Personnel Update. Dr. Klausner introduced Dr. Dinah Singer, newly appointed Director, Division of Cancer Biology, and newest member of the NCI Executive Committee. He acknowledged the work of Dr. John Sogn, who has been acting in that capacity pending finalization of the appointment. Dr. Klausner announced the departure from the NCI of Dr. George Vande Woude, Director, Division of Basic Sciences, to assume a position as head of the Van Andel Institute in Grand Rapids, Michigan. On behalf of the NCAB, Dr. Klausner presented Dr. Vande Woude with a commendation for

his work as a leader of science, and for his leadership in revitalizing basic science research at the NCI and setting the course for a future rich in discovery.

Questions and Answers

In response to a question from the Board about the sources for the evidence upon which guidelines and decisions about quality of care will be based, Dr. Klausner noted that evidence gathering will take place in multiple settings, from population-based studies to studies in particular types of care-giving settings. An RFA is planned to look for broad approaches to gathering information on different types of patient populations. Another Board member emphasized the need to ensure that cancer care research with respect to quality covers public health prevention of cancer as well as the continuum of cancer care from detection to diagnosis. The Chair noted that health maintenance organizations (HMOs) deliver approximately 60 percent of health care and have extensive research in this area, and asked how they will be incorporated in the proposed quality cancer care initiative. Dr. Klausner pointed out the variety of research interactions that already exist between NCI and the health care delivery systems of managed care organizations, including a new cancer research network based in HMOs. He added that the issue will continue to be addressed in the complicated task of coordinating the effort within the NCI and DHHS, across the federal government, and with private partners, insurers, providers, and professional societies. Dr. Elmer Huerta commented that the proposed initiative would present an opportunity to incorporate all recommendations of the IOM report on cancer and the underserved and minorities.

PRESIDENT'S CANCER PANEL REPORT
Dr. Harold Freeman

Dr. Harold Freeman, President, North General Hospital, and Chair, President's Cancer Panel, presented highlights of the Panel's 1997–1998 report to the President entitled *Cancer Care Issues in the United States: Quality of Care, Quality of Life.* He pointed out that the report presents another perspective on the issue of quality cancer care and dovetails well with the work of the IOM report and NCI's proposed quality cancer care initiative. He reviewed the Panel's charge: to identify barriers to the optimal development and implementation of the National Cancer Program in the continuum from discovery in basic research laboratories, to translation in academic settings, to application in patients with cancer nationwide. In a series of six meetings held during 1997 and 1998, the Panel addressed issues related to quality of and accessibility to cancer care. To address the these issues, the Panel heard testimony from a cross-section of leaders nationwide in cancer research, medicine, and consumer groups. Testimony to the Panel was complemented by research efforts and recommendations of the NCPB.

Dr. Freeman stated that the Panel believes important steps are needed now to address issues related to defining and providing quality cancer care and improving quality of life. In its report to the President, the Panel recommended that: (1) the welfare of the patient

must inform the quality of cancer care; (2) the definition of quality should embrace both individual and public health concerns; (3) quality definitions and critical practice guidelines are important but should be updated as clinical advances are demonstrated and must not become barriers to access or reimbursement; (4) evaluation of quality cancer care should be based on evidence from randomized, controlled trials, if possible, or on other forms or evidence using agreed-upon evaluation methodology; (5) quality evaluation of cancer care should take into consideration the quality of life and economic survival; (6) the data needed to make this assessment include socioeconomic status, cultural values, quality-of-life perceptions, impact of cancer on family members, and patient-focused outcomes measures; (7) all stakeholders should share the cost of guideline development; (8) coordination of guideline development and dissemination is important; (9) survivorship issues must be addressed, including long-term effects of treatment, family issues, socioeconomic status, employability, and evolving or changing definitions of survival; (10) funding should be balanced across the spectrum of cancer research, from prevention to end-of-life concerns; (11) effective strategies must be developed to educate patients, their families, and the public on how to evaluate options; (12) appropriate training in the quality of care/quality of life area of concern is needed for physicians, both old and new; (13) an assessment is needed as to whether quality care is being impeded by socioeconomic factors; (14) the issue of the un- or underinsured Americans must be addressed; and (15) participation in clinical trials should be a part of the standard of care.

Dr. Freeman summarized Panel recommendations stemming from the 1997-1998 meetings as follows: expand and standardize data collection on quality cancer care; establish a consistent methodology for evaluating various levels of evidence; increase research on short- and long-term patient outcomes; establish a centralized mechanism to systematically disseminate evolving concepts and descriptions of quality cancer care; ensure that descriptions of quality cancer care reflect the priority of the patient's welfare over the cost of treatment. The Panel in its 1999 meetings has been and will continue to explore the current state of the NCP as a whole and seek recommendations for future directions. Included in the agenda will be public health models in the context of cancer that distribute benefits to a larger number of people, e.g., an expansion of prevention strategies.

Questions and Answers

Dr. Sandra Millon-Underwood pointed out the need for training of other types of health care providers involved in cancer care, in addition to physicians. In response to a question, Dr. Freeman agreed and noted that the Panel recommendation included a focus on short- and intermediate-term effects of treatment on survivorship, as well as long-term effects. Dr. Larry Norton asked what the Panel saw as NCI's role in coordinating the effort of the many and diverse interest groups—some with conflicting goals—to implement Panel recommendations. Dr. Freeman expressed the view that the NCI is the critical element in cancer research and also could be in cancer control if that area expands as proposed. He noted the need for somewhat of a change in philosophy from the present concentration on discovery and some translation research to encompass the entire spectrum of what has to be done. Dr. Klausner agreed that the NCI needs to play a larger

role in the overall effort, but from the viewpoint of its expertise. He described NCI's role as developing real and reliable data and helping to convene groups with overlapping responsibilities so that the coordinated effort will ultimately be successful in addressing the difficult social and political issues.

NEW BUSINESS
Dr. Marvin Kalt

Dr. Marvin Kalt, Director, Division of Extramural Activities (DEA), requested Board action on a document entitled "National Cancer Advisory Board Statement of Understanding." He explained that the document is a statement of principles for the electronic expedited concurrence process for members of the Board whose role it is to concur with the initial peer review process. If approved, the document would permit the delegation of authority to four NCAB members to act in the future on applications for R01s and R21s that are within the payline. The expedited review process is part of an NIH-wide initiative that is being tested with the current round of applications. It is an effort to address the fact that, in FY 1999, the threshold of 8,000 was reached for the number of applications assigned to the Institute, raising concerns about the volume of information to be digested.

Motion: A motion was made to approve the "NCAB Statement of Understanding with NCI Staff on Operating Principles in Extramural Awards." The motion was seconded and unanimously approved.

UPDATE: OMB CIRCULAR A-110 AND THE FREEDOM OF INFORMATION ACT (FOIA)
Dr. Marvin Kalt

Dr. Kalt reminded Board members that the Notice of Proposed Rule Making (NPRM)—Circular A-110: Uniform Administrative Requirements for Grants and Agreements with Institutions of Higher Education, Hospitals, and Other Non-Profit Organizations had been issued by the Office of Management and Budget (OMB) in implementation of the mandate related to public access to research data that was included in the Omnibus Appropriations Act for FY 1999. Dr. Kalt reported that about 9000 responses to the NPRM had been received, including those from the Board and NCI. The OMB subsequently issued a request for "Comments on Clarifying Changes to Proposed Revision on Public Access to Research Data," with responses due September 10. Dr. Klausner's comments on behalf of the NCI had been delivered on the due date and presented the view that, although many of the issues had been clarified, critical ambiguities and problems remained. (Copies of the memo were included in the Board's meeting notebooks.) Dr. Kalt further explained that OMB's first response outlined reasonable approaches in regard to: (1) limiting the definition of research data to peer-review and published data; (2) limiting the scope to that data used by the federal government in developing a regulation with a societal impact of at least $100M; and (3)

recognizing the need for a cost-recovery process for both awardees and agencies in providing data under such requests. Subsequent steps will include OMB's issuance of the next, and presumably final, rule based on the September 10 responses, possible legal challenges, and the need to distinguish between Freedom of Information Act (FOIA) requests and legal suits. Dr. Kalt noted that areas with potential impact on the Institute and awardees included tobacco, environmental carcinogens, nutrition and foodstuffs, health care delivery, third-party payer roles, and the practice of medicine as defined by other government agencies in federal regulations. He then reviewed areas needing better definition as specified in Dr. Klausner's response which related to the need for a notification and appeals system; extension of protection to entities, as well as individuals; limiting requests to publications where the majority of data were collected with federal funds; oversight of the use of information that has been released; and reimbursement procedures.

Dr. Kalt then summarized the published comments of Senators Nighthorse-Campbell, Lott, Shelby, and Gramm in response to OMB's clarifying changes to Circular A-110, noting that the senators view them as a "significant retreat from OMB's original February 4th proposal" and "contrary to the plain meaning of the statute and Congress's intent in passing the law." Dr. Kalt concluded by noting that this update was presented to bring closure to an issue that had been addressed in a Board resolution and to remind members of the need be cognizant of and responsive to the publication of a final rule and further developments as individuals and representatives of institutions.

STATUS REPORT ON CONFIDENTIALITY MEETING
Ms. Mary CcCabe

Ms. Mary McCabe, Director, Office of Clinical Research Promotion, reported that a December 1–2 meeting has been planned to develop best-practice models for maintaining confidentiality of research data as proposed at a recent NCAB meeting. Participants from a variety of disciplines and organizations will be asked to focus on particular research areas across the research continuum, including clinical trials, human genetics, epidemiology, databases, surveillance, and archived human specimens. A preliminary working session in October is being considered to draft best-practice characteristics and models for use at the large meeting. Although model development is the primary objective of the meeting, additional products could be the identification of knowledge gaps and development of recommendations for Dr. Klausner's consideration. Dr. Klausner emphasized the importance of these issues, in part because of the potential impact of the new technologies on research information, and he noted the need for recommendations from the Board. Information on the meeting will be provided to Board members. As a further item of information, he reminded members that the Secretary, DHHS, will be promulgating guidelines about medical confidentiality by February as mandated in the Kassebaum-Kennedy Health Insurance Portability Act because Congress has defaulted in doing so before the deadline.

CODING OF RESEARCH APPLICABLE TO SPECIAL POPULATIONS
Dr. Susan Sieber and Dr. Frederick Li

Dr. Susan Sieber, Associate Director for Special Projects, Office of the Director, NCI, and Dr. Frederick Li, Chief, Division of Cancer Epidemiology and Control, Dana Farber Cancer Institute, presented the draft report from the NCAB Subcommittee on Coding for Research on Minorities for Board review and acceptance. The Subcommittee had been appointed in early April to review the process and terms the NCI uses to estimate funding levels directed at research on ethnic/racial minorities and had submitted a preliminary report to the NCAB in June. Questions to be addressed were: (1) How best to characterize the NCI's research portfolio on ethnic/racial minority research? (2) How to define "targeted" and "relevant?" (3) How to determine the level of detail needed in the financial coding of minority research? (4) How to analyze large, multi-site projects like SPOREs and program project grants (P01s)? (5) How to analyze minority participation in clinical trials and SEER? (6) How to deal with projects at foreign sites? and (7) Where in the NCI should coding responsibility reside? In the course of its analysis, the Subcommittee evaluated more than 40 projects active in FY 1997, which had previously been coded by NCI. Dr. Sieber noted that the level of concordance was good when the results of the analyses were compared within the group and the group average scores were compared with NCI funding estimates. She stated that discussions of the differences among Subcommittee members and between the Subcommittee and the NCI helped shape the overall analysis of coding issues and the final recommendations. The work of the Subcommittee indicated that guidelines for NCI coders were needed to ensure consistency and served as a reminder that all research is to some extent relevant to special populations.

Dr. Li summarized the recommendations of the Subcommittee as presented in the draft report: (1) the term "racial" should be deleted from the phrase "racial/ethnic minority group;" (2) questions related to ethnic minorities should be separated from the issue of medically underserved; (3) for purposes of coding, special populations should be defined as ethnic minorities, rural, low income, and low literacy groups; (4) ethnic minority research is defined as research in which the question asked relates to specific minorities; and (5) minority-targeted research is defined as research that is specifically focused on answering a question about a U.S. minority group or groups, or differences among them; (6) use of the term "relevant" should be discontinued; (7) projects less than 100 percent targeted should be assigned a target level by knowledgeable NCI staff; a schema for assigning target levels was suggested; (8) the ethnic proportion represented in projects that involve more than one minority should be identified to the extent possible; a multi-cultural category should be used for multiple minority populations; (9) training and information dissemination grants should be separate from research projects grants; (10) for P01s and other large grants, each subproject should be identified for its level of funding and the aggregate dollar amount computed; (11) studies of cancer in foreign countries should be placed in a separate category; (12) coding responsibility for extramural grants and contracts should reside with the program director or, for intramural projects, with the principle investigator or designee; (13) the Office of Special Populations Research should monitor the quality control of coding results and ensure that

uniform guidelines are prepared and used when training coders; (14) SEER program coding can be based either on the overall minority representation in the U.S. population or on minority representation in the SEER population; and (15) funding estimates for clinical trials should be based on the proportion of minorities represented in a given study. Dr. Li noted that, based on its analysis and review, the Subcommittee was usually in agreement with the funding levels NCI has reported for minority cancer research projects examined, although it believed that some refinements and modifications to the coding process are in order. The Subcommittee believed also that the tracking of research funding represents a first step in the commitment to reduce the cancer burden among minority populations, the ultimate mission being to ensure that discoveries lead to reducing the burden of disease. The Subcommittee's final recommendation was that a standing Subcommittee of the Board be established to provide category guidance and advice on coding issues as they relate to NCI's support of research on cancer in minorities.

Questions and Answers

Dr. Freeman commented on the need for another initiative to address the issue of the medically underserved because of the role poverty and low socioeconomic status may play in the disparities seen in cancer statistics. Dr. Klausner noted that a process has been set up to develop a working definition of "medically underserved" as a prelude to establishing coding guidelines. He suggested that the NCAB can at some point receive a progress report on that effort. Dr. Freeman noted that OMB Circular 15 defines five racial categories and he asked how the Subcommittee's recommendation on the word "racial" would relate to the government requirements under that directive. Dr. Klausner responded that the NCI would follow the legal requirements specified in OMB Circular 15, and the new guidelines would probably be used for coding the types of research that is addressing the issue of disparities of cancer burden in minorities and ethnic groups. In response to another question from Dr. Freeman, Dr. Li explained that the Subcommittee did include cultural issues and personal behavior based on cultural background as part of the definition of "ethnicity." In response to a question from Dr. Alfred Goldson, Dr. Li explained that the Subcommittee will finalize and release the report to the NCI for implementation. After further discussion, it was agreed that the work of the Subcommittee and the final report of the Subcommittee's discussions, comments, and recommendations for coding NCI's minority research portfolio will be helpful in responding to accountability-type queries from the public and Congress, as well as for planning purposes. It also was agreed that ethnicity as a coding factor is not specific enough and further work by the entire community will be necessary to expand and refine the definitions of sub-populations that should be studied differently in order to fully address the problem of the unequal burden of cancer.

Dr. Sharp asked for Board acceptance of the Subcommittee report in the context of coding, recognizing that larger issues have been raised by the discussion. Asked whether the report was perceived as fulfilling the NCI's needs in regard to its reporting responsibilities, Dr. Klausner expressed the view that the recommendations would be helpful in responding to issues raised by the IOM report. He noted that the

recommendations would also be presented to the NIH advisory committee that is working on the issue of coding of activities vis-a-vis the unequal burden of disease.

RECENT RESEARCH PROGRESS IN KIDNEY CANCERS
Dr. Richard Klausner, Dr. James Yang

Introduction—VHL: Bench to Bedside. Dr. Klausner presented information on research over the past few years on a tumor suppressor gene identified as being responsible for a particular inherited cancer syndrome, von Hippel Lindau (VHL) disease. He demonstrated how this research has come close to explaining the mechanism of action of the VHL gene and how the understanding of its targets and functions in the cell have raised predictions about molecularly targeted therapy. One intervention suggested by this basic research is now the focus of a translational research clinical trial in the Clinical Center. Dr. Klausner emphasized the public health consequences of this research. Although VHL syndrome itself has a very low frequency (1 in 36,000), the loss of function of the VHL gene appears to be the cause of the vast majority of cases of sporadic clear cell carcinoma (about 25,000 to 28,000 new cases per year).

Dr. Klausner described the progression of research on the VHL gene in a collaboration between his laboratory and that of Dr. Marston Linehan, Chief, Urologic Oncology Branch, Division of Clinical Sciences (DCS). He described a series of experiments in the nude mouse model to determine how VHL functions as a tumor suppressor gene and how the gene acts in relation to tumor development. Dr. Klausner showed that VHL appears to act: (1) as a growth factor in an early phase of the cell cycle; (2) as a late phenomenon in cancer development to inhibit invasiveness; and (3) as an inhibitor of vascular endothelial growth factor (VEGF) in angiogenesis associated with tumor development. Dr. Klausner stated that all of the data on VHL suggest that it is a conductor gene model (part of the master pathway), predicting that further study of almost any tumor suppressor gene will show that multiple phenotypes are coordinately regulated for different tissue lines by a few critical pathways, or maybe only one. Dr. Klausner's interpretation of these genetic events, and for which there is partial evidence, was that the loss of the VHL gene is necessary for the deregulation of all pathways but is not sufficient of itself. There may be for each pathway other genes that work with VHL, and answering questions about how these complexes coordinate sensing and what is being regulated in the cells was the focus of further research. Dr. Klausner then described recent studies, now in press, that have confirmed that VHL is a complex that biochemically recognizes substrates in the cell and ubiquitinates them. These studies have led to the identification of targets for the development of molecularly based treatment interventions. One target is VEGF, which the VHL gene studies suggest drives the angiogenesis that allows the expansion of tumor, and high levels of VEGF have been found in patients with kidney cancers associated with VHL mutations. Dr. Klausner introduced Dr. James Yang, Senior Investigator, Surgery Branch, DCS, to present information on a Clinical Center protocol for treatment of advanced and rapidly progressive kidney cancer.

Evaluation of Recombinant Humanized Monoclonal Antibody (rhMAB)-VEGF in the Treatment of Patients with Metastatic Renal Cell Carcinoma (RCC). Dr. James Yang listed as those involved in this clinical effort included Surgery Branch (SB) investigators

and physicians, the laboratories of Drs. Klausner and Linehan, and Genentech collaborators, who assisted in the preclinical studies and with drug development. As background and rationale for this clinical trial, Dr. Yang noted that there are 30,000 new cases of RCC and 12,000 deaths annually and RCC as a malignancy is rapidly increasing in incidence. He described the extensive and ongoing interest of the NCI intramural program in RCC, including the identification of VHL by Dr. Linehan and the development in the Surgery Branch of interleukin-2 (IL-2) therapy, the only proven and approved therapy for this advanced malignancy. In the search for other modalities to benefit patients who are not benefitting from immunotherapy, SB investigators became interested in the possibility of using an anti-angiogenic approach partly because of the demonstrated link between mutations in the VHL tumor suppressor gene and VEGF overproduction and partly because of the morphology of the tumor. It was decided that RCC would be a good histology in which to test rhMAB-VEGF, a new drug being developed at Genentech.

Dr. Yang presented preclinical evidence of the drug's effectiveness from studies in prostate and colon cancer xenografts, as well as in human tumor xenografts of a rhabdomyosarcoma and a glioma. Evidence from the colon cancer xenograft was used to predict biologically effective doses in humans based on the mouse serum levels of antibody attained with low and high doses of murine antibody. A Phase I dose-escalating study in patients with advanced solid tumors showed: no dose-limiting toxicity at 10 mg/kg; low incidence of non-specific symptoms, not dose related; isolated episodes of tumor bleeding; no development in patients of antibody to rhMAB-VEGF; one response in a patient with RCC; and stable disease over the 72-day followup period in 13 of 25 patients. These findings led to the design of a Phase II randomized trial in patients with progressive, measurable metastatic clear cell renal carcinoma. This study was designed as a three-arm, randomized, placebo-controlled, double-blind study. Treatments are placebo and low- and high-dose antibody; endpoints are response rate, time-to-progression, and survival. On the basis of historical SB data, the trial was designed with 50 patients per arm to detect a two-fold hazard ratio for either antibody arm versus placebo with a power of 0.80 and a corrected p-value 0.05. Dr. Yang noted that, because evaluating stable disease and time-to-progression endpoints is difficult, a co-study has been designed to try to correlate disease regression and progression with a variety of imaging modalities. In collaboration with investigators in Radiology and Nuclear Medicine in the Clinical Center, the co-study will use positron emission tomography (PET) and dynamic magnetic resonance imaging (MRI) to monitor blood flow within the tumors and attempt to make other correlations with the endpoint trial. The expectation is that correlations derived from this co-study can be used in the increasing number of anti-angiogenesis trials that are expected in the future. Dr. Yang described the characteristics of FDG glucose, carbon monoxide with C11 isotope, and water with the oxygen 15 isotope, which recommended them for use as imaging agents with PET. He then illustrated the types of physiologic imaging achieved with PET and MRI modalities in other SB studies to demonstrate their potential as good short-term surrogates for following the anti-angiogenesis trials.

Dr. Yang reported that, as of August, 52 patients have been randomized to the Phase II trial, which opened in October 1998. Antibody and bioactive VEGF levels are being measured; the development of antibodies against rhMAB-VEGF is being assessed blindly in an extramural site. Toxicity has been minimal with only about 10 percent of patients

developing a mild to moderate limited proteinuria. The projected accrual total is 150, and the projected end of study at 2 years appears likely. Dr. Yang noted that, as a blinded investigator, he is unaware of the study drug administered to individuals, but progress against disease has been observed: clear partial regression of mediastinal lymph nodes that was ongoing at 3 months in one patient; regression at 5-months follow-up of mediastinal and hilar lymph nodes in a second patient; disappearance and regression of pulmonary lesions maintained at 3 months in a third patient; and disease stability for 7 months before progression of a lesion in a fourth patient.

Dr. Yang stated that the experience of the fourth patient seems to suggest that VEGF may not be the only mediator of angiogenesis in RCC (although laboratory data indicate that it is a very important one) and that there is likely to be a source of angiogenesis that is not addressed by rhMAB-VEGF. He noted that studies are being conducted in his own and other SB laboratories that may lead to the next generation of reagents to be tested in future trials. For example, in pursuing an interest in identifying immune targets of lymphocytes in cancer, his laboratory found that a cytotoxic T-lymphocyte (CTL) developed from a patient with RCC showed the ability to recognize its own cancer. A series of experiments led to the finding that CTL was recognizing a specific protein in the context of HLA-A3 and that the protein being recognized was fibroblast growth factor 5 (FGF-5). These studies have led to the conclusions that: (1) FGF-5 is a potentially transforming growth factor produced by approximately 60 percent of RCCs as well as other adenocarcinomas and (2) FGF-5 is both a tumor-specific T-cell antigen and a potent angiogenic factor. Dr. Yang stated that ongoing studies are evaluating FGF-5 not only for vaccine therapies, but also as an anti-angiogenic target alone and in combination with VEGF neutralization.

Questions and Answers

In a follow-up discussion of the science, Dr. Yang responded to questions from Dr. Norton as to: (1) whether the VHL genotype had been examined germ line and in tumor; (2) what the mechanism of inhibition was in the preclinical studies conducted at Genentech and whether the intention was to begin to combine anti-VEGF therapy with anti-mitotic or pro-apoptotic therapy to understand what is happening in terms of the proliferation characteristics of the residual tumor cells; and (3) whether there were any plans to use rhMAB-VEGF in the active setting post-nephrectomy for early-stage disease. In regard to the latter question, Dr. Yang noted that most of the clinical models show inhibition rather than frank regression and what is needed to mount such large adjuvant studies is evidence that there is an effect in a more specific, smaller group of patients. He added that the Phase II trial is intended to demonstrate clinical efficacy for an agent that could then be taken into the adjuvant arena with some confidence. In response to a question from Dr. Goldson, Dr. Yang noted that the Phase II trial was designed with time-to-progression and survival as endpoints to avoid the possibility that the drug could be rejected incorrectly because it does not show frank regression. In response to Dr. Sharp's question about the possibility of identifying other angiogenic factors in this tumor, Dr. Yang noted that would be known only after other combinations are tried. Dr. Klausner added that the ongoing systematic study of total gene expression across many tumors with 20,000 gene arrays has the potential to discover other angiogenic factors. In response to Dr. Sharp's question, Dr. Klausner stated that after extensive investigations, both functionally and in terms of mutation, into whether other types of tumors have been

have exhibited VHL deregulation, investigators have not seen that VHL is involved in other tumors with the exception of hemangioblastomas. Dr. Yang provided the information in response to questions from Dr. Ivor Royston and Dr. Arthur Neinhuis that patients in the Phase II trial are maintained on their assigned drug as long as there is evidence that they have not progressed. Dr. Paul Calabresi asked if other anti-angiogenic agents (e.g., endostatin, thalidomide) had been combined with anti-VEGF. Dr. Yang replied that very little combination therapy has been investigated yet, but it is an area of promise in anti-angiogenesis and very likely where the field will go in the future.

SPIRAL COMPUTED TOMOGRAPHY (CT) SCANNING FOR DETECTION OF LUNG CANCER

Dr. Barnett Kramer, Dr. Christine Berg, Dr. Nicholas Wald, Dr. Kay Dickersin, Dr. Frederick Li, and Dr. Susan Love

Developments in Spiral CT Screening for Lung Cancer. Dr. Barnett Kramer, Deputy Director, Division of Cancer Prevention (DCP), stated that the impetus for considering an NCI initiative using spiral CT scanning to screen for lung cancer was a case series by Dr. Claudia Henschke and colleagues reported recently in *Lancet*. Dr. Kramer reviewed the study design and results of the Early Lung Cancer Action Project. One thousand asymptomatic volunteers age 60 and older, all with a 10+ pack-year history of cigarette smoking, were screened for suspicious lesions with a low-dose spiral CT scan plus chest x-ray. Patients were followed and worked up using an algorithm based upon the size of abnormalities. Dr. Kramer noted that the important finding in this study was the impressive shift to earlier stages of cancer when compared with the SEER distribution (85% in Stage I versus 22% in SEER). A pre-publication presentation of these findings by Dr. Henschke to NCI investigators triggered a discussion about how the technology could be developed, what are appropriate types of studies, and how the technology can be evaluated. Dr. Kramer listed the following as being among the options: (1) accept the case series as sufficient to institute widespread population screening in smokers and former smokers; (2) replicate the findings in additional multicenter series; (3) conduct a randomized trial with surrogate endpoints such as survival after diagnosis or stage shift, and (4) conduct a large randomized trial with sufficient power to detect a lung cancer mortality benefit.

Dr. Kramer reviewed and compared the findings in four randomized studies of lung cancer screening to provide some perspective for considering a randomized trial. He concluded that the four trials have a commonality and that the outcomes are of interest even though different screening tools were used. The Mayo Lung Project showed no change in mortality and a significantly improved 5-year survival; the Johns Hopkins/Memorial Sloan-Kettering trial reported no change in mortality and a significantly improved 5-year survival; the Czechoslovakian Trial showed no difference in mortality, but did show stage-shift and lead-time bias. The ongoing Prostate, Lung, Colorectal, and Ovarian (PLCO) trial is designed with a 90 percent power to detect a 10 percent improvement in mortality and should achieve some of the lung cancer mortality endpoints within the next several years.

Dr. Kramer then discussed how these findings factor into the decision about accepting surrogate endpoints to replace cause-specific mortality, thereby enabling the randomized trial to be smaller, faster, and cheaper. He presented the following questions as yardsticks by which to evaluate the validity of results from a trial with surrogate endpoints: (1) Is there a strong, independent, consistent association between the surrogate endpoint and the clinical endpoint? and (2) Is there evidence from randomized trials with similar, as well as with unrelated, detection tests that improvement in the surrogate end point has consistently led to improvement in the target outcome? Results from the four completed randomized lung cancer screening trials showed that survival after lung cancer diagnosis and stage shift were inadequate reflections of screening impact on lung cancer mortality. Dr. Kramer cited estimates of $880K to screen 1,000 high-risk individuals such as in Dr. Henschke's case series and more than $39B to screen the nation's 44.8 million smokers and ex-smokers, ages 45 and above, he pointed out that cost-effectiveness is not ascertainable with current data. He presented information on Medicare and HMO payments for local, regional, and distant disease which showed that treating early-stage disease is more costly than late-stage, invalidating the assumption that lung cancer screening would be cost-saving because treating early-stage disease is less costly. This is because lead time bias also occurs in disease-related expenditures.

Possible Plans for NCI Follow-up. Dr. Christine Berg, Acting Head, Research Group for Lung Cancer and Aerodigestive Malignancies, DCP, noted that although spiral CT screening represents one of the exciting new imaging technology developments, the window of opportunity for rigorous assessment may not be long. In addition, the planned and ongoing smoking cessation strategies have the potential to increase the population of ex-smokers, who remain at elevated risk, adding to the public health significance of an appropriate evaluation of any potentially effective screening technology. Dr. Berg summarized the status of NCI initiatives currently in place or planned for the further evaluation of spiral CT, including Dr. Henschke's case series, an ongoing lung nodule diagnostic enhancement study at Mayo Clinic, and a Phase II chemoprevention study supplement to evaluate baseline and follow-up CTs in individuals receiving inhaled steroid. Other initiatives include an open workshop with representatives from diverse communities to be held on October 26 to discuss how to further evaluate spiral CT as a screening tool and a proposal to establish an American College of Radiology Imaging Network (ACRIN), which is in the concept and planning phase. Dr. Berg noted that the ACRIN as planned would conduct a multi-institutional trial to evaluate the impact of spiral CT. Additional NCI initiatives include the development of common data elements for reporting results of spiral CT research protocols, and an RFA for image databases, which has just been prepared. Dr. Berg reported that the Lung Cancer Biomarkers and Chemoprevention Consortium, in conjunction with her research group in DCP and the Diagnostic Imaging Program in the Division of Cancer Treatment and Diagnosis (DCTD), is developing standardized elements for reporting results for spiral CT research protocols.

Study Design Issues. Dr. Nicholas Wald, Professor, Saint Bartholomew's Hospital and the Royal London School of Medicine and Dentistry, University of London, and Editor-

in-Chief, *Journal of Medical Screening*, concurred in the view expressed earlier that, other than avoidance of smoking, the only potential for having a serious impact in reducing the disability and premature death from lung cancer is screening. To begin the discussion of possible next steps and study design issues in the evaluation of spiral CT screening, Dr. Wald analyzed the findings by Dr. Henschke and colleagues in their case series and made the following observations: (1) spiral CT examination is simple and fast; (2) a positive rate of 23 percent (233 positives in 1,000 patients screened) after the first scan could be unique and raises concern about the screening test; (3) the results showing that 28 of the 233 had a second abnormal scan and 27 of the 28 were defined histologically as having lung cancer are striking; (4) the odds of being affected, given a positive result (OAPR), is 27:206 or 1:8 after the first positive result and 27:1 at the biopsy stage; (5) the study does not distinguish between current smokers and ex-smokers, which would affect the design of a trial because ex-smokers approach non-smoker risk after 10 years; (6) the detection rate of cancer that kills is not known from this study; and (7) the false positive rates are 23 percent after the first scan and 0.1 percent at the biopsy stage. Dr. Wald concluded that the Henschke study supports the contention that spiral CT is a technique that is simple, safe, feasible to use in a clinical trial, and not prohibitively expensive. He expressed the view that the only way to judge the efficacy of spiral CT as a screening technique is to test it in a randomized trial that counts the number of deaths in people who are screened and treated and compare them with the deaths that occur in the control group. Other considerations in designing a trial are sources of morbidity (e.g., psychological stress at having a positive scan, biopsy complications) and the need to balance efficacy, safety, and a containable cost. Dr. Wald expressed the view that a large, simple randomized trial of spiral CT screening for lung cancer with lung cancer mortality endpoints is feasible, affordable, and should be conducted now. The study should have a mortality endpoint from lung cancer as the primary. He estimated the need for a study population of the order of 20,000 if smokers only (10,000 in each arm) are included or 40,000 if smokers and ex-smokers are combined (20,000 in each arm) and a trial period of about 5 years.

In discussion, Dr. Sharp asked how a 5-year prospective study as described could be designed to accommodate the appearance of new and better technology before the study's end. Dr. Wald advised that the way to deal with the potential for rapid change is to plan well and execute rapidly, and put much effort into establishing a data committee that is responsible for assessing efficacy and monitoring safety (e.g., the consequences of biopsies and subsequent surgery), and whether the state of knowledge has reached the point where the trial should be stopped because it has been superseded by an advance. In response to a question from Mr. James McGreevey, Dr. Wald explained that lessons to be learned from the trial as outlined would be whether the spiral CT scan reduced mortality from lung cancer, its feasibility in practice, how to control performance quality on a multi-center basis, and what the key cost components are. In response to questions from Mr. McGreevey and Dr. Sharp, Dr. Wald indicated that the trial he used in his example was powered to detect a halving in lung cancer mortality and he emphasized that the key endpoint would have to be mortality from lung cancer, not total mortality. He also emphasized the need to limit the study design to answering one specific question, in this

case, what is the efficacy of spiral CT as a screening test for lung cancer mortality reduction.

NCAB Discussion: Approaches to Decision-Making Processes for Large-Scale Trials.
Dr. Dickersin, Associate Professor, Department of Community Health, Brown University, outlined overarching concerns to be considered in the decision-making process: (1) whether a screening program is appropriate; (2) the potential for many false positives; (3) the fact that mortality is the endpoint, not survival; and (4) the fact that the only available data are uncontrolled, unrandomized, and based on surrogate endpoints. She briefly reviewed the advantages and disadvantages of the available options for screening this new technology and expressed a preference for a large and simple multicenter randomized, controlled trial (RCT) as outlined by Dr. Wald, with a simple protocol, immediate randomization, and minimal data collection. She suggested further that support could be solicited from HCFA and other third-party payers, and that the participation would not be contingent on affiliation with a cooperative group or cancer center. Other issues to be addressed would be the identification of comparison groups and outcomes, the possibility of conducting a simple trial, and whether the approach would be accepted by providers, insurers and the public.

Dr. Li, stated that his initial response to the possible trial was that the Henschke case series and other material received from the NCI were hypothesis-generating, but that the science should proceed in an orderly manner. His concerns focused on the need for more information on costs, follow-up, quality-of-life measures, potential cost-effectiveness of screening for lung cancer using spiral CT versus costs for alternative approaches to screening, cost-effectiveness of early detection versus alternative strategies to reduce lung cancer morbidity and mortality, unintended consequences of the effort (e.g., sending the wrong public health message to teenagers and current smokers), and the potential for backlash if a large, costly trial ends negatively. Dr. Li stated that he continues to believe that as much data as possible should be extracted from the Henschke study, and that he now leans toward proceeding with a definitive, randomized trial. He acknowledged that his decision was influenced by arguments in regard to the possibility that a sound and informative trial would be less costly to the nation than the cost that would accrue if spiral CT screening became the standard of care without appropriate evaluation and was subsequently found to be ineffective.

Dr. Susan Love, Adjunct Professor, Department of Surgery, University of California School of Medicine, stated that she favored a large, simple multicenter trial as described by Drs. Wald and Dickersin. She noted that, although the slow, scientific path of development would be ideal, the actuality is that spiral CT screening is attractive and lucrative enough to become the standard of care with no supporting data, and a randomized study after the fact would be hard to do. She cited the recent example of autologous bone marrow transplant for patients with breast cancer and the difficulty in reversing the use of such procedures after the infrastructure has been built in institutions and budgets set accordingly. Dr. Love suggested that a negative result from a study as proposed would save money in the long run by stopping the use of a procedure that did

not work. She also favored the aspect of study design in which the technology would be tested in the real world, as well as in isolated, quality-controlled situations.

Questions and Answers

Dr. T.G. Patel, Veterans' Administration (VA), stated that the VA, which has approximately 3.8 million patients who would be eligible and has CT equipment available in most of its hospitals, would be interested in participating in a randomized clinical trial because lung cancer is a high morbidity and mortality disease in the VA population. Dr. Huerta expressed concern about the public health message that could be sent, as was the case when combinations of drugs were found to be successful in managing AIDS. In response he received assurances that the NCI would continue to act in terms of sponsoring research on early prevention, early detection, and treatment, even if the latter is smoking related. Dr. Neinhuis asked what additional insights on spiral CT screening might be provided by the two R01-supported studies that are being conducted and how long it would take to find out that the technology was not efficacious if a randomized trial was not conducted now. Dr. Peter Kirchner, Department of Energy, expressed his support for randomized trials and the evaluation of new technology. He suggested the need also for addressing the broader issue of when the NCI, NIH, or other agencies decide there is enough information to launch a major study. Dr. Norton stated that he was not opposed to a randomized trial as proposed if it comes forward to the appropriate review bodies. He raised questions, however, about the size requirements of such a trial and suggested that a smaller trial also might answer the question. Dr. Kramer noted that there are competing philosophies about developing a sample size for such a trial, and although the ideal would be to see a very large difference in benefit, smaller decrements in mortality would be of immense medical importance in a disease as highly mortal as lung cancer. Dr. Dickersin pointed out that the NCI has the building blocks for addressing the question of when to launch a major trial, particularly in the new partnerships with third-party funders, a changing mindset in researchers, and a system of cancer centers for research. Dr. Goldson suggested that an effort should be made to redirect some of the tobacco settlement money toward this lung cancer effort. Dr. Li asked how finding a positive benefit in the lung cancer screening effort in the PLCO trial would affect decisionmaking in regard to spiral CT screening. Dr. Kramer acknowledged that PLCO outcomes could affect the choice, for example, of a control arm and noted that all possibilities are being discussed. He pointed out that benefits and risks are always weighed in the planning phase and comparison studies would be undertaken. Dr. Wald reiterated that changing the existing protocol to accommodate new developments would be the function of the data monitoring committee, in conjunction with the steering committee. He emphasized the need to remain neutral until the results of PLCO are known and then address them.

Dr. Kramer thanked all presenters and participants in the discussion and stated that the spectrum of opinion expressed in the discussion would be taken into account. Dr. Klausner added his thanks to presenters and participants, emphasizing that this discussion and the soon-to-be-held open workshop representing many diverse viewpoints are part of a process. He expressed the importance of understanding that the Institute often confronts

issues of screening and evidence because of the current emphasis on early detection. Relevant issues are windows of opportunity, changing practices—when the NCI should step in and develop evidence about an important disease for which few treatments exist, and the ethics of even considering a randomized trial. Dr. Klausner noted that there is purportedly a 6-month waiting list for people to get a spiral CT scan in New York City and elsewhere and the benefit to the public health of having information, positive or negative, will have to be weighed into the final decision.

LEGISLATIVE UPDATE
Ms. Dorothy Foellmer

Ms. Dorothy Foellmer, Director, Office of Legislation and Congressional Activities (OCLA), reviewed the status of FY 2000 budget, which currently is in markup. The overall 9.2 percent increase for the NIH in the House mark represents an increase of $1.3B over the FY 1999 appropriation. The NCI would received an increase of $261M, the largest dollar increase within that mark for the NIH budget. Ms. Foellmer explained that the difficulty has been that the allocation to the Subcommittee was low to begin with and difficult choices were necessary to report the bill out of committee, details of which are available on the House Appropriations Committee Web site. Ms. Foellmer noted the likelihood that the NIH would be operating for a time on a continuing resolution at FY 1999 levels, pending Senate markup, conference deliberations, passage by both House and Senate, and the signing by the President.

Ms. Foellmer reported that Drs. Edward Trimble and Richard Kaplan, Cancer Therapy Evaluation Program, testified at hearings before Congressman Burton focusing on complementary and alternative medicine (CAM) and women's cancers and CAM and prostate cancer. In other hearings, Dr. Klausner presented the NIH 5-year plan for prostate cancer research to Senator Specter of the Senate Appropriations Committee and Dr. Robert Hiatt, DCCPS, testified before a meeting of the Senate Cancer Coalition on cancer care in the United States and how the NCI works to effectively upgrade the quality of cancer care across the nation.

In regard to areas of emphasis in pending legislature, Ms. Foellmer discussed the increasing support of the whole issue of clinical trials, pointing out that about 14 bills in the Legislative Update include some type of provision for allowing patient access to clinical trials and provider reimbursement for routine patient care costs. She noted that the future of these health care reform bills is uncertain, however, because of the provisions that would allow patients to sue.

UPDATE ON CANCER VACCINES
Dr. Richard Klausner, Dr. Jay Berzofsky, Dr. Larry Kwak

Introduction. Dr. Klausner explained that the update on cancer vaccines to be presented reflects the National Cancer Program's longstanding interest in immune system approaches to cancer prevention and treatment, the need for the community of cancer

immunology to evaluate changes in immunology over the past few years, and the potential for coupling immunology with new technologies. He noted that the NCI has been addressing the problem of the infinite variety of approaches for moving immunologic observations from bench to bedside extramurally through meetings and workshops and intramurally in the DCS. The focus of the presentation would be the intramural program's recent efforts in immunology vaccine development and the evaluation of the NCI's approach to the testing of vaccines and immunologic manipulation aimed at cancer.

Cancer Vaccine Working Group. Dr. Jay Berzofsky, Chief, Molecular Immunogenetics and Vaccine Research Section, Metabolism Branch, DCS, stated that the Vaccine Working Group (VWG) was established by Dr. Klausner and DCS Director Dr. Edison Liu to facilitate research efforts within the DCS and across the Institute targeted to the development of novel vaccines for cancer and HIV immunotherapy. Goals of the VWG were to assemble a diversity of scientific disciplines within the NCI, NIH, and extramural community to provide new insights and ideas; strengthen old and encourage new collaborations; identify organizational and reagent needs for the vaccine community; help develop the optimal infrastructure for vaccine development; and arrive at novel clinical trial approaches for unique vaccine studies. Dr. Berzofsky reviewed the organization and operating process of the VWG. Co-chaired by Dr. Berzofsky and Dr. Larry Kwak, the VWG has met in plenary session about every two months since its inception in June 1998 with about half of its 100 members in attendance at each meeting. In addition, a Steering Committee and two Subcommittees have been organized and have met individually.
Dr. Berzofsky highlighted some of the Working Group's discoveries and accomplishments. In the meetings on new approaches to vaccine development, discussions related to the breakthrough discovery in recent years that CD8+ cytotoxic T cells recognize antigenic proteins even if they are not expressed intact on the cell surface. These discussions resulted in the identification of desirable characteristics for different types of tumor antigens and two valid and complementary approaches to vaccine development—one based on existing host response and the other on tumor characterization and how it differs from normal cells. In meetings on types of assays that could be used for measuring particular T-cell responses to vaccine immunization, discussions focused on two categories—assays of bulk populations of lymphocytes and single-cell enumeration assays. Dr. Berzofsky noted that the single-cell enumeration assays generated much excitement. Four types of single-cell enumeration assays—limiting-dilution analysis of CTL precursors, ELISPOT, intracellular cytokine staining, and peptide-MHC tetramer staining—were compared and found to have advantages for different purposes. The Working Group believes these assays have potential in monitoring the responses of patients to vaccines.

A third area of emphasis for the Working Group was adjuvants that can be added to a vaccine antigen for greater efficacy in inducing an immune response. Because very few data exist on adjuvants for cancer immunotherapy, the Working Group considered unpublished data from a viral vaccine study comparing adjuvants in an animal model and in human trials, presented by Dr. Fred Vogel, Division of AIDS, National Institute of Allergy and Infectious Diseases (NIAID). The Working Group also considered new data

from Dr. Arthur Krieg, University of Iowa, on immunostimulatory DNA complexes that mimic bacterial DNA. Dr. Berzofsky reported that the Working Group has met to evaluate options for moving some intramural program discoveries to Phase III clinical trials and to organize an implementation planning subcommittee. Clinical trials are being developed within the intramural program for a peptide vaccine for melanoma and for an idiotype vaccine for follicular lymphoma (Dr. Larry Kwak, PI). Another focus of Working Group investigations has been early clinical trial development. A subcommittee has been formed to address design issues related to vaccine clinical trials. The subcommittee has developed recommendations for a Phase II clinical trial design tailored to the unique requirements of vaccine trials and has prepared a manuscript for publication to share the subcommittee's ideas with the wider community. Dr. Berzofsky concluded that the Working Group is expected to serve many useful functions for the Institute's program to develop cancer vaccines by continuing to generate new strategies and by evaluating and importing new technologies.

Dr. Klausner introduced Dr. Gary Nabel, Director of the recently established NIH Vaccine Research Center (VRC). He reminded Board members that a major goal of this new trans-NIH initiative has been the creation of an HIV vaccine, but the Center also will be the intellectual and technologic center for all vaccinology on the campus. Oversight rests with the NIH, NCI, and NIAID Directors and funding will derive from the NCI, NIAID, and NIH Office of AIDS Research.

Vaccine Approaches for Lymphoma. Dr. Larry Kwak, Investigator, DCS, Experimental Transplantation and Immunology, and Working Group Co-Chair, presented an overview of preliminary research that led to the soon-to-be initiated Phase III clinical trial of a vaccine against lymphoma. He briefly reviewed the hypothesis underlying the development of vaccines for treating cancer and noted that his laboratory's studies have focused on the activation of CD8+ T cells, which are capable of killing tumors. The antigen selected for these studies was the malignant B-cell receptor, and research over the years has reproduced the basic phenomenon of what is known as idiotype-specific tumor resistance. In a Phase II single-arm trial of a treatment for follicular low-grade lymphoma begun 5 years ago, patients with minimal residual disease following chemotherapy were administered a vaccine made with their own tumor cells, with the goal of eradicating the residual tumor cells. The vaccine formulation chosen was a combination of custom-made tumor antigen conjugated to the protein keyhole-limpet hemocyanin (KLH) and administered with granulocyte macrophage colony-stimulating factor (GM-CSF). The vaccine formulation had been preclinically tested in animal models, and GM-CSF was found to induce a CD8+ T-cell immune response and enhance the potency of the vaccine. Dr. Kwak reported three independent observations from this completed Phase II single-arm study: (1) in 19 of 22 patients, vaccination against idiotype elicited the first evidence for CD8+ T cells specific for autologous lymphoma, and in most of these cases, this comprised the lysis of autologous follicular lymphoma target cells; (2) 9 of 11 patients whose tumors were positive for the t(14;18) major breakpoint region, converted to polymerase chain reaction (PCR) negativity, providing the first systematic evidence for an antitumor effect of idiotype vaccination; and (3) the clinical outcome of this entire

group of patients was that 18 of 22 remain in continuous first clinical remission, with a median follow-up now of 48 months after completion of induction chemotherapy.
Dr. Kwak characterized the key questions for human cancer vaccine development as whether it is possible to immunize against a self-tumor antigen (answered by the phase II results) and whether immunization can produce clinical benefit. The Phase III randomized, controlled study being planned as part of the VWG initiative is intended to provide definitive answers to the latter question. As planned, it will be a multicenter study involving a consortium of five extramural sites in addition to the NCI. The design will be similar to that of the Phase II study, except that patients will be randomized to either vaccine or a control arm, where unconjugated carrier protein and GM-CSF will be administered. An enrollment of 300 patients will be required to get 200 patients who are in complete remission and eligible for randomization, and patient accrual is anticipated to begin within the month. Several correlative laboratory studies are planned to follow-up on the observations, including one to establish T-cell lines and clones from peripheral blood samples to use as reagents for mapping the precise peptide idiotype epitopes that are being recognized by those T cells.

Questions and Answers

In discussion, Dr. Kwak responded to questions from Dr. Royston about whether rituximab had been considered for the control arm and whether consideration had been given to using a fusion protein with idiotype GM-CSF. Dr. Schein suggested that Dr. Saul Rosenberg at Stanford University should be consulted to ensure that patient characteristics for the Phase III study are appropriate.

DISCUSSION OF THE CENTER FOR SCIENTIFIC REVIEW (CSR) PANEL ON SCIENTIFIC BOUNDARIES REPORT
Dr. Marvin Kalt, Dr. Robert Wittes, NCAB Members

As background to the NCAB discussion, Dr. Kalt reminded the Board that the 15-member CSR Panel on Scientific Boundaries, headed by Dr. Bruce Alberts, National Academy of Sciences, had been organized to conduct a comprehensive examination of the organization and function of the review process carried out by the CSR. The purpose of the evaluation was to optimize the CSR review system in a time of rapid growth (about 40,000 grant applications received by the NIH in FY 1999) and to keep pace with an increasing work load and with changes in how biomedical research is performed. The Phase I report of the Panel has been advertised on the Web with a request for commentary by October 15. Dr. Kalt noted that the purpose of this presentation, therefore, was to review the content of the report, give a sense of the issues seen as having been raised by Panel's careful and deliberate analysis and proposal, and solicit questions or comments from the Board for use by the NCI in crafting a response before the deadline. Dr. Kalt also reviewed how the structure of the study sections formed to handle the case load for peer review affects the funding of grants even though decisions

about funding paradigms applied to the priority scores are made in the individual institutes, i.e., the NIH funds a fixed percentage of applications out of any one initial review group.

Dr. Kalt stated that the focus of the Panel on Scientific Boundaries Report was on: (1) organization of CSR Initial Review Groups and Study Sections; (2) how oversight of that organization and the function of individual parts should be conducted; and (3) "cultural norms" that should govern the review process. Panel goals for the proposed research grant review process were to set high standards of scientific excellence, contribute to the advance of science, encourage innovation and risk taking, exercise fairness, be subject to continuous monitoring of throughput and outcome (e.g., appropriate structure and balance in workload), and be clearly explained to scientists and the public. Dr. Kalt explained that the peer review organization as recommended by the Panel would have 21 Initial Review Groups (IRGs) or clusters of study sections. He briefly reviewed the principles followed by the Panel in arriving at this particular organization, and raised two overarching issues also to consider in formulating a response: (1) the purpose of peer review at the NIH and participation in the process by the individual institutes and (2) whether the initial classification of IRGs appears to be satisfactory and how the scientific expertise and appropriate peers for the oversight panel will be selected.

Dr. Wittes prefaced his review of issues seen as having been raised by the Report, by noting that the lack of detail in the report (e.g., on the study sections) hindered the evaluation of likely consequences and the potential for improvement compared with the present system. He emphasized, however, that the CSR does hear comments and reactions from the intra- and extramural cancer research communities and has been willing to reform and revamp sectors within CSR and how it functions on the basis of what it hears. Dr. Wittes noted that NCI staff comments and concerns about the Report related to the following: (1) the lack of tangible evidence of the need for changing the present system; (2) how the culture change in the new system would be implemented; (3) who is a peer and where the senior reviewers will come from; (4) configuration of the proposed IRG arrangement, particularly in regard to orientation and integration of the study sections; and (5) the makeup and role of advisory groups.

To begin the discussion, Dr. Kalt asked each member to comment briefly on their initial reactions and submit more detailed comments by e-mail to his office for transmission to the CSR. The following points were made by Board members: (1) measurement tools (hard data) are needed to assess whether the current process has worked; a critical review of the peer-review process is a starting point; (2) the difficulty of getting support for high-risk research remains to be addressed; (3) the process is dependent on people so the challenge will be to identify, recruit, and motivate reviewers; (4) reviewers should receive training and orientation to the goals of peer review and the mission of the NIH; (5) reviewers must learn to communicate and work together in multidisciplinary teams in an integrated review process; (6) measurement tools also are needed to assess outcomes, i.e., whether the quality and diversity of proposals is such that science in the broadest context is advanced; (7) some flexibility is needed in terms of composition of the committees to address needs that may develop as science moves forward; (8) an effort

should be made to identify the periods of time when good reviewers can make themselves available and then to utilize them as appropriate during that interval; (9) in practice, multidisciplinary and integrated reviews will be difficult to achieve; (10) the review process should be structured around the applications that are received, similar to the system used by the Department of Defense for their breast cancer reviews; (11) the Report presented a good overview; (12) individuals who receive funding from the NCI should be required to serve on a peer-review study section; (13) the cultural norms are well stated but lack the authorities necessary for implementation; (14) advocates should be part of the peer-review process; (15) clarification is needed as to how nursing science is to be assigned and evaluated; (16) the peer-review process should be continuously evaluated; (17) radical changes to the peer-review system should be pretested and evaluated before general implementation; (18) there is a need for attention to detail and proper balance in applications involving innovative, high risk research; (19) the definition of "peer" requires clarification; 20) a hybrid of the present and proposed systems should be considered; (21) the peer review teams should be multicultural; and (22) an additional IRG is needed to focus on cancer among the underserved and minorities.

ADJOURNMENT
Dr. Frederick Li

There being no further business, the 111th meeting of the National Cancer Advisory Board was adjourned at 11:29 a.m. on Friday, September 24, 1999.