NATIONAL CANCER ADVISORY BOARD

convenes at the:
National Institutes of Health
9000 Rockville Pike
Conference Room 10, C Wing, Building 31
Bethesda, Maryland 20892

ATTENDEES

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The National Cancer Advisory Board (NCAB) convened for its 102nd regular meeting at 8:30 a.m., June 17, 1997, in Building 31, C Wing, 6th Floor, Conference Room 10, National Institutes of Health.

NCAB MEMBERS

Dr. Barbara K. Rimer (Chairperson)
Dr. J. Michael Bishop (absent)
Dr. Richard J. Boxer (absent)
Mrs. Zora K. Brown
Dr. Pelayo Correa
Dr. Robert W. Day
Dr. Kay Dickersin
Mrs. Barbara P. Gimbel
Dr. Alfred L. Goldson
Dr. Frederick P. Li (absent)
Dr. Sandra Millon-Underwood
Dr. Ivor Royston
Dr. Philip S. Schein
Dr. Phillip A. Sharp
Dr. Ellen V. Sigal
Ms. Ellen L. Stovall
Dr. Vainutis K. Vaitkevicius
Dr. Charles B. Wilson

PRESIDENT'S CANCER PANEL Dr. Harold P. Freeman (Chairperson)
Dr. Paul Calabresi
Ms. Frances M. Visco

ALTERNATE EX OFFICIO NCAB MEMBERS Dr. Prem C. Srivastava, DOE
Dr. Alison Martin, FDA
Dr. Marilyn A. Fingerhut, NIOSH
Dr. Sheila A. Newton, NIEHS
Dr. Ralph Yodaiken, DOL
Ms. Rachel Levinson, OSTP
Col. Louis F. Diehl, DoD
Dr. Hugh McKinnon, EPA
Dr. Lakshmi C. Mishra, CPSC

MEMBERS, EXECUTIVE COMMITTEE, NATIONAL CANCER INSTITUTE, NIH Dr. Richard Klausner, Director, National Cancer Institute
Dr. Alan Rabson, Deputy Director, National Cancer Institute
Mr. Philip D. Amoruso, Associate Director for Extramural Administrative Management

Ms. MaryAnn Guerra, Associate Director for Intramural Administrative Management
Dr. Faye Austin, Director, Division of Cancer Biology; Chairperson, Extramural Advisory Board
Dr. Joseph Fraumeni, Director, Division of Cancer Epidemiology and Genetics
Dr. Peter Greenwald, Director, Division of Cancer Prevention and Control
Dr. Marvin Kalt, Director, Division of Extramural Activities
Dr. Robert Wittes, Director, Division of Cancer Treatment, Diagnosis, and Centers
Dr. Edison Liu, Director, Division of Clinical Sciences
Dr. Claude Klee, Chairperson, Intramural Advisory Board, Board of Scientific Counselors
Dr. George Vande Woude, External Advisor, Division of Basic Sciences; Director, Advanced BioScience Laboratories, Inc., NCI-Frederick Cancer Research and Development Center
Dr. Edward Harlow, External Advisor, Office of Science Policy; Member, Massachusetts General Hospital
Dr. Martin Abeloff, External Advisor and Co-Chair, Clinical Sciences Subcommittee A of the NCI Intramural Board of Scientific Counselors; Professor and Director, Johns Hopkins Oncology Center
Dr. David Livingston, External Advisor, Chairperson of the NCI Extramural Board of Scientific Advisors; Professor of Medicine, Dana-Farber Cancer Institute
Dr. Matthew Scharff, External Advisor and Co-Chair, Basic Sciences Subcommittee A of the NCI Intramural Board of Scientific Counselors; Professor, Albert Einstein College of Medicine
Dr. Alfred Knudson, External Advisor, Special Advisor to the NCI Division of Cancer Epidemiology and Genetics; Acting Director, Intramural Genetics Program; Senior Member, The Institute for Cancer Research, Fox Chase Cancer Center
Dr. Maureen O. Wilson, Executive Secretary of the President's Cancer Panel

LIAISON REPRESENTATIVES

Dr. John Currie, American Association for Cancer Education, Inc.
Dr. Marc E. Lippmann, American Association for Cancer Research
Dr. Robert Martuza, American Association of Neurological Surgeons
Dr. John Stevens, American Cancer Society
Ms. Kerrie Wilson, Association of Community Cancer Centers
Dr. Stanley Zinberg, American College of Obstetricians and Gynecologists
Dr. Bernard Levin, American Gastroenterological Association
Dr. Edward P. Gelmann, American Society of Clinical Oncology
Dr. Edwin Mirand, Association of American Cancer Institutes
Dr. Robert Frelick, Association of Community Cancer Centers
Ms. Laura Liebermann, Candlelighters Childhood Cancer Foundation
Mr. Thomas Brandt, Intercultural Cancer Council
Ms. Jean Ard, Leukemia Society of America
Dr. Robert Phillips, National Cancer Institute of Canada
Ms. Marguerite Donoghue, National Coalition for Cancer Research
Dr. Tracey Walton, National Medical Association
Dr. Eve Barak, National Science Foundation
Dr. Linda Krebs, Oncology Nursing Society
Ms. Pearl Moore, Oncology Nursing Society
Dr. Jeffrey Norton, Society of Surgical Oncology, Inc.
Dr. Marston W. Linehan, Society of Urologic Oncology

CALL TO ORDER AND OPENING REMARKS
Dr. Barbara Rimer

Dr. Barbara Rimer called to order the 102nd meeting of the National Cancer Advisory Board (NCAB), and introduced guests representing cancer education and research associations and

advocacy organizations. She 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 February 1997 meeting. They were approved by the Board unanimously.

FUTURE BOARD MEETING DATES
Dr. Barbara Rimer

Dr. Rimer asked Board members to review future meeting dates as listed and report any conflicts. She noted a date change for the September 1997 meeting. It had been scheduled to being the evening of Wednesday, September 24. By action of the Board, it will now begin on Tuesday evening, September 23, 1997.

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

Dr. Richard Klausner reported on aspects of NCI budget and program activity since the NCAB meeting in February. The funding plan presented earlier in the year set the paylines in the research project grant (RPG) pool at the 22nd percentile for R01s and 135 for P01s because of expected increases in the number of applications received. The NCI was able to raise all paylines as the fiscal year progressed, consistent with its goal of increasing the opportunities for investigator-initiated research. The payline for R01s was raised to the 23rd percentile, and 650 new and competing R01s are expected to be funded. With a payline at the 30th percentile, 107 new FIRST (R29s) awards will be funded. At the higher priority score of 140, 41 competing P01s will be funded. In addition to research supported automatically by virtue of priority score, the NCI allocates 12 percent of the competing RPG budget line for mechanisms such as the Accelerated Executive Review (AER), administrative and competitive supplements, interim and bridge support funding, and grant funding by exception to facilitate research. The NCI funded 26 AERs for about $6.7M in FY96, a success rate of about 50 percent. To date in FY97, 25 grants have been funded through the AER mechanism and 5-6 more are expected, for an overall success rate in FY97 of 55 percent equally divided between basic science and patient-oriented research.

In addition to these mechanisms, the NCI uses the Request for Application (RFA) to initiate research in response to internal and external planning processes and to the needs of the community. In FY97, RFAs will represent about 6 percent of the competing RPG funds, down from about 10 percent in previous years. Examples of research recently advertised through RFAs are: (1) chemoprevention studies in genetically identified high-risk groups, which will result in the award of U01s; (2) studies on the prevention and cessation of tobacco use by children and youth (R01s); (3) a new cooperative group for trials in diagnostic imaging; (4) novel technologies for the evaluation of molecular alteration in tissues, especially high through-put technologies; (5) improved technologies for the production of full-length human cDNAs; (6) the Cancer Genetics Network; and (7) innovative approaches to diversity generation and smart assay development for cancer discovery (P01s).

Dr. Klausner next reviewed the funding plan for cooperative groups. In the area of base funding, the groups have been provided a cost-of-living increase, and grants are being funded to a higher percentage of recommended funding than has been possible in the past. In addition, about $5.5M is being used to support certain special initiatives within the groups, such as the maintenance of tissue banks as an infrastructure to facilitate translational and correlative biologic studies. Four groups will receive funds to meet increasing NCI obligations under the recently negotiated Veterans Administration (VA) and Department of Defense (DoD) agreements. Funding has also been allocated to the groups to support the establishment of electronic informatics infrastructures, which are essential to the development of an integrated

and standardized informatics base for the clinical trials program.

NCI Training Initiatives. Dr. Klausner reported on the progress of the three new NCI training initiatives. The first offering of the Howard Temin Award (K01), which provides transitional funding between a mentored and independent position, attracted many applications. Final decisions are pending, but projections are that about 7 awards will be made. The RFA for the AIDS Oncology Clinical Scientist Development Program was advertised and will result in K12 awards. The Division of Cancer Epidemiology and Genetics (DCEG) has advertised a Program Announcement (PA) to stimulate the development of comprehensive research training programs in the genetic epidemiology of cancer. The emphasis of this PA is on cross-discipline training that will link observational epidemiology with molecular studies in a process that will form the basis for a targeted approach to cancer prevention. Granting mechanisms in response to this PA will include institutional research training grants (T32s), career grants (the K series), and education grants (R25s).

Cancer Survivorship Initiative. Dr. Klausner stated that NCI has received 49 applications in response to an RFA for competitive supplements to currently funded cooperative agreements to support research concerning long-term cancer survivorship. The RFA was addressed to cooperative group chairs; Community Clinical Oncology Program (CCOP) research-based principal investigators (PIs); Surveillance, Epidemiology, and End Results (SEER) Program contractors; and others in the NCI portfolio who have access to or may develop access to cohorts of long-term survivors. A set-aside of $2M is expected to fund up to 15 proposals, each for a maximum of 2 years. This administrative supplement is meant to facilitate the development of new research and the necessary infrastructure to address issues pertinent to survivorship.

DoD Clinical Trials Agreement. Dr. Klausner emphasized the importance of these agreements not only in themselves, but also as a model of NCI's policy commitment to ensure that the complete range of U.S. medical care delivery and payer systems is able to participate in clinical research and clinical trials. To assure the success of the DoD agreement, which is completing its first year, NCI efforts have focused on increasing the level of participation by military physicians and increasing access for Civilian Health and Medical Plan of the Uniformed Services (CHAMPUS) beneficiaries to the sponsored and covered trials. These efforts included extensive joint promotional activities, supplemental funding to enable the cooperative groups to provide per-case payment to military physicians for increased clinical trials accrual, and negotiations with the DoD to expand the agreement to include Phase I trials and a broad range of prevention and diagnostics trials. The NCI is also participating in meetings with the new TRICARE/CHAMPUS managed care contractors to ensure that the clinical trials option is a well-known and well-advertised part of the benefits package.

VA Clinical Trial Agreement. Extensive changes in the VA medical system have resulted in the formation of Veterans Integrated Service Networks (VISNs) for the administration and delivery of medical care. The NCI has been working with the VA to assure continuation of the longstanding collaborations between the VA and cancer centers and cooperative groups. These steps have included the commitment of supplemental funds to provide per-case payment to VA physicians for increased clinical trials accrual, and discussions with the VISN directors to ensure that the regional health delivery system, as it undergoes reorganization, includes strong support for clinical research and a specific commitment to the joint NCI/VA clinical trials agreement.

FY98 Budget. Dr. Klausner reported that budget hearings for the National Institutes of Health (NIH) FY98 budget were held in both houses of Congress. The status of the FY98 budget process was not known at the time of the June NCAB meeting.

Dr. Klausner stated that Dr. Varmus, Director, NIH, and he were called back before the House appropriations subcommittee to discuss the issue of priority setting at the NIH. In addition, Dr. Klausner and Dr. John Bailar were invited as witnesses at a special hearing to discuss the issue of how decisions are made in the NCI. This hearing was held in response to the recent New England Journal of Medicine commentary by Dr. Bailar and Dr. Gornik called "Cancer Undefeated."

Intramural Research Program. Dr. Klausner stated that consolidation of many of the structural changes made in the Intramural Research Program (IRP) over the past 2 years has resulted in a growing integration of activities across the three intramural divisions. Integration has been achieved through the continuing modification of the evaluation and resource allocation processes and through the development of approaches for dealing with shared programs, cooperative research, and shared resources. He cited initiatives within the DCEG as examples of successfully integrated activities in the IRP. The DCEG has hosted a series of important conferences and workshops in cancer genetics. Over the past 2 years, familial cancer registries and consortia have been developed for cancer of the breast, ovary, colon, lung, and prostate. Registries of cancer-prone families are being used to study and investigate familial melanoma, familial lymphoma, basal cell nevus syndrome, Li-Fraument syndrome, Cowden's disease, and others. Genes for many of these diseases have been discovered. During the summer, the three fellows receiving awards under the new DCEG training program will begin their first year of training, which will include didactic courses on clinical, molecular, and population genetics, as well as rotations through familial cancer genetic counseling clinics and a genetics laboratory. The program for subsequent years will be tailored to each individual's research goals, with opportunities in all of the NCI intramural divisions.

Dr. Klausner next highlighted a recent scientific discoveries made by IRP investigators. Following discovery of the BRCA-1 mutation in Ashkenazi Jewish families, intramural investigators examined the frequency of specific mutations in BRCA-1 and BRCA-2 in a population-based study conducted in conjunction with the local metropolitan area Jewish community. By age 70, penetrance of these mutations for breast cancer in the carriers or their first-degree relatives was found to be 56 percent compared with 13 percent for non-carriers. By comparison, penetrance for prostate cancer was 16 percent for carriers and 3.5 percent for non-carriers. Although these estimated risks for breast cancer were high, they were significantly lower than the estimates made at the beginning of the study, suggesting that understanding penetrance is a major challenge in cancer genetics.

In a multicenter study of oral cancer, DCEG investigators found that the risk increased with intake of alcohol even among non-smokers, but multiplied to a 37-fold risk when alcohol and smoking were combined. Findings in studies of oral cancer in Puerto Rico and Japan emphasized the need to correlate susceptibility with risk.

Dr. Klausner reviewed scientific developments from other intramural NCI and trans-NIH collaborations. Several new genes have been identified with cancer syndromes. For example, the papillary renal cancer syndrome has recently been attributed through the work of Drs. Burton Zbar and Marston Linehan to germ line mutations in the met protooncogene. Of interest is the finding of relatively low penetrance in patients in the study who had germ line mutations. The extent to which inherited mutations in cancer susceptibility genes are responsible for so-called sporadic cancers is not yet known. In a Division of Clinical Sciences (DCS) collaboration with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the National Center for Human Gene Research (NCHGR), a new gene, named the MEN-1, was identified on 11q3 and linked with multiple endocrinal neoplasia syndrome. In another NCI laboratory, Dr. Michael Dean and colleagues found mutations in the "patch" gene to be responsible for the Gorlin syndrome. Mutations of the patch gene were identified in virtually all cases of sporadic basal cell carcinoma. Because so much is known about the patch gene from

Drosophila, it can be predicted that a cancer syndrome is possible where there is overexpression of the ligand for this receptor. As a result of these findings, an excellent animal model for basal cell carcinoma was developed by Dr. Scott Kern and colleagues.

INITIATIVES FROM THE DIVISION OF CLINICAL SCIENCES
Dr. Edison Liu, Dr. James Mitchell

Dr. Edison Liu, Director, DCS, presented an update of accomplishments in the Division during his first year at NCI. Currently, the DCS is made up of 10 branches with 983 employees, including PIs, senior research staff scientists and physicians, trainees, technical and administrative staff, and research nurses. Within the IRP, the DCS represents the interface between science and patient in a population-based context. With the strengths of its large cadre of investigators dedicated to studying cancer problems, secure research funding, and freedom from managed care restrictions, the DCS maintains a position of importance in the NCI portfolio and continues to be attractive to new recruits. The presence of 400 trainees on the staff underscores the importance of the DCS to the future of cancer research in the United States.

Dr. Liu stated that one initiative during the year has been to address organizational issues. To promote program integration, four former branches were consolidated to form the current Medicine Branch, in which investigators have been regrouped into departments of cell biology, genetics, experimental transplantation and immunology, and developmental therapeutics. More importantly, a critical mass for clinical investigations is now present within the largest intramural clinical branch. With the specific goal of developing innovative clinical trials, working groups are being established to promote trans-branch discussions in the areas of systemic radiation, lymphoma, and prostate, breast, and ovarian cancer. Resources will be directed to those working groups for trans-branch projects. In addition, the Intramural Research Award (IRA) was instituted with the double purpose of supporting a more integrated program of investigator-initiated research and improving the system of rewards within the division. Tenure track or scientists sponsored by a tenure track individual are eligible to apply and the proposed project, in addition to excellence of science, must include cross-branch collaboration. From the 38 applications received in the first offering, 16 awards of $60K per year for 3 years were made for a total of approximately $1M.

To address the need for strategic planning, DCS and Division of Basic Sciences (DBS) investigators formed the Advanced Technology Consortium to promote the application of novel technologies to biological questions. The Consortium also reviews intramural investigator-initiated applications for the newly instituted Advanced Technology Awards, the technologic version of the IRA. One initiative of the Consortium has been to work with the extramural contractor Affymetrix on the development of a technology platform for the entire IRP. As an outgrowth of this effort, an off-site Advanced Technology Center is being formed for biological applications using such novel technologies as high through-put mapping, multiplex mutational analysis, array technologies, and functional imaging. Three intramural divisions—DCS, DBS, and DCEG—are collaborating with the National Human Genome Research Institute (NHGRI) in this effort.

Dr. Liu reviewed initiatives being undertaken to strengthen the concept of the clinician scholar. In line with the recommendations of the Straus Committee, which had been convened by Dr. Varmus, salaries were increased for tenure track clinicians to achieve parity with the extramural community, and a separate tenure subcommittee was formed. The Clinician Teaching Award was instituted, with a monetary component, for the individual identified by first-year fellows as their best clinical teacher. In addition, the Protocol Review and Monitoring Committee (PRMC) was reorganized to focus on ways to improve clinical protocols and promote interaction among the branches. The PRMC also has been charged with identifying a group of protocols that are important to the DCS mission, which would receive additional resources. The growing

insularity of the intramural program is being addressed as part of the effort to stem the decline of the clinician scholar. Resources will be provided to develop a scientifically attractive package for clinician scientist recruitment. Intramural and extramural interaction is also being cultivated through the new fellowship program sponsored jointly by the NCI and the Gynecologic Cancer Foundation (GCF). Under the NCI/GCF Fellowship, two gynecologic oncologists will be selected to join the IRP for 2 years in a laboratory with selected mentors, with funding from both sponsors. Another DCS interaction with the extramural community is the collaboration with the National Surgical Adjuvant Breast and Bowel Project (NSABP) in which the senior NSABP pathologist will spend time in the IRP working on the technology base with the Advanced Technology Consortium. The technology will ultimately be incorporated in the cooperative group mechanism. Finally, a sabbatical program is being considered in which intramural scientists would spend from 3 to 6 months in extramural laboratories or clinical situations.

Dr. Liu described a review process for clinical activities, which has been instituted. With assistance from the Board of Scientific Counselors (BSC), three panels with expertise in clinical trials, pathology, and radiation biology have been formed. Finally, a communications network, which includes an internet site and e-mail processes, has been instituted to strengthen communication.

Dr. Liu reported that the division is currently recruiting chiefs for the Pediatric and Radiation Oncology Branches, and Dr. Phillip Taylor has transferred from the Division of Cancer Prevention and Control (DCPC) to head the clinical program in developmental therapeutics. Dr. Liu stated that the DCS focus for the future will be on cancer genetics, cancer vaccine, molecular therapeutics (including therapeutic vaccines), experimental transplantation, and advanced technology. He introduced Dr. James B. Mitchell, Chief, Radiation Biology Branch (RBB), to report on a new direction in imaging made possible by the application of advanced technology.

Dr. Mitchell explained that the project, initiated in the RBB in 1990, deals with the development of in vivo free radical imaging techniques that involve Fourier transform electron paramagnetic resonance imaging (FT EPRI). He reviewed the association in varying degrees between oxidative damage and various disease states—such as atherosclerosis, immune response, allergies, and neurological disorders—and between oxidative damage and cancers of the breast, colon, and lung. Some theories indicate that there is a leakage of free radicals produced as part of the breathing and oxygen-metabolizing processes beyond the protection afforded by antioxidant enzymes. The challenge has been to measure the leakage of dangerous free radicals such as hydroxyl radical. Prior to the RBB project, this could be done only in vitro using electron paramagnetic resonance (EPR). A noninvasive measure of in vivo free radical production was needed, which could be achieved only through the use of EPRI. EPRI depends on faster electronics than were available prior to 1990; therefore, the challenges to the RBB investigators were to find a suitable probe and develop faster electronics. Two probes became available: nitroxide, which is a stable free radical molecule, and a carbon-centered free radical probe developed by NYCOMED, which was found to be nontoxic in animals. RBB investigators solved the second challenge by developing fast electronic gating switches, which operate in the nanosecond time frame. In addition, they developed detection systems capable of nanosecond response to recover minute signals coming from the free radicals. Finally, they used Fourier transform, an existing technology, for signal detection and image reconstruction, and, after a series of developmental stages, successfully imaged a free radical in vivo. In some of their earlier EPRI systems, a nitroxide spin probe called 3CTPO was found to be a free radical that protected against radiation. RBB investigators are studying the possibility that 3CTPO may be used to provide selective radioprotection in normal tissue compared with tumor tissue.

Dr. Mitchell noted that RBB electronics have progressively improved since the early studies

with the 8mm resonator that could image only small volumes. A 25mm resonator is being perfected, a 44mm resonator is being evaluated, and an 80mm resonator has been built. Dr. Mitchell showed the first in vivo image of a mouse tail produced using NYCOMED's spin probe and pulsed EPR. The imaging time was 2 minutes and the resolution about 0.5mm. Further refinements to the system include the capability to resolve the image 3 dimensionally and to image larger objects. The goal is to move EPRI into a clinical setting where the potential applications are assessment of oxygen levels in tissues; noninvasive detection of ischemia, stroke, myocardial infarction and pulmonary emboli through the vascular pathophysiology; identification of the physical architecture and metabolic profile of tumors; and in vivo assessment of free radical production, for example, to assess cancer susceptibility, chemopreventive and antioxidant agents, and changes in tumor and normal tissue during conventional chemotherapy and radiation therapy, as well as in a setting of reperfusion injury.

Questions and Answers

Dr. Royston suggested that the EPRI technology had a potential application in the early diagnosis of Alzheimer's disease in light of the recent demonstration by a group in San Diego of mitochondrial DNA defects and free radical formation in patients with Alzheimer's disease.

In answer to Dr. Philip Schein's question about a plan to ensure the rapid conveyance of new discoveries from intramural NCI laboratories to the extramural community, Dr. Liu described the two processes already in place: (1) the export and import of new technology through the Advanced Technology Consortium and (2) the transmission of ideas and technologies across bridges being built with the cooperative groups and the professional organizations.

Asked to clarify the unique contribution the intramural clinical program can make to clinical research, Dr. Liu emphasized that this question is kept constantly in the forefront of intramural operations. He suggested two unique contributions the intramural program can make to the excellent science ongoing outside the NCI: (1) high-risk projects without restrictions imposed by managed care, and (2) studies requiring a high level of patient surveillance, such as that required in experimental transplantation.

NCAB Citation for Dr. Sigal. Dr. Rimer presented a citation to Dr. Ellen Sigal on behalf of the NCAB. Dr. Sigal was recognized for her individual efforts to reduce the cancer burden in the United States through her tireless efforts in creating the Friends of Cancer Research (FOCR), a coalition of people and major cancer organizations working together to increase public awareness about the importance of cancer research. Dr. Klausner added to this citation the gratitude of the NCI not only for Dr. Sigal's effectiveness in communicating the need for prevention, treatment, and other research activities, but also as a model for uniting diverse communities to address an issue that touches everyone.

REPORT OF THE PRESIDENT'S CANCER PANEL
Dr. Harold Freeman

Dr. Harold Freeman, Chair, President's Cancer Panel, reported on the first of four Panel meetings to be held in 1997 on the overall topic "Concerns of Special Populations in the National Cancer Program." At this meeting held at Columbia University in April, nationally recognized experts in such disciplines as sociology, philosophy, anthropology, genetics, and epidemiology addressed the topic "The Meaning of Race in Science—Considerations for Cancer Research." Dr. Freeman reviewed areas of agreement across the disciplines, such as the contention that the biological concept of race is no longer tenable and that race should no longer be considered a valid biological classification. Race, as presented by the speakers, is the product of the nation's social and political history, and is a social construct. It is becoming increasingly difficult to classify people by race in a society that is moving toward a more multiracial identity

that embraces one's entire ancestry and cultural environment. Questions that arise are as follows: (1) How can race be characterized in this context and validly applied to research studies to improve health care for specific populations? and (2) How is the wide racial diversity just within the African-American or Native American communities, for example, accounted for in the design, interpretation, and application of scientific research. Dr. Freeman stated that these issues raise questions about the accuracy and usefulness of cancer statistics and racial subsets as they are currently collected, for example, through the SEER program.

Dr. Freeman summarized the remarks of several speakers at the Panel meeting. Dr. Sandra Harding, Professor of Philosophy at the University of California, pointed out that scientists work in society and the framework of society is often reflected inside the natural sciences. Assumptions that may be made in science often reflect the social conditions under which scientists survive. The questions, therefore, are how to select problems worthy of scientific pursuit with respect to race, shape the central concepts for research projects, or develop hypotheses to be tested and the research design used to test the hypotheses. Dr. Harding encouraged the scientific community to recognize these cultural frameworks and address them directly to increase knowledge. Dr. Marcus Feldman, a respected geneticist and Professor of Biological Sciences at Stanford University, indicated that studies using the new technologies for understanding, measuring, and conceptualizing the sources of human variation reveal that 85 percent of genetic variation occurs within populations—the so-called races—and 15 percent occurs between populations. He concluded that race does not exist from a genetic point of view, and stressed that the study of population genetics would lead to the best understanding of differences among groups. Dr. Solomon Katz, an anthropologist from the University of Pennsylvania, revealed a statement prepared by the American Association of Physical Anthropologists (AAPA) which notes that all racial categories were based on externally visible traits, primarily skin color and features of the face and underlying skeleton. The presumption was that visible traits could measure all other traits within an individual population. The AAPA statement concluded that there is no necessary correlation between biological characteristics and culturally defined groups. This conclusion leads to the question of how to characterize race so it can be applied validly to scientific research.

Dr. Freeman explained that the Office of Management and Budget (OMB) in its Directive 15 sets racial and ethnic standards in Federal reporting to respond to social and political needs of the Executive Branch and Congress. These same standards are being applied by directive in science. At the Panel meeting, Dr. Robert Hahn, Centers for Disease Control and Prevention (CDC), spoke about the public health implications of race and concluded that statistical counts, rates, and rations that distinguish by race, as it is currently defined, may not be truly meaningful. Dr. Freeman noted that the Panel believes, however, that race should continued as a category in science but with an understanding of the underlying assumptions being made when the categories are used. The Panel challenged the scientific community to review the social values that shape its scientific perspectives. The Panel believes that science and scientists need to examine the fundamental assumptions that have been made about race, including the biases and social context which have shaped the intellectual process with regard to race and scientific investigation.

Dr. Freeman pointed out that the SEER data show racial classification, but do not indicate the meaning of the classification. The Panel believes there is a need to separate the meaning of race from the meanings of poverty and culture, as well as to separate the social and political meaning of race from what is considered to be a biological meaning. The Panel concluded after the April meeting that racial classifications are socially and politically determined and not based on biological determinations. A question to be addressed is the extent to which biological differences are assumed by scientists and how these assumptions influence scientific conclusions. At issue is the need to disentangle the social and political meaning of race from its assumed biological meaning.

Questions and Answers

Dr. Rimer stated that the Subcommittee on Policy and Advocacy should consider addressing the role of the NCI in responding to some of the questions raised in the Panel meeting on the meaning of race in science. She noted that the topic should be revisited by the NCAB as a whole.

In response to a question about plans for disseminating the report of this meeting, Dr. Freeman stated that the Panel is considering a separate report for the President and that he hoped the NCAB would continue its efforts on behalf of the issue to ensure that the right questions are asked and the correct assumptions are made. Dr. Freeman has also been asked to write an editorial on the topic for a major cancer journal.

Dr. Klausner congratulated the work of the Panel on this important topic and concurred that the NCI should continue to emphasize these issues. He stated that in the discussions about how genetics will more and more define medicine, the NCI has the responsibility to deal not only with specific issues such as privacy and discrimination, but also with more subtle, insidious, and pervasive misconceptions about genetic determinism and genetic reductionism, which are the dangerous and inappropriate interpretations of genetics.

NEW BUSINESS SESSION I
Dr. Barbara Rimer

Dr. Rimer called on Dr. Robert Day and Ms. Ellen Stovall to moderate a discussion of priority issues to recommend for consideration by the National Cancer Policy Board (NCPB). Dr. Day noted that the recently established NCPB has held two meetings and is in the process of formulating an agenda of activities. He introduced Dr. Robert Cook-Deegan, staff director, NCPB, to present an update of efforts in this regard. Dr. Cook-Deegan explained that, unlike other committees convened by the National Academy of Sciences (NAS) and the Institute of Medicine (IOM), the newly established NCPB has not been given a particular task. Rather, it has been charged with setting an agenda and then pursuing that agenda in the form of reports and convening activities. To date the NCPB has made a commitment to balance its activities among cancer prevention, control, diagnosis, and treatment, with tobacco control as its first initiative. Current plans are to follow a July workshop on tobacco control with a white paper, a policy statement that would be sanctioned by the NCPB. Dr. Cook-Deegan solicited ideas from NCAB members as to how the NCPB could be useul. He stated that the NCPB is beginning to develop a process for reviewing and prioritizing recommendations that are received. The Request for Comments document included in Board materials represents the first step in that process. He pointed out that the analytical capacity of the NCPB will be limited by the availability of staff, funding, and time. When asked if a mechanism is in place to deal with issues that require accelerated review or comment, Dr. Cook-Deegan stated that because the NCPB is operating under a standing contract, it should be able to move faster when needed. In response to questions, Dr. Cook-Deegan stated that the NCPB plans to operate in an open fashion, except when formulating recommendations or attending internal matters and that any NCPB report that contains findings and recommendations would be released to the NCAB and the public only after being subject to the standard NAS review process.

NCAB members recommended agenda topics for NCPB consideration as follows: (1) the formal consideration of what the National Cancer Program should encompass, for example, whether a national patient database is needed; (2) Food and Drug Administration (FDA) issues as part of the development of translational research into effective, useful products; (3) issues not being addressed by other bodies, such as the dissemination of education about cancer; (4) the distinction between cancer control research and cancer control application and dissemination in practice, not only for diagnostic and therapeutic technologies, but also for behavior change and

preventive technologies; and (5) the issue of payment for clinical trials. Dr. Cook-Deegan invited further suggestions by telephone, fax, or through the NAS Web site, WWW2.NAS.EDU/CANCERBD. Dr. Schein emphasized that communication is essential among the various groups working toward the same end, such as the President's Cancer Panel, NCAB, and NCPB.

Turning next to topics for the following day's business session, Dr. Rimer listed issues to be addressed as follows: (1) the resolution urging senior scientists in the extramural community to participate in the review process; (2) the proposed recommendations of the Task Force on Genetic Testing, particularly the need to monitor issues related to laboratory credentialing; and (3) the role of the NCAB in responding to concerns of special populations in the National Cancer Program raised by the President's Cancer Panel.

REPORT OF THE CANCER PREVENTION PROGRAM REVIEW GROUP
Dr. Richard Klausner, Dr. Edward Bresnick

To provide a frame of reference, Dr. Klausner stated that the report of the Cancer Prevention Program Review Group, chaired by Dr. Edward Bresnick, is one of the five commissioned in response to findings in the Bishop-Calabresi Report. Dr. Klausner commended the work of this Program Review Group and noted that, taken together, these reports promise to be defining events for aspects of the National Cancer Program and the activities of the NCI for years to come.

Dr. Bresnick stated that the key message of the report is that outstanding cancer prevention must be a key component in the National Cancer Program and must be appropriately funded. Prevention was defined as the development and evaluation of strategies for reducing cancer incidence aimed at preventing the initiation of the neoplastic process or at avoiding progression to malignancy of already initiated cells. One early activity of the Review Group was to decide that a division of prevention and control should exist as an organizational entity. Dr. Bresnick then reviewed the topics addressed in each chapter of the report and gave a summary of the Review Group's recommendations.

Modifiable Risk Factors. Modifiable risk factors considered were tobacco, diet and nutrition, physical activity, and infectious agents. Recommendations related to tobacco and tobacco products usage were: (1) develop more effective prevention and cessation interventions in populations where tobacco use has remained high; (2) recruit a senior investigator for a leadership role in developing and coordinating the tobacco research agenda; and (3) increase the proportion of investment in basic research and in effective interventions; decrease the investment in large-scale dissemination efforts. Recommendations for addressing diet and nutrition as a modifiable risk factor were: (1) recruit an outstanding scientist to assume a leadership role; (2) identify biomarkers for consumption of key dietary components; and (3) develop better methodology for the conduct of dietary intervention trials and to clarify promising research designs and strategies. Recommendations related to physical activity as a modifiable risk factor were: (1) identify objective markers of short- and long-term physical activity; determine mechanisms whereby reduction in cancer risk is achieved by physical activity; and (2) use intervention trials to identify behavioral strategies to enhance physical activity and assess the impact on cancer risk. In the area of infectious agents, the recommendation was to support better understanding (through basic and applied studies) of the role of microorganisms (including viruses) in the etiology of cancer, and develop appropriate vaccines.

Animal Models in Prevention. The Review Group considered the role of existing animal models, most of which derive from carcinogenesis models, in providing information that can be extrapolated to the human situation. They recommended that, for use in prevention research,

new in vivo and in vitro models should be developed that would use up-to-date knowledge on genetic and molecular alterations in carcinogenesis. A further recommendation was to develop intermediate biomarkers for the assessment of exposure and biological effects applicable in prevention studies and fully validate their use in appropriate animal model systems.

Genetic Predisposition and Detection of Precursor Lesions. Recommendations were: (1) expand identification of high-risk healthy populations based on genetic predispositions and develop new molecular markers; (2) investigate diverse nongenetic factors influencing expression of genetic predispositions and the response to interventions, including environmental exposures; (3) develop and expand existing biorepositories and provide appropriate access to such materials; (4) develop and improve new high-throughput technologies for implementation of promising molecular diagnostics; and (5) validate novel prevention detection strategies in comprehensive trials in targeted high risk populations.

Chemoprevention Trials in Human Populations. Recommendations were: (1) ensure that the randomized trial mechanism is the gold standard for demonstrating ways to affect incidence by developing a well-defined process of decision-making and by completing extensive preclinical studies, epidemiological analyses, and toxicity assessments in humans before randomized trials are initiated; (2) design recruitment strategies to attract healthy people as participants in cancer prevention trials; (3) restructure the Chemoprevention Preclinical Drug Development Program with the help of an Advisory Committee to be formed from the BSA; (4) continue to upgrade in vivo animal model systems for screening efficacy and safety of chemopreventive agents through use of the R01 grant mechanisms in addition to the present contract mechanism; (5) have frequent open competition for entry into master agreement contracts for development of new assays; (6) develop and validate biomarkers and intermediate endpoints in concert with those to be used in humans; (7) establish a Cancer Prevention Trials Group patterned after the oncology cooperative groups; (8) form a Committee for Biological Studies that could stimulate and review proposals for ancillary studies on tissues or DNA in ongoing prevention trials, as well as stimulate the use of best available methods for validating intermediate endpoints in existing trials; and (9) devise and implement mechanisms for furthering collaboration among the NCI, other NIH institutes, and organizations with interests in prevention to incorporate noncancer endpoints into trials.

Behavioral Research and Cancer Prevention Trials. The Review Committee believed strongly that behavioral research must be an integrated but independent component of the NCI prevention program. This would necessitate the recruitment of individuals who are capable of directing outstanding research programs. The program would be conducted at multiple levels, from laboratory-based research to small-scale hypothesis testing, to larger studies with the power to assess efficacy. Interventions that are developed would be ethnically, culturally, and gender appropriate. The priorities in developing the research agenda should focus on preventing tobacco use in children and teenagers; encourage cessation among heavy smokers and women; increase use of early detection tests, and improve behavioral outcomes of genetic testing. The Review Group recommended that an outstanding program should contain an epidemiological foundation, expertise in measurement and evaluation, a national database on key behaviors, knowledge of theories of behavior, understanding of the research basis for behavior change, and expertise in cancer risk communication. Further, the behavior research initiatives should be carried out through mechanisms that crosscut NCI, all of the institutes, and other organizations. Finally, the Review Group found the existing training programs to be deficient and recommended that new programs be created for the behavioral scientists who will function in the new scientific paradigms.

Training in Prevention Research. Recommendations in this area were: (1) assess current and future personnel needs in cancer prevention; (2) develop and support new mechanisms for retraining health professionals in cancer prevention and provide them opportunities to

contribute; (3) form a working group to make recommendations for training prevention researchers in the new scientific paradigms and evaluate the effectiveness of the programs; and (4) encourage the development of innovative training opportunities for prevention researchers.

Organization and Infrastructure of the NCI Prevention Division. The Review Group recommended that the NCI Prevention Division should be restructured by recruitment of outstanding investigators who would assist in formulating and implementing a strategic plan, assist in prioritizing goals, assess the need for and obtain the necessary resources, and facilitate interactions among and between the intra- and extramural communities. Other recommendations were: (1) stimulate interactions among units with cancer prevention research interests to facilitate translation of research results; (2) expand the current NCI BSA to include additional prevention research investigators and form a BSA subcommittee, supplemented by other experts, to serve as an advisory group to the Prevention Division; (3) evaluate the CCOP program to ascertain its contributions to prevention and consider best organizational site for the CCOP; (4) reevaluate and modify the preclinical cancer prevention drug development program with the help of the new BSA subcommittee; (5) form a Prevention Trials Group patterned after the Oncology Therapy Trials Groups; (6) develop mechanisms to rapidly respond to new research developments and fund outstanding spinoff studies in populations already in a trial; (7) develop databases on clinical prevention trials and on the availability of blood and tissue products from clinical trials; ensure that they can be accessed by all prevention researchers; (8) strengthen collaborative relationships with other prevention groups; and (9) work more closely with the FDA on matters affecting cancer prevention, e.g., utilization of validated biomarkers.

Questions and Answers

Dr. Sigal agreed that the Review Group identified many areas of scientific inquiry that are appropriate to pursue, but suggested that it may not be possible, within the context of the existing budget, to probe all of the areas adequately and yet maintain a balanced program. Dr. Bresnick pointed out that the current level of support for the cancer prevention effort within the NCI represents a significant investment, and he suggested that the recommended new initiatives could be done in the context of an evaluation of the expenditures for the existing program. He recommended cancer prevention as an avenue of opportunity that should be included in the Bypass Budget. Ms. Stovall pointed out that the group of about 7.4M cancer survivors represents a powerful cohort of people for behavioral and preventive strategies and interventions.

Dr. Peter Greewald, Director, DCPC, expressed appreciation for the report, which the Division would proceed to study in depth. He commented that the need for recruitment of additional people requires a resource allocation to make recruitment possible and a clear public commitment to help in the recruitment process. He suggested that continued advice might be needed, and he looked forward to interacting with the Cancer Prevention Program Review Group as the Division works to prioritize the list of recommendations.

Dr. Freeman asked if the prevention studies envisioned in the Report would approach the groups of people whose disease is related to poverty and culture in addition to those whose risks can be measured scientifically. He also asked whether the assumptions made by scientists in creating the new paradigms for prevention studies would be sufficiently sensitive to these issues. Dr. Bresnick pointed out that the Review Group dealt extensively with the issue of getting these populations into clinical trials. Methods and mechanisms must be developed to have an impact on these communities and get them involved in prevention trials and into the health care system, an important mission for the Cancer Prevention Division.

Dr. Pelayo Correa commented on the importance of prevention research and the inherent problems. He viewed the report not only as a concrete formula for application, but also as an

invitation for all scientists to help solve the problems. Dr. Paul Calabresi noted that the President's Cancer Panel would be holding its next meeting on aging and cancer and additional studies in this highly motivated population would probably be recommended. Dr. Hugh McKinnon, representing the Environmental Protection Agency (EPA) on the NCAB, commended the Report as the first step in developing a coherent intellectual framework for looking at cancer prevention, as well as for its emphasis on coordination between the NCI and other public and private agencies. He looked forward to the opportunity for increased collaboration with the NCI on cancer prevention activities and research. Dr. Ralph Yodaiken, the Department of Labor representative, agreed with the need for collaboration among the agencies and with the statement in the Report that "controlling carcinoma in the environment and in the workplace is really a political as well as a scientific chore." He challenged the statement that chronic exposure to carcinogens probably contributes to 5-10 percent of the deaths, noting that the figure is closer to 25 percent. He also suggested that these deaths are totally preventable.

Dr. Sigal cautioned about how funding figures for prevention are reported by mechanism, noting that the NCI is spending more in this area than is reflected in the NCI budget data. Dr. Klausner pointed out that the categorizing expenditures presents a coding problem, and he recommended moving toward more qualitative discussions and evaluations of program goals and activities. He listed steps to be taken in response: (1) members of the NCAB and BSA will be asked for written comments; and (2) an implementation group within the Institute will be appointed to begin organizing NCI responses, with advice and clarification from members of the Cancer Prevention Program Review Group. Dr. Klausner pointed out that the numerous recommendations in the Report encompass procedural and structural changes, intellectual challenges, and medium- to long-term responses. In addition, there is overlap between this report and the reports on cancer control, clinical trials, and therapeutics. The NCI will integrate the implementation and response to all of these reports in an ongoing process, and would report formally to the NCAB and the BSA on progress.

NEW INITIATIVES IN COMMUNICATION
Ms. Susan Hubbard

Ms. Susan Hubbard, Director, International Cancer Information Center (ICIC), reported on an NCI project begun in mid-1996 to develop prototype consumer-oriented summaries of Physician Data Query (PDQ) breast cancer clinical trials in collaboration with the National Association of Breast Cancer Organizations (NABCO). The completed summaries have been posted on CancerNet and on the NABCO home page. After the breast cancer summaries were prepared, other advocacy organizations were invited to assist critiquing them. With the help of the NCI Office of Liaison Activities (OLA), letters were sent to all advocacy organizations on the OLA mailing list, all organizations represented on the OLA Working Group, and chairpersons of cooperative groups with advocacy committees. The letters requested nominations of advocates who would be willing to participate in the review. A total of 92 reviewers were proposed, and each received a letter explaining the project, six sample summaries, and the glossary. Included in the letters was a list of questions designed to elicit information on preferences related to depth of information provided in the summaries, format, reading level, location of definitions, choice of format for receiving the summaries, and probable mode of dissemination. Many suggested changes in content and format were received and incorporated into the consumer-oriented clinical trials summaries. Although most of the responding advocacy groups indicated that they planned to circulate the information in hard copy rather than electronically at this time, the ICIC is preparing to provide the summaries in a format that will represent the full spectrum of communication media.

Ms. Hubbard showed slides comparing the original and modified versions of one summary. The modified consumer-oriented summaries of the protocols will feature an underlined hyperlink to

the full PDQ summaries and to a list of frequently asked questions designed to simulate a dialogue between physician and patient when a protocol is being presented. The questions were formulated with the help of physicians in the Medicine Branch, DCS, who have agreed to evaluate the reformatted abstracts of their own protocols and the frequently-asked-questions dialogue with newly diagnosed cancer in their clinics and inpatient units. Ms. Hubbard reported that she plans to conduct an evaluation of the entire protocol file this year to determine what kinds of elements should be added or removed.

Questions and Answers

In response to a question, Ms. Hubbard stated that NCI plans to include the consumer-oriented summary as a part of the PDQ protocol document. She noted that a continuing dialogue with consumer advocates promises to provide more ideas on presentation and that physicians who have reviewed the revised summaries consider them greatly improved.

When asked if the NCI was soliciting input from patients as to the amount of information to include, Ms. Hubbard explained that the Medicine Branch tests of the summaries with newly diagnosed patients being offered clinical trial participation will be the first opportunity for gathering first-hand information. In response to a suggestion about incorporating strategies that would allow patients to obtain increasingly detailed levels of information, Ms. Hubbard agreed that a series of questions with links to other resources could be included.

Dr. Phillip Sharp questioned whether the clinical trials summaries in themselves would convince a patient to enter a clinical trial and he pointed out the need for contact with a physician. Ms. Hubbard noted that the telephone number of the PI is included in each summary to put the patient in touch with someone who can provide counseling about the suitability of that specific protocol for the patient. NCI's objective in disseminating the protocol summaries is to respond to a demand on the part of patients to be able to know the full spectrum of choices. Dr. Sharp suggested that patients might be interested in receiving information in lay terms about the novel aspects of a particular approach to treatment, as well as the potential benefits to be derived from the treatment itself.

Dr. Kay Dickersin asked about plans to expand this initiative by starting trials from pharmaceutical companies that are currently not in PDQ. Ms. Hubbard stated that the report of a recently completed pharmaceutical industry survey, conducted in collaboration with the FDA, will be circulated to the NCAB in the fall. The survey attempted to identify any obstacles to submitting a trial to PDQ or any other clinical trials registry. Two tangible benefits from the survey are that the FDA is proactively promoting PDQ to pharmaceutical companies and the dialogues have begun with several large pharmaceutical companies on ways to encourage submission.

LEGISLATIVE UPDATE
Ms. dorothy Tisevich

Ms. Dorothy Tisevich, Director, Office of Legislation and Congressional Activities (OLCA) briefly reviewed recent hearings before Senate and House Subcommittees where Dr. Varmus and Dr. Klausner testified on biomedical research priorities and resource allocation issues. A full appropriations hearing was held before the Senate Appropriations Subcommittee on Labor, Health and Human Services, and Education where Dr. Varmus testified on the fiscal year 1998 budget, accompanied by all institute directors. In addition Dr. Klausner testified before Senator Arlen Specter and the Subcommittee on Labor, Health and Human Services, and Education at a hearing organized by the Friends of Cancer Research commemorating the 25th anniversary of the National Cancer Act, and at another hearing on the progress in cancer research. Ms. Tisevich next presented a summary of bills introduced in areas of particular interest to the

NCAB to indicate the volume of activity and the variation among the bills. The OLCA is tracking seven bills dealing with biomedical trust funds. Funding or financing for the trust funds would come from a variety of sources, mostly voluntary check-off on income tax returns. In the area of clinical research, an attempt to pass the Medicare Cancer Clinical Trials Coverage Act as a rider to another bill was unsuccessful, but sufficient interest exists for pushing this bill forward. The One Stop Shopping Information Service Amendment is gaining momentum in the 105th Congress, and the Department of Health and Human Services (DHHS) and NIH are actively assessing what enactment of this bill would mean for the NIH, because of the requirement to create one central data bank or information resource to provide information about all serious or life-threatening diseases. Two bills in the area of genetic privacy and discrimination, the revised Genetic Confidentiality and Non-discrimination Act of 1997 (S. 422) and the Genetic Information Nondiscrimination in Health Insurance Act of 1997 (H.R. 306/S. 89) are in early stages of deliberation, and it is not clear whether one of them will gain momentum and move forward. Although it has been modified, S. 422 is still regarded as too directive because of the potential for adversely affecting research.

The OCLA is also tracking legislation in the areas of health care reform, breast cancer (a total of almost 40 bills introduced, including one related to environmental causes of breast cancer) tobacco (directed toward labeling and advertising, insurance for children, smoking prevention in youth, federal regulation, and smoke free environment), and cloning research. Ms. Tisevich reported that neither chamber of the 105th Congress has introduced a revitalization bill for the NIH, but a few bills have been introduced that could potentially be folded into any reauthorization that might be introduced. These are the bill authorizing creation of a National Center for Integral Medicine within the NIH and the DES Education and Research Amendments, the latter with more emphasis on the education of health professionals and the public.

Questions and Answers

Dr. Freeman asked if Congress was thinking about how to tax the managed care system to pay for clinical research and development. Ms. Tisevich noted that the Clinical Research Enhancement Act raises some of those issues and attempts to identify remedies that would protect academic medicine in the managed care environment and provide incentives to attract medical school graduates into clinical research. Dr. Sigal asked for clarification about the budget mark-up and the OMB's interpretation of the budget deal as it relates to the NIH appropriation. Dr. Klausner noted that the question was raised at the House and Senate hearings as to whether their numbers are consistent with the numbers in the total health bill sent forth by the OMB, from which the NIH appropriations will come. There has been no suggestion of a change in the President's proposal for the NIH. Dr. Day asked whether the tax proposal for reductions in Medicare would affect the direct and indirect reimbursement for medical education in hospitals. Ms. Tisevich agreed to research this and report back.

PROGRESS REPORT OF CANCER CENTERS PROGRAM: PROGRAMMATIC ISSUES; REVIEW ISSUES--
Dr. Brian Kimes, Dr. David Maslow

Dr. Marvin Kalt reminded the NCAB that the NCI has agreed to be provide periodic reports tracking the progress of implementation of the recommendations of the Cancer Centers Program Review Group. He introduced Dr. Brian Kimes, Associate Director for Centers Training and Resources, DCTDC, to describe the programmatic aspects of implementation and Dr. David Maslow, Scientific Review Administrator, Grants Review Branch, DEA, to describe the grant review process that applies to the new guidelines.

Programmatic Aspects. Dr. Kimes reported on progress in developing the Interim Policies and Guidelines for Cancer Center Support Grants (CCSGs), that describe the purposes and objectives of the Cancer Centers Program and provide guidelines for submission and review of applications. Parts I and II of the guidelines are essentially complete. Accomplishments include elimination of redundancies and restrictions that were present in the old guidelines, de-emphasis of budget caps except for new centers, emphasis in the peer review and funding on the quality of science and value-added characteristics that the center provides, limitation of instructions to applicants and peer reviewers; flexibility to rebudget and pursue new scientific opportunities, and change in the review for comprehensiveness. The review for comprehensiveness will be conducted in two stages: the first is a review of the science and how the center is interacting across the range of basic, clinical, prevention, control, and population sciences to have an impact on cancer incidence and mortality reduction. The second part of the review will focus on center activities in the areas of outreach, cancer education, and cancer information. Parts III and IV of the guidelines are still in draft form, although Part III is essentially complete. In those sections that deal with the format for competing and noncompeting applications, the goal has been to minimize instructions, reduce the amount of required information, and limit the number of pages. Dr. Kimes reported that Parts I, II, and III were implemented in the grant cycle with the June 1 deadline and very few complaints were received from applicants. The draft for Part IV has not been released to applicants who are submitting noncompeting renewals. Other than that, all cancer centers are operating under the new guidelines.

Dr. Kimes reviewed changes in the planning grant mechanism, which was initiated in the late 1960s to stimulate the growth of the National Cancer Program. The planning grant is now an investigator-initiated mechanism, with a cap of $175K in direct costs per year. Although the new mechanism extends the grant to 5 years compared with the previous 3-year duration, an interim peer review to assess progress will be conducted by the parent committee for CCSGs. Another difference is the reduction to one receipt date per year, January 7. Dr. Kimes reported that a PA was recently advertised for the new mechanism and interest from the community has been high. A transition plan was developed for holders of the two active planning grants to bring them in line with the 1997 guidelines, and both have accepted one of the two options offered.

Dr. Kimes described the planned changes to guidelines for designation as a comprehensive cancer center. Because most CCSGs will receive 5-year approvals under the 1997 guidelines, centers that do not receive the comprehensive science approval initially will have a one-time opportunity during that grant period for re-review. A transition plan is now in place to move the current centers into greater equity in terms of the comprehensive designation relative to the new scientific standard for review. Dr. Kimes noted that Dr. Day, Chair of the NCAB Subcommittee on Cancer Centers, and Dr. Robert Diasio, Chair of the parent committee for CCSGs have agreed to review the applications for re-review. The DCTDC is working to develop a standard information format for use by all comprehensive centers to satisfy the outreach requirement. An outline for the plan is expected to be ready for the October meeting of the American Association of Cancer Institutes. Until the new format is developed, comprehensive cancer centers will be in compliance with the guidelines if they submit a statement of willingness to comply with that particular requirement.

Grant Review Process. With the task of rewriting the guidelines almost complete, the focus has shifted from the DCTDC to the DEA where NCI Grants Review Branch staff are preparing for the peer evaluation of CCSG applications submitted under the new cancer center guidelines. Dr. Maslow expressed confidence that the DEA review staff can meet the challenge of ensuring a fair review consistent with the spirit of the Cancer Center Program Review Group's report and the new guidelines. Because the 1997 guidelines are less detailed and have fewer review criteria, the judgment of the peer review teams in interpreting each element assumes greater significance. Moreover, it will be the responsibility of the parent committee to maintain a level

playing field among all the centers under review. Dr. Maslow emphasized that, to accomplish these objectives, the DEA will depend on the willingness of leaders in a broad range of scientific disciplines and leaders of the cancer centers community to participate in the reviews and serve on the committee.

Dr. Maslow stated that DEA cancer centers review staff have assisted in the development of the review criteria based on the new guidelines, worked with the DCTDC Cancer Centers Branch toward a consistent interpretation of the guidelines, and discussed review-related issues with the Cancer Centers Review Committee prior to the first reviews. Modifications in the process include simplification of the evaluation of shared resource budgets and incorporation of the comprehensiveness review in the core grant site visits and parent committee meetings. There is also an ongoing effort to educate the cancer centers community about the changes in the guidelines, the need for careful recordkeeping in support of shared resources, and the enhanced emphasis on research presentations. Finally, Dr. Maslow pointed out the importance of assessing the efficacy of DEA efforts and progress toward successful reorientation and reinvigoration of cancer center review. To that end, DEA staff will be in frequent contact with Dr. Robert Wittes, Director, DCTDC, and Cancer Centers Program staff to obtain feedback. Comments and suggestions are also requested from the NCAB Subcommittee.

MINI-SYMPOSIUM: MANAGED CARE'S IMPACT ON CLINICAL INVESTIGTIONS

Dr. Philip Schein, Dr. Lee Newcomer, Dr. William T. McGivney

Before introducing the speakers, Dr. Schein, Chair, Subcommittee on Clinical Investigations, reviewed the current perspective of the NCAB on the issue of managed care's impact on clinical investigations. In NCAB discussions and as a result of the survey conducted by the President's Cancer Panel, the consistent message has been that the new policies and practices accompanying managed care are not only having a profound effect on how medicine is practiced in the United States, but they are also having a serious adverse impact on clinical investigation, particularly translational research. In addition the impact on investigation, training, and education will be reduced priorities in certain academic programs. Dr. Schein noted that the Subcommittee is preparing for NCAB consideration a statement of policy in response to important concerns raised as a result of this growing trend. To provide a balance, the Subcommittee invited presentations from recognized national leaders of the managed care industry who are in a position to articulate the current thinking of that industry. The purpose of the symposium is twofold: (1) to ensure that the Board's perspective on these issues is sufficiently broad and that the rationale for decisions adopted by the managed care organizations is understood; and (2) to solicit suggestions for possible remedies or models by which patients, investigators, the NCI, and pharmaceutical industries can interact with managed care in the future. Dr. Schein introduced Dr. Lee Newcomer, Chief Medical Officer, United Healthcare, and Dr. William McGivney, Chief Executive Officer, National Comprehensive Cancer Network (NCCN), to participate in the discussions.

Dr. Newcomer examined the issue—How is managed care affecting clinical research trials?—by exploring three questions: (1) Is the problem really managed care? (2) How good is clinical trial performance? and (3) Should we do cancer research at all?

Is the problem really managed care? Dr. Newcomer presented facts to support his contention that managed care is unlikely to be the causative agent for the low accrual to clinical trials. In 1988, Dr. Vincent DeVita, then-Director, NCI, reported that only 1 percent of the eligible patients were being placed on clinical trials. At that time, managed care accounted for 13 percent of the market. Since then, accrual to clinical trials has increased to 3 percent, a time of growth also for managed care. Moreover, a United Healthcare offer in 1992 to pay for any woman who entered the priority transplant trial for breast cancer was taken up by only two

woman of 15M people covered by the company. Dr. Newcomer hypothesized that a more plausible cause for low enrollment in clinical trials could be that clinical research is competing with the economics of private practice. A second hypothesis was that patients have become consumers and expect the service and convenience offered by private practice that is often not delivered by academic medical centers. He acknowledged these as alternative hypotheses, but pointed out that available data suggest that managed care may not be the problem.

How good is clinical trial performance? Dr. Newcomer emphasized the importance of having performance data to judge the effectiveness of a venture. He contended that an undertaking that cannot be measured cannot be managed. For evaluating clinical trials, the criteria are valid study designs, adequate accrual, and published results. Dr. Newcomer related the difficulties encountered when he and his staff tried to determine how many of the 9,351 closed or completed clinical trials listed on the PDQ met these criteria. A second concern related to performance was that clinical trials do not appear to be driving relentlessly toward an answer. Dr. Newcomer supported this contention with the example of the North American Autologous Bone Marrow Transplant Registry which is funded by the NCI and yet succeeded in enrolling only 5 percent of its transplant patients to NCI high priority trials from 1989 to 1993. He pointed out that as a health care manager, he cannot identify a single study on which to base a decision to cover the procedure. An offer from United Healthcare to fully underwrite a retrospective study of the Registry's patients was refused on the grounds that to do so would prejudice accrual to clinical trials. Finally, Dr. Newcomer cited the Government Accounting Office report that stated "A large number of clinical trials are being conducted on bone marrow transplants for breast cancer apart from NCI randomized trials....Some experts have argued that many of these trials will contribute little useful information because the study population is too small, because the trial is not sufficiently well designed, and because the results will not be published." Dr. Newcomer noted that the challenge would seem to be to develop performance measures for improving clinical trials before a valid discussion can occur about coverage.

Should we do cancer research trials at all? Dr. Newcomer maintained that standards of care established through good research are not being translated to patient care by family practitioners or by specialists. In support, he cited the results of a study published in the *New England Journal of Medicine* designed to compare the therapy prescribed in a hospital setting for heart attack patients by cardiologists and by family practitioners. He also presented data from United Healthcare plans to show that, even with open access to specialists, diabetics most often do not receive the ophthalmology exam shown to significantly delay the onset of blindness or the standard of care blood test shown to prevent the complications of diabetes. Dr. Newcomer concluded that there is a barrier between finding good medical information and translating that into clinical practice.

Dr. Newcomer proposed an agenda for change: (1) set up a collaboration between managed care and the scientific community to identify ten priority trials for managed care sponsorship; (2) ensure that the results of every trial are published, whether the results are negative or positive; establish performance measures for clinical cancer centers; and (3) channel patients into the high-priority trials and support experimental denials by managed care outside those trials. He emphasized that the managed care industry must know what is good medicine in order to make coverage decisions. Dr. Newcomer expressed disagreement with a statement in the President's Cancer Panel document "Managed Care Role in the War on Cancer." In rebuttal, he cited studies from a United Healthcare monograph containing more than 65 studies taken from the literature, which documented the effectiveness of managed care and demonstrated a greater interest in improving health care than in saving costs. Finally, Dr. Newcomer eschewed the legislative solution to funding clinical trials and supported a collaboration among all who share the mission of improving health care to work together on finding and fixing the problems.

Dr. McGivney spoke from the perspective of one who has dealt with these issues on many

fronts, having worked for the American Medical Association (AMA) and Aetna Health Plans before joining the NCCN. He framed the issue as the question: What is the responsibility and role of managed care companies, specifically in the financial support of the clinical trial process? He proposed, however, that the issue should more importantly be: How can managed care companies and cancer centers work together to get patients, physicians, payers, and society definitive answers about the safety and effectiveness of promising technologies? Dr. McGivney pointed out the natural alliance that exists between academic medical centers and managed care companies in that both are dedicated to basing decisions on outcomes data in an era of accountability.

Dr. McGivney reviewed the evolution of the issue in terms of support of clinical research in the United States. Through the mid-1980s, the focus was on the fact that biomedical research funding was not keeping pace with inflation and many good ideas and proposals were not being funded. Managed care became a factor in the late 1980s, when insurance companies established formal processes and based their coverage policies on the availability of specific outcomes data in reaction to the litany of studies in the 1980s about inappropriate utilization. Moreover, the companies began enforcing the investigational exclusion provision already present in policies through retrospective denial of coverage or precertification requirements. The issue was polarized by the widespread use of two technologies—high-dose chemotherapy (HDCT) with bone marrow transplantation (BMT) or post-surgical chemotherapy support and interferon. In particular, the use of HDCT/BMT became a disaster for the health care community because of its promise for cancer patients failing standard therapy, the great expense, the potentially high-volume use, and the significant morbidity and mortality associated with it.

Dr. McGivney pointed out that, in terms of understanding technologies, two basic principles apply: (1) technology evolves along a continuum of accumulating evidence about safety and effectiveness; and (2) the risk/benefit analysis applies along the continuum of clinical policy and coverage policy. Because of the investigational exclusion clause, managed care companies are circumscribed by a binary decisionmaking process—a therapy is investigational or it is established. Dr. McGivney noted that the AMA, for its evaluations, has established the category "Promising" between "Investigational" and "Established" to recognize technology for which positive evidence for safety and efficacy is beginning to accumulate. He supported the recognition of this categorization by anyone making policy about either the use or coverage of particular technologies. Dr. McGivney next summarized significant initiatives in this regard (1) Aetna has integrated language about promising technology into its contracts (e.g., coverage for drugs used in Phase III NCI trials or for treatment IND/Class C drugs); (2) Dr. Wittes and managed care companies have met and formulated a general agreement whereby patient care costs will be covered for specific important clinical trials; (3) the Health Care Financing Administration (HCFA) is collaborating with the National Heart, Lung, and Blood Institute (NHLBI) in a clinical trial for lung volume reduction surgery which HCFA will cover; and (4) National Blue Cross/Blue Shield is applying a policy of conditional approval for coverage of BMT patients in cooperation with the NCI.

Dr. McGivney contended that individual discussion with the companies should be promoted and that the more progressive companies are ready to support patient care cost and work with the NCI. He maintained that managed care companies understand the concept of collaborating on clinical trials: they understand technologic evolution and want the data; they believe that they pay for most clinical trials anyway; and they want to work with cancer centers with a track record of distinction in research and publication. Dr. McGivney emphasized the importance of funneling patients to those centers. He also agreed that some managed care companies clearly seek to limit their exposure on this issue.

Dr. McGivney noted that although both sides are in conceptual agreement on this issue, several barriers exist on the part of the companies. The first is the investigational exclusion requirement

in all contracts, which insurers are legally bound to fulfill and which would be no small task to change. The second is the concern about the possibility of adverse selection. Another issue is the avoidance of arbitrary and capricious decisionmaking in terms of liability and the need for consistency in the decisionmaking process. A final barrier is the threat of antitrust liability, an issue in terms of directing patients to specific institutions and excluding other centers from access to those patients. Dr. McGivney noted that these barriers have been considered and are clearly surmountable. He concluded his presentation with a series of recommendations for managed care and for cancer centers. He proposed that managed care should: (1) explicitly pay for trials of promising technologies; (2) define the important trials through the scope of payment and begin to forge a relationship that will facilitate and enhance the capacity to do clinical research in the United States; and (3) develop a process where the companies and cancer centers can work together in integrating clinical trial participation into the company's case management system. In like manner, cancer centers should: (1) abandon a technology when the data define the therapeutic index as unacceptable; (2) work to define and communicate the inclusion/exclusion criteria and the appropriate referral points and work with case management; and (3) work with managed care to educate members about the clinical trial process.

Questions and Answers

Dr. Rimer called on Dr. Schein to moderate the discussion and asked that the focus be on the next steps that can be taken. Dr. Schein challenged Board members to consider the perspectives presented by Drs. Newcomer and McGivney and begin to prepare responses. Specific issues would include how to increase the percentage of the cancer patients in the United States participating in clinical trials; how to see that important questions in clinical research are addressed; how to ensure quality, efficiency, translation in the form of publications and rapid dissemination of information; and how to promote implementation of new technologies in the practice of medicine throughout the nation. He emphasized the need for developing a process for identifying the critical studies that require the active support of the NCI, industry, pharmaceutical companies, and investigational groups with the ultimate goal of determining the best and most cost-effective treatments.

Dr. Schein pointed out the reality that guidelines in the field of oncology are difficult to establish. The work of cancer researchers may always appear to be a little or very investigational because of the critical need to improve on current management of these tumors. However, investigators believe that financial exposure to managed care companies from participation in well-designed, efficiently executed trials would be limited, because the therapy or diagnostic is typically provided free and routine patient care costs already are an obligation assumed by third-party payers in any instance where care is being used. Dr. Schein asked the panelists to clarify the concerns of managed care companies in regard to financial exposure under the terms he had described. Dr. Newcomer responded that the primary issue is not the financial implications but the question of what managed care companies realize in results from the sponsorship of research. Dr. McGivney concurred that cost is not a major issue with larger, more progressive companies. He suggested that medical directors of managed care companies, on the whole, have a level of understanding of the broader issue such that individual discussions about participation in nationally sponsored versus institution-specific trials would be useful.

Dr. Dickersin recommended the clinical trials registry being developed through the Cochran Collaboration as a source of the types of data sought by the panelists. The goal of the registry is to identify all randomized trials that have ever been conducted worldwide, published and unpublished. Dr. Newcomer pointed out that the PDQ serves that purpose but repetition and overlap exists that calls for a process whereby investigators are encouraged to support existing trials rather than start a new one. He stated that preventing the overlap and repetition is difficult for the fragmented American medical system so the task must be addressed by managed care companies mandating for their own customers or in a broader forum like the NCAB. Dr.

Newcomer pointed out the dilemma that exists in that shareholders of the for-profit companies believe that funding clinical research is the role of the government and Congress, acting on behalf of the American public through the budget process, also appears unwilling to pay. A public policy debate may be needed to address these issues.

Dr. Klausner agreed that the problems will not be solved by casting blame but rather through discussion in forums such as the NCAB symposium. He agreed that the clinical trials system needs reform and the solutions proposed by the panelists are one approach. A more complicated aspect of the problem, however, is how to make participation in clinical trials user-friendly for the patients, doctors, and third-party payers. Dr. Klausner noted that the discussions with managed care proceed smoothly until the charged issues of criteria and antitrust liability are debated. He believed the NCPB in the National Academy of Sciences would be a neutral venue for a public policy debate on all of these issues.

Dr. Freeman concurred in the suggestions to bring all parties together and noted that representatives from the major businesses served by managed care should probably also be invited to join the forum. He agreed that the evolution of American health care brought on the need to manage costs. However, the new system pays for care as managed care defines it to be and does not permit the shifting of money to pay for indigent care and for training and research. Dr. Freeman contended that the combination of managed care and government cuts in Medicare/Medicaid leaves a void that must be addressed. He referred to the variety of managed care enterprises taking place, such as the acquisition of hospitals and the conversion to for-profit systems. He suggested that a greater percentage of the dollar is used for a combination of administrative costs, advertising, and distribution to stockholders, with little evidence of willingness, except for a few companies, to put money back into the system for teaching and research. Dr. Freeman suggested that a more equitable system would be for business, the government, managed care companies, and private industries to play a role in funding the future of medicine, including research and teaching.

Dr. Newcomer agreed that the cost shifting in medicine has ended, but noted that managed care has served a useful purpose in that it has become necessary for the nation to decide on a public policy as to whether the nation believes research and training are worth supporting, and if so, how to fund them in a direct, open, and accountable manner. Dr. Newcomer emphasized that managed care companies make choices on the basis of the value of the service, that improving the quality of the service is the most effective cost-cutting measure. Doctors are asked to perform to the medical literature standards.

Dr. Freeman explained that the President's Cancer Panel adopted the topic of managed care in response to concerns expressed by major investigators about the difficulty of doing clinical research in the present environment. He pointed out that the excellences apparent in the United Healthcare philosophy of operation are not consistent across the broad spectrum of companies in the United States. The Panel is seeing a market-driven, managed cost system at this point in the evolution in the country as a whole. The research that is being done is mainly directed toward evidence-based medical care, and much research enterprise is being denied that has to do with investigator-stimulated research. Dr. Freeman concluded that, with notable exceptions, the Panel saw that medicine is being treated more like a commodity than a human concern.

Dr. McGivney reiterated his call for individual negotiations with managed care companies, not a public policy debate, to convince the large companies that supporting NCI clinical trials would give them a competitive advantage in the market place. Dr. Royston expressed concern for the future of clinical investigators if they are constrained from conducting local clinical trials, which are the source of material for publications and, thereby, promotion. Dr. Newcomer agreed that the incentives for individual investigators are misaligned at this point, but he reemphasized the belief that the clinical trials seeking answers to the nation's most pressing problems should

have the highest priority among all investigators, without exception. Dr. Day raised the issue that the large global trials will not be good for young clinical investigators, who have the potential to bring new insights into clinical practice, largely through Phase I and Phase II trials. Dr. Schein agreed with the need for a balance between the smaller, innovative studies that create ideas and the larger trials, which exploit the ideas to conclusively demonstrate the safety and efficacy of the new treatment.

Dr. Calabresi commended the presentations as a clear picture of the managed care side of the story. On the other side, the President's Cancer Panel has heard much concern around the country about the changing medical care system. Although not solely responsible for the changing picture, managed care companies are very diverse and heterogeneous, making the problem harder to solve. Dr. Calabresi described the legislative approach taken in Rhode Island to create an equitable basis in which all companies can operate. Two laws mandate support for NCI-sponsored Phase II, III, or IV studies that were peer-reviewed according to NIH guidelines and reviewed by the CDC and FDA. Subsequent assessments reveal no increase in costs to the insurers. Dr. Calabresi pointed out that a funding source is needed only for Phase I studies and translational research in Rhode Island, and he favors a uniform tax for all managed care companies or a requirement for a set aside of money for clinical trials. He asked for comment. Dr. Newcomer questioned whether having managed care pay for the Phase I development of drugs, then also pay a profit to the pharmaceutical company for doing their R&D, would make good public policy.

Dr. Rimer stated that a subgroup of the NCAB would be formed to consider some of the suggested solutions and develop a policy statement about managed care in general and a set of recommendations as to what the Board thinks would be suitable next steps for the NCI.

NEW BUSINESS AND SUBCOMMITTEE REPORTS
Dr. Barbara Rimer

Dr. Royston raised the possibility of scheduling full 2-day meetings to allow adequate time for full discussion of topics such as those that followed the managed care symposium. An alternative solution was the scheduling of fewer items on the agenda to allow for more indepth discussion of some issues. Dr. Rimer agreed to ensure that future agendas reflect these suggestions.

Proposed items for the September agenda were: (1) NCAB policy statement on managed care and recommended next steps for the NCI, including a presentation by Dr. Edward Wagner who has been working on NIH-wide solutions in the office of the Director, NIH,; (2) report of the Clinical Trials Program Review Group; (3) race and science as it relates to cancer, for example, in the National Marrow Donor Program, with leadership from the Subcommittee on Policy/Advocacy; (4) the Cochran Collaboration as a model of a registry for systematic review of clinical trials; (5) RFAs and their use by the NCI; and (6) genetic testing and the draft recommendations of the Task Force on Genetic Testing.

Cancer Centers -- Dr. Robert Day

Dr. Day presented the minutes of the Subcommittee on Cancer Centers meeting for review and acceptance. The Subcommittee has been tracking the FY97 and FY98 budget for the cancer centers and will continue to review the appropriateness of the interim guidelines, as well as progress in implementing them. Because experienced and distinguished scientists will be important to successful implementation, the Subcommittee recommended that the NCAB make a commitment to developing a list of potential reviewers who have agreed to serve and who understand what is involved. Dr. Day presented a resolution prepared by the Subcommittee for Board action urging leaders in the cancer research community to participate. He moved

approval, and the resolution was adopted. A motion was made to accept the minutes of the Subcommittee meeting. The motion was seconded and passed.

CANCER SURVEILLANCE UPDATE
Dr. Peter Greenwald

Dr. Rimer introduced Dr. Peter Greenwald, Director, DCPC, to present an update on trends in cancer statistics as a response to Board questions about the sufficiency and accuracy of NCI systems for the tracking of mortality data. Dr. Greenwald explained that the DCPC Surveillance Program monitors the cancer burden on the population of the United States through measurement of cancer incidence, mortality, and survival. In addition, the program assesses individual societal and health service factors that affect these cancer measures, directly and indirectly. Incidence and survival statistics are derived from the SEER cancer registry system. The mortality statistics are for the entire United States and are almost 100 percent complete, affected only by the quality of reporting. Eleven reporting areas in SEER cover 14 percent of the U.S. population—12.5 percent of the U.S. white population, 12.3 percent African-American, 24.9 percent Hispanic, and more than 25 percent Native Americans, Asian Americans, and Hawaiians. The SEER budget is $16.5M for routine reporting, with an additional $4M for special studies. Dr. Greenwald noted that SEER data are adjusted for age according to the rates for each age group per 100,000 people as derived from the 1970 population census. The rates will be based on the 1998 projection of the 2000 census when that is completed, per a recent agreement with other agencies in the DHHS.

Dr. Greenwald stated that age adjustment permits a more valid assessment of the trends. He compared mortality data for cancer in the period 1969-1994 age adjusted for 1940 when the population was younger, for 1970 as in the SEER data, and for 1990 as used by Dr. Bailar in his *NEJM* article. According to the 1940 age-adjusted figures, the trend showed a 3 percent decrease in overall cancer mortality. The SEER data showed a 2.5 percent decrease; and the Bailar article reported a 1 percent decrease. Dr. Greenwald noted that, by all projections, this downward trend is expected to persist and grow over time. Incidence figures for all sites, according to the SEER data, indicated an increase in the early 1990s before tapering off, largely reflecting the effect of PSA testing and lung cancer trends. Dr. Greenwald explained that changes in a risk factor are not reflected in mortality figures for a couple of decades. For example, smoking by males began to decline in 1965 after the Surgeon General's 1964 report, but mortality in white males continued to increase until 1987, when it then began to decline. For African-American males, the peak and beginning of decline occurred in 1990. For all females, the decrease in smoking began in the mid-1970s, but a decline in mortality has not yet been seen. Decreases in incidence of colorectal cancer and mortality are believed to be affected by early detection and changes in certain dietary and lifestyle factors.

Breast cancer incidence trends showed an increase in 1974 attributed to publicity surrounding the reports of the disease in Mrs. Betty Ford and Mrs. Happy Rockefeller and through the 1980s coincident with the increase in mammography use. Breast cancer mortality trends began a decline after the NIH Consensus Conference and the consequent widespread adoption of adjuvant therapy. In prostate cancer, the dramatically increased incidence in 1992 was driven by the rapid introduction of PSA testing, which tends to identify prevalent as well as incident cases.

Dr. Greenwald reported that minority populations are tracked. Using slides showing the 5-year relative survival rates for men and women combined, he pointed out substantial differences in the overall survival rates for white and nonwhite men and women in prostate and breast cancer, some difference in colorectal cancer, and little difference in lung and bronchus cancer. Possible causes of the differences are socioeconomic level, access, etiologic factors, and biologic differences.

To illustrate the overall trends in incidence and mortality, Dr. Greenwald showed a graph of the estimated annual percentage change (EAPC) over the period from 1990 to 1994 for all sites measured together and separately. The only increase in incidence occurred in prostate cancer, but all sites taken together showed a decline. Mortality declined for all sites over the same period. By age group, the EAPC indicated that cancer mortality declined for both sexes below age 65 in all sites and increased above age 65.

Dr. Greenwald reported that the American Cancer Society (ACS) in 1996 estimated that 334,000 men would get prostate cancer. In 1997, this figure was changed to 210,000 by mutual agreement between the NCI and ACS, based on the new SEER analysis. Other new trends include the finding that breast cancer increased only in stage I. Dr. Greenwald concluded with a slide showing that the SEER program does attempt to factor out the impact of medical practice trends in its modeling. The SEER Web site makes the SEER database available to everyone, and was accessed 34,000 times in 1996. In addition, about 500 public use files have been distributed since October 1996, and NCI's Surveillance Program responds to thousands of inquiries from the public, Congress, and researchers. The program staff also collaborate with many scientists across the country to do or support projects related to patterns of care, costs, health behavior, and methodology and modeling. Finally, the SEER database has a Medicare linkage that partially satisfies the need for a database on cancer patients.

Questions and Answers

In response to a question, Dr. Brenda Edwards, Associate Director, Cancer Control Research Program, DCPC, reported that the program is working in each cancer site to disentangle the effects on incidence trends of the dissemination of screening information, detection tests, and new treatment strategies. Research and analysis strategies include modeling, comparing and synthesizing information from many sources, and meta-analysis. For example, incidence is being tracked through the Medicare/SEER linkage using data on the rate of biopsy and of PSA testing. The incidence of prostate cancer is being analyzed to factor out the effects of early detection, change in risk factors, and dissemination of some new therapy. Dr. Klausner added that he has asked a working group to answer questions about the continuously changing rates and to identify other approaches to surveillance and to the problem of disentangling the effects of emerging detection, diagnostic, and treatment interventions.

Dr. Correa asked if changes in diet are monitored as well as tobacco exposure. Dr. Edwards answered that health questions are being asked in conjunction with the American Stop Smoking Intervention Study (ASSIST) project, through the cancer control supplement of the National Health Interview Survey (NHIS), and through the National Health and Nutrition Examination Survey (NHANES). Dr. Greenwald provided the following information in response to other questions: (1) Surveillance Program staff have extensive contact with the CDC, the National Center for Health Statistics (NCHS), and the ACS to coordinate data collection and avoid duplication; (2) the ACS uses SEER data as a basis for their analyses; (3) NCHS mortality data are being provided earlier than previously so that the most current data can be used to arrive at SEER estimates; (4) the risks as calculated for prostate and breast cancer are lifetime risks, not risk over 5 years; and (5) an entire literature of studies, some from the 1960s, indicates that breast feeding is not a major factor in promoting breast cancer. Dr. Day asked how the changes in health care delivery affect incidence reporting. Dr. Edwards stated that it has become harder to get information because so much is taking place in an outpatient setting; however, the problem is more a delay in reporting rather than a deficit of information. The Surveillance Program is working with the CDC to study the question of coverage in the outpatient setting and the extent of the impact to SEER data collection. Dr. Greenwald described the cost implications of identifying and tracking the growing number of patients treated as outpatients to maintain the quality of data from SEER reporting areas like Detroit or Puget Sound where the populations are growing overall. He noted, however, that the Surveillance Program has been

well supported in this effort. Dr. Day observed that the change in mortality is an important phenomenon and constitutes the first step in controlling cancer. He emphasized the importance of the SEER database and the need to find the reasons for the changes in mortality and accelerate them.

MAMMOGRAPHY UPDATE: FUTURE RESEARCH
Dr. Barbara Rimer, Mr. Paul Van Nevel, Dr. Rachel Ballard-Barbash

Dr. Rimer introduced Mr. Paul Van Nevel, Associate Director, Office of Cancer Communications, NCI, to present an overview of the Breast Cancer and Mammography Communications Plan developed in response to the Board recommendations on screening mammography that were adopted by the NCI in March. Mr. Van Nevel described the communications objectives as increasing the percentage of women who have accurate perceptions about their risk, are aware of the new mammography recommendations from the NCI, and understand the risk factors for breast cancer and the importance of regular mammography. Another objective is to increase the percentage of health care providers who are aware of the latest, most accurate information on breast cancer and mammography, as well as the percentage of women with suspicious mammograms who understand the importance and availability of diagnostic and treatment options. Gateway audiences will be used to reach out to women age 40 and older, who are the primary audiences, and to health care providers. These gateway audiences include the Cancer Information Service (CIS), cancer-related organizations, volunteer and advocacy groups, other government agencies, and the mass media. Meetings have been held with all of the groups, and they have contributed to the planning process.

Strategies and tactics to reach the primary and gateway audiences include: (1) a national public education campaign done primarily through women's magazines; (2) a media event to launch the national campaign in September in collaboration with other sponsors of National Breast Cancer Awareness Month; (3) promotion of the NCI Web site as a source for mass media materials and for information on the new guidelines, as well as the risks and benefits of mammography; and (4) partnership with health professional organizations, federal agencies, the CIS and other cancer-related organizations to provide resource materials. An evaluation and research plan has been initiated, which includes conducting focus groups with intended audiences, pretesting materials, conducting baseline and intermittent tracking surveys, doing content analysis of media coverage, and tracking the percentage of women age 40 and older who are regularly screened for breast cancer by using the cancer control component of the NHIS; monitoring public service announcement airplay and media coverage of the issue; and analyzing bounce-back cards. Finally, the CIS quality assurance program will be used to provide information on the outreach contacts with 4,500 partners around the country. Mr. Van Nevel noted that Board members who expressed interest would be asked to help the CIS modify education materials as needed. The results of the research conducted in implementing this information program will be published, and some of the individual reports will be made available, before publication, to the Board and collaborating organizations. In a separate project, the CIS is working with Dr. Susan Blumenthal to develop information on how to communicate risk information about breast cancer for inclusion in the plan that has been developed. Ms. Zora Brown suggested that the list of gateway audiences be expanded, and she agreed to help Mr. Van Nevel in that task.

Dr. Rimer next introduced Dr. Rachel Ballard-Barbash, Chief, Applied Research Branch, DCPC, to discuss the Branch's international collaboration in the area of breast cancer screening information. The presentation was scheduled as part of the mammography screening follow-up to give Board members an overview of some research. Dr. Ballard-Barbash presented one model for a breast cancer screening effort that might be relevant if there is an interest in developing international breast cancer screening surveillance systems. The International Breast Cancer Screening Database (IBCSDB) was conceptualized by Dr. Sam Shapiro and initiated in

1988 through a series of meetings with scientists in 11 countries that had initiated or planned to initiate population-based screening programs. The purpose was to provide a mechanism for the comparison of data from population-based screening programs in various countries, in order to facilitate the most effective and efficient contribution of screening for breast cancer control worldwide. Dr. Barbash-Ballard emphasized that this effort does not address the efficacy of mammography or obtain data from randomized clinical trials. The various programs were asked to structure the following types of data into their data collection systems: (1) screening policies recommended; (2) target groups for screening; (3) number of women actually screened; (4) outcomes of these screening examinations in terms of follow-up biopsy and recall rates; (5) follow-up of screened women; (6) trends of breast cancer incidence and mortality in each country; and (7) quality assurance procedures. The following objectives of the Database have been accomplished or are in progress: (1) facilitate collection of comparable data; (2) develop a standard set of tables and definitions; (3) facilitate agreement on the outcome measures to evaluate program effectiveness; (4) use these measures to compare the effectiveness of policies in the different countries; and (5) encourage communication regarding research results and use of these population-based programs. She suggested as an excellent reference document the European guidelines published in June 1996 by the Europe Against Cancer (EAC) Program. Additional information is available in a manuscript summarizing the results from two surveys. The first in 1990 was conducted in 10 countries. The second involved 22 countries and was a collaboration with the EAC, which had initiated a series of pilot programs to assist the implementation of breast cancer screening programs throughout Europe.

Dr. Ballard-Barbash concluded by noting the growth in the number of countries with organized breast cancer screening programs, most of which are structured to allow comparable data collection for research and evaluation purposes. Her entry into the IBCSDB working group came at a point when the EAC had already been funding the pilot programs and was midway through developing a statement on quality assurance. With the increased organization of European programs under EAC, the IBCSDB working group is focusing on targeted data collection. Still needed is international sponsorship to facilitate data collection; in particular, research grants on targeted issues from an international group would provide more information on utilizing a database of this sort. Finally, she reported that the data collection recommendations of the IBCSDB effort were considered in the development of the U.S. Breast Cancer Surveillance Research Consortium through which data on community screening are being collected at nine sites throughout the United States.

Questions and Answers

Dr. Rimer asked whether the Database has reached a point in development where investigators would provide the individual level data needed to assess what is happening in women of different ages. Dr. Ballard-Barbash explained that the Database had not yet reached a point where data have been provided to a central source from all countries. She estimated that it would not be a source for such data within the next year. Moreover, the EAC has found many differences among the various programs and how they collected data, greatly increasing the time needed to analyze the collected data and make a statement with some validity.

PROPOSED MODIFICATIONS OF NIH REVIEW AND AWARD POLICIES
Dr. Marvin Kalt

Dr. Kalt reported on extramural policies evolving within corporate NIH that have potentially profound implications on the makeup of the research portfolio that falls within the RPG budget line. The policies also affect how the NCI considers applications for funding. Applications received on or after October 1 will be reviewed according to the new RPG criteria statements in the February 1998 review cycle. The new criteria, which are being implemented across the NIH, were recommended by the Peer Review Oversight Group (PROG), an advisory body assembled

by Dr. Wendy Baldwin, Deputy Director for Extramural Research, NIH, at the request of Dr. Varmus. The evaluation criteria to be applied to R01s, R29 FIRST awards, and P01s are significance, approach, innovation, investigator, and environment. Reviewers will be asked to write structured remarks against these criteria and consider them in assigning the overall score, but the criteria will not be weighted individually. Dr. Kalt noted that the explicit requirement for innovation caused concern among clinical researchers about how innovation in the area of clinical research would be defined. In the end, the individual study sections, which will receive comparable instructions, will define how these criteria are applied to specific kinds of research. The overall approach to voting a priority score remains unchanged, but the summary statement will contain references to the five required elements. Dr. Kalt reported that discussions within the PROG suggest that the question of impact or significance of the proposed research will contribute largely to scoring decisions. The NCI Grants Review Branch will adapt the new criteria to P01 applications as needed. Interpretations developed in response to areas of ambiguity will be brought to the NCAB in the next round so that the procedures used by the NCI to implement these criteria can be seen. Dr. Kalt postponed his presentation on the Modular Grant Award until a later date, but directed Board members to the material contained in their meeting notebooks.

Questions and Answers

Dr. Rimer emphasized the need to ensure that the research community is made aware of the new grant rating system. Dr. Kalt replied that the changes have been covered in all of the scientific press and are available on the NIH Web site. He introduced Dr. Olivia Preble, Chief, Grants Review Branch, NCI, to describe the most recent implementation decisions of the Review Policy Committee (RPC), a trans-NIH committee of all review chiefs. Dr. Preble reported that a subgroup of the RPC is considering how the new criteria will be applied to program projects and other multi-project awards. Staff in the NIH Office of Extramural Research are planning several announcements in the NIH Guide, which will apply to applications received on or after October 1. Dr. Preble noted that there will be an emphasis during the summer on educating the applicant community and both types of reviewer groups the study sections and the targeted review committees in the institutes.

OFFICE OF LIAISON ACTIVITIES
Dr. Alan Rabson, Ms. Eleanor Nealon

Dr. Alan Rabson briefly reviewed the origins of the Office of Liaison Activities (OLA), which was organized by Dr. Klausner primarily to develop and strengthen NCI relationships with the consumer advocacy community and later expanded to include liaison with scientific and professional organizations and other Federal agencies. Ms. Eleanor Nealon, a distinguished medical journalist in the NCI Office of Cancer Communications, was appointed Director of the new office. Dr. Rabson stated that a program of introductory meetings has been initiated in which representatives of scientific and professional organizations and Federal agencies meet with him, Dr. Klausner, OLA, and other NCI staff to discuss mutual expectations and identify areas where joint activities can be planned.

Dr. Rabson then introduced Ms. Nealon to present an update on the newly organized Director's Consumer Liaison Group (DCLG). Ms. Nealon noted that the 15-member group will bring together advocates from diverse communities to interact directly with the scientific community at the NCI on a wide range of programs and issues. The group will meet twice a year to advise and recommend to the Advisory Committee to the Director (ACD). Ms. Nealon reviewed the roles of the DCLG: (1) to help the NCI increase advocate representation on NCI advisory committees and other groups; (2) to provide a forum to help the NCI develop programs and research priorities; and (3) to increase collaboration with the cancer advocacy community. Ms. Nealon stated that the advocacy community has been involved from the beginning in forming

the DCLG. Also involved were the OLA Working Group and their Advocates Committee. The DCLG Planning Group (advocates and NCI staff) worked together since January to design the blueprint for the DCLG. They helped define its initial role, the eligibility and criteria for members, characteristics of the group as a whole, and the nomination, screening, and scoring processes. Nominations received will be screened for eligibility requirements, then scored according to individual criteria. Those receiving the highest rankings will be interviewed by telephone, and a final list will be presented to the NCI Director for his selection. Requests have already been received for 400 packages, but the number of actual nominations that the OLA will receive is not known. The nomination process is expected to be completed over the summer and a final slate drawn up in time to hold a first meeting of the DCLG in December. A plan has been developed wherein demographic information on all qualified individuals who cannot be included in the 15-member DCLG will be maintained in a special database, after receiving their permission. These individuals will be called on as opportunities arise to participate in the many NCI groups and committees.

Questions and Answers

Ms. Stovall commended the NCI commitment to opening the Institute to the public representation. Dr. Dickersin praised the quality of the information materials that were sent to advocacy organizations by the OLA. She asked about the policy for including consumers on all NCI committees, including peer review groups. Ms. Nealon stated that the NCI has an impressive record, with consumer representation on almost all groups, and efforts will be made to work with the review offices to improve and widen the pool of qualified people who could be called upon. Dr. Dickersin recommended that an evaluation of advocate experiences on study sections be conducted similar to that ongoing in the Department of the Army. Dr. Rabson noted that Colonel Rich, the Department of Army, has issued an invitation to NCI staff to attend a meeting about initial review groups with consumer representation, and plans are for appropriate NCI staff to attend. Ms. Nealon referred members to the meeting notebooks for further information on OLA projects and for results of a survey of OLA communication efforts with the advocacy groups.

ADJOURNMENT
Dr. Barbara Rimer

There being no further business, the 102nd meeting of the National Cancer Advisory Board was adjourned at 1:00 p.m. on Wednesday, June 18.

Advisory Home
Funding Opportunities

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