



NATIONAL CANCER ADVISORY BOARD

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

February 25-26, 1997

ATTENDEES

TABLE OF CONTENTS

[Call to Order, Opening Remarks, and Consideration of Minutes of Previous Meeting](#)

Dr. Barbara Rimer

[Future Board Meeting Dates](#)

Dr. Barbara Rimer

[Report of the Director, National Cancer Institute](#)

Dr. Richard Klausner

[Cancer Genome Anatomy, Project Update](#)

Dr. Richard Klausner

[Questions and Answers](#)

Dr. Lance Liotta
Dr. Kenneth Katz
Dr. Gregory Schuler

[Report and Discussion: American Association for Cancer Research](#)

Dr. Louise Strong

[Mammography for Women Under Age 50](#)

Dr. Richard Klausner

[Questions and Answers](#)

Dr. Donald

Berry
Dr. Otis
Brawley
Barbara
Rimer

[Subcommittee Report: The NCI Cancer Centers Program and Revised
Cancer Center Guidelines](#)

Dr. Elvera
Ehrenfeld

[Questions and Answers](#)

[Report of the Director, Division of Research Grants](#)

Dr. Edward
Bresnick

[Questions and Answers](#)

[Legislative Update](#)

Ms.
Dorothy
Tisevich

[NIH Annual Report: Implementation of NIH Policy on the Inclusion of
Women and Minorities as Subjects in Clinical Research](#)

Dr. Marvin
Kalt

[Questions and Answers](#)

[Annual Review of Delegated Authorities
Intramural Training Initiatives](#)

Dr. Marvin
Kalt
Ms.
MaryAnn
Guerra

[Questions and Answers](#)

[Report and Discussion: Association of Community Cancer Centers](#)

Dr. James
L. Wade, III

[Questions and Answers](#)

[New Business and Subcommittee Reports](#)

Dr. Barbara
Rimer

[Subcommittee on Planning and Budget
Ad Hoc Subcommittee on Policy/Advocacy
Future NCAB Agenda Items](#)

Dr. Ellen
Sigal
Dr. Kay
Dickersin

[President's Cancer Panel/NCAB: Discussion of Managed Health Care and
Panel report to the President](#)

Dr. Barbara
Rimer

[Questions and Answers](#)

[Update on DoD/VA Agreements](#)

Ms. Mary
McCabe

[Annual DEA Director's Report: FY96 Summary](#)

Dr. Marvin
Kalt

[Adjournment](#)

Dr. Barbara
Rimer

The National Cancer Advisory Board (NCAB) convened for its 101st regular meeting at 8:30 a.m., February 25, 1997, in Building 31, C Wing, 6th Floor, Conference Room 10, National Institutes of Health.

NCAB Members President's Cancer Panel

Dr. Barbara K. Rimer (Chairperson)

Dr. J. Michael Bishop

Dr. Richard J. Boxer

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

Dr. Sandra Millon-Underwood

Dr. Ivor Royston

Dr. Philip S. Schein

Dr. Phillip A. Sharp (absent)

Dr. Ellen V. Sigal

Ms. Ellen L. Stovall

Dr. Vainutis K. Vaitkevicius

Dr. Charles B. Wilson (absent)

Dr. Harold P. Freeman (Chairperson)

Dr. Paul Calabresi (absent)

Ms. Frances Visco

Alternate Ex Officio NCAB Members

Dr. P.C. Srivastava, DOE

Dr. Alison Martin, FDA

Dr. Marilyn A. Fingerhut, NIOSH

Dr. Gerald Poje, NIEHS

Dr. Ralph Yodaiken, DOL

Ms. Rachel Levinson, OSTP

Col. Louis F. Diehl, DoD

Dr. Hugh McKinnon, EPA

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

CALL TO ORDER, OPENING REMARKS, AND CONSIDERATION OF MINUTES OF PREVIOUS MEETING

Dr. Barbara Rimer

Dr. Barbara Rimer called to order the 101st meeting of the National Cancer Advisory Board (NCAB) and introduced guests representing cancer education, 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 November 1996 meeting. They were approved by the Board unanimously. Dr. Rimer welcomed Dr. Richard Boxer back to the Board after a successful bone marrow transplant. Dr. Boxer thanked the members of NCAB for their support and acknowledged the contribution to his recovery of the science and technology promoted by the National Cancer Institute (NCI) and supported by the American public.

FUTURE BOARD MEETING DATES

Dr. Barbara Rimer

Dr. Rimer called attention to the fact that the September 1997 meeting will start on a Wednesday. She asked Board members to review the 1999 meeting dates as listed and report any conflicts.

REPORT OF THE DIRECTOR, NATIONAL CANCER INSTITUTE

Dr. Richard Klausner

Dr. Richard Klausner reported on aspects of the NCI budget and program activity since the NCAB meeting in November, noting that the NCI remains on target with its funding plan for FY97. The overarching principle for allocation of the 1997 budget continues to be to fund the best science across all NCI funding mechanisms. Through the research project grant (RPG) pool, the NCI currently supports the payline through the 22nd percentile, plus those grants funded through Accelerated Executive Review (AER) in the exceptions process. The NCI was able to increase the payline from the 15th to the 23rd percentile in FY96, and the 23rd percentile is expected to be maintained even though the NCI funding policy for FY97 started at the 22nd percentile.

Dr. Klausner reported that the RPG portion of the budget, which represented 44 percent of the FY96 budget, was expected to increase to 45 percent in FY97, with a dollar level over \$1.1B for a total of 3,480 grants, up from the 3,300 grants funded in FY96. About 690 competing ROIs are expected to be funded compared with 670 in FY96, and the number could increase as the year progresses. Based on the current submission rate, a significant increase is projected in the number of RO1, R29, and PO1 applications that will be submitted to the NCI and recommended for funding. In contrast, preliminary data suggest that the number of applications received by the National Institutes of Health (NIH) as a whole may be decreasing.

Program project grants (POIS) represent a particular challenge. Current estimates are that 117 competing applications eligible for funding will be received; 89 applications were received in FY96. When the FY97 funding plan was developed, the payline was set at a score of 135

because an increase in the number of competing PO1 applications was anticipated, and the pattern of scores could not be predicted. The PO1 payline in FY96 was 140, and 39 competing grants were funded, 8 of which were exceptions. Dr. Klausner projected that the NCI would be able to fund significantly beyond the score of 135 through its exception process. In addition, a recent initiative has provided the division directors with additional funding and greater autonomy over grant exceptions funding; a significant portion of the additional funding is expected to go toward program project grants.

In FY96, the NCI funded 26 single research project grants totaling \$6.7M through the AER process, a success rate of approximately 41 percent; 40 percent of these were for patient-oriented research. In FY97, to date, the NCI has funded \$2.2M in patient-oriented research and \$2.8M in basic research. About \$8.3M has been allotted for an expanded AER. Patient-oriented research is at the 33rd percentile for the AER process, and all other RO1s are at the 27th percentile. The Institute maintains its commitment to hold the Intramural Research Program (IRP) to the highest level of scientific scrutiny, while continuing to reduce the IRP's share of the total NCI budget. In FY97, the IRP accounts for about 17 percent of the total budget, down from the August 1995 level of 22.8 percent.

Dr. Klausner announced that the President has submitted his FY98 budget to the Congress. Although the budget process for 1998 is still in the early stages, the NIH and NCI budget prospects are favorable. The President has requested a total budget for the NCI of \$2.44B, a \$61M (2.5%) increase over the FY97 budget. Within that amount, approximately \$225M is identified with AIDS research, which is proposed to be centralized to the Office of AIDS Research (OAR) and then allocated to each NIH institute. More than 80 percent of the increase will be directed into grant-specific programs, increasing the RPG pool to more than 45 percent as a function of the total NCI budget. The proposed funding for both noncompeting and competing grants provides for a 2 percent increase in the average cost, consistent with the agreed-upon NIH Cost Management Plan, compared with 4 percent in the FY97 budget. Although the Intramural Research budget line will increase slightly in actual dollars, its percentage of the NCI total will drop below 17 percent.

The budget for research management and support activities will remain flat for the third year. This was possible because of significant savings realized through the implementation of a number of streamlining initiatives. Excluding the Frederick Cancer Research and Development Center (FCRDC), savings are projected to be more than \$4M from a streamlined and accelerated contract review process for both research and support contracts; a threefold reduction in procurement time for scientific equipment; and improvements and changes in NCI information technology. Changes in information technology have included consolidating 48 information networks into 1 centralized network; consolidating 9 employee database systems into 1 system; using credit cards for procurement transactions; consolidating or eliminating animal care contracts; and implementing cost-management principles.

Streamlining initiatives at FCRDC have saved \$3.8M by reducing and consolidating clinical programs, redesigning administrative protocols, implementing more productive procurement strategies, and promoting the use of shared resources. Savings were achieved by initiating demand-side, management ordering agreements for more efficient energy utilization.

Dr. Klausner next reviewed NCI initiatives. The Intramural Advisory Board (IAB) has been working directly with the Board of Scientific Counselors (BSC) to update the review process and rewrite the manual of principles. Extensive changes have been realized in the Division of Clinical Sciences (DCS) under the leadership of Dr. Edward Liu. Two new initiatives within the DCS are the program to award competitive grants for interactive research and the Advanced Technology Consortium. In the first, 101s' National Cancer Advisory Board Meeting DCS scientists compete for Intramural Research Awards, which are funded jointly by the DCS and

the Office of the Director (OD), by preparing applications for collaborative research with individuals from within their division or across NCI divisions. The Advanced Technology Consortium will serve as the organizational structure for technology development, acquisition, importation, exportation, and implementation within the DCS. This new group will facilitate the transfer of state-of-the-art technology within the DCS and foster the movement of those technologies into patient care. Associated with this initiative is the new Advanced Technology Award, for which individuals can compete by writing applications setting forth innovative ideas for technology that can translate to changes in both research and patient care within that division.

Next, Dr. Klausner described NCI-wide initiatives introduced through Request for Applications (RFAs) that had been approved by the Board of Scientific Advisors (BSA). Three training awards are: (1) the Clinical Oncology Research Career Development Award, a K12 institutional award to stimulate recruitment and development of clinicians oriented to translational research and cancer; (2) a Mentored Career Development Award (KO1) to foster development of cancer research careers of outstanding minority junior scientists; and (3) an AIDS Oncology Clinical Scientist Development Program, an institutional K12 program to train people in the areas of both HIV and AIDS oncology. Another new initiative is a pivotal clinical trials program for agent development for chemoprevention, which will fund intermediate-size Phase I/II studies requiring well-defined biomarkers aimed at cancers of the prostate, breast, lung, colon, and bladder. Another chemoprevention initiative is a cooperative version of POIS in genetically identified high-risk groups. A BSA-approved initiative to be funded jointly with the National Institute of Child Health and Human Development (NICHD) and the National Institute of Nursing Research (NINR) focuses on the prevention and cessation of tobacco use by children and youth. This RFA was based on recommendations of the NCAB Behavioral Working Group.

Dr. Klausner listed another series of proposed initiatives that have been approved by the Executive Committee (EC) and are scheduled for BSA review: (1) an RFA funded through RO1s and R03s to promote research that will lead to a decrease in the physiologic and psychologic morbidity associated with long-term cancer survival—this initiative was based on the report of the November 1996 Cancer Survivorship Workshop; (2) an RFA to create a Health Maintenance Organization Cancer Research Network to begin to address the issue of the changing health care environment, focusing specifically on clinical trials, survivorship, behavior prevention and control, and surveillance and outcomes research; (3) an RFA to fund innovative approaches to diversity generation and smart assay development for cancer drug discovery; (4) an RFA to create a standing group for cooperative trials in diagnostic imaging; and (5) an RFA to establish the NCI Scholars Program through a K-type award. Under this new career development program, outstanding individuals would come to the IRP as independent but mentored investigators for 3 to 4 years. They would then move to an extramural institution and take with them a pre-funded K-type funding mechanism to smooth their transition.

Dr. Klausner reminded the Board that his report in November on the new Strategic Technologies Office (STO) included a request that the Strategic Technologies Task Force (STTF), an internal group, report to the EC on recommendations for integrating the whole area of technology development as it relates to the discovery process. Dr. Klausner commended the recently completed STTF report for its series of recommendations in six areas, and he encouraged review of the STTF report by NCAB members, noting that the EC has approved, endorsed, and would be acting on it.

Dr. Klausner reported that the Office of Science Policy (OSP) continues to move with its new informatics initiatives towards developing a dynamic science information system. One resource under development is the NCI Science Reports Database, which contains descriptive information about 150 meetings, conferences, workshops, and symposia sponsored or co-sponsored by the NCI from 1991 to the present. The Database, currently a single Web-based

document categorized by cancer site, is updated as information on recent meetings is provided by the NCI divisions. In addition to the title, date, location, and a brief description of each meeting, the Database provides links to meeting reports that are available in electronic format. A contract is in place to add a search capability, and a beta version is expected to be available to selected users by July. In a related informatics initiative, the Division of Extramural Activities (DEA) is developing a Web-based calendar and scheduling system that will allow on-line posting and viewing of information about NCI-supported meetings and related information. Users will also be able to link to existing meeting reports through this user-friendly interface to the World Wide Web (WWW).

Dr. Klausner reported progress in the NCI's efforts to establish the Director's Consumer Liaison Group (DCLG). The 15-member group will meet several times a year to help develop and establish processes and criteria for identifying appropriate consumer advocates to serve on NCI program and policy advisory committees, to serve as the primary forum for discussing issues and concerns that are important to broadening the development of NCI program and research priorities, and to establish and maintain collaborations between the NCI and the cancer advocacy community as a more formal process. The DCLG, whose membership will be chosen from nominations received from the consumer advocacy community, will provide advice and make recommendations to the Advisory Committee to the Director, NCI (ACD).

CANCER GENOME ANATOMY PROJECT (CGAP) UPDATE

Dr. Richard Klausner, Dr. Lance Liotta, Dr. Kenneth Katz, Dr. Gregory Schuler

Dr. Klausner reported rapid progress in the implementation of the Cancer Genome Anatomy Project (CGAP). The CGAP was an outcome of discussions with outside advisors in response to opportunities identified in the NCI Bypass Budget and is expected to accelerate the discovery process produce results that could alter approaches to cancer detection and diagnosis, choice of therapy, and prevention. The first of two goals of the CGAP is to develop the Tumor Gene Index (TGI), a comprehensive set of indices of genes and gene products that are expressed or altered in normal and to premalignant cells, malignant lesions, and other ~issues that are important in the process of malignancy. The second goal is to ensure that these indices, as they are developed, are coupled to the development and dissemination of new types of technologies to enhance discovery, detection, diagnosis, and the approach to patients, as well as the approach to populations in molecular epidemiology and in the growing new field of reverse epidemiology.

The CGAP represents a collaborative effort with funding from the NCI and other components of the NIH, the Department of Energy (DOE), and four industrial partners-Glaxo, Merck, Genentech, and Bristol-Myers. The specific aims in developing the TGI are: (1) identification of additional members of the minimal unique gene set with expressed sequence tags, such that expressed human genes are accessible through public databases; and (2) development of technologies for generating full-length 101s' National Cancer Advisory Board Meeting in *Science* on November 8, 1996. To simplify the process, Dr. Liotta and colleagues have implemented a fourth generation prototype. The film upon which the cells are transferred is incorporated into the cap of a vial so that, when the transfer is done under a routine microscopic visualization, the microdissected material can immediately be put into a vial for processing. The system is integrated into a pathologist's microscope so that the cells are microdissected, transferred to the cap, and then rotated into a vial by a rotating arm in a hands-off operation. Dr. Robert Bonner, a bimolecular engineer from the National Center for Research Resources (NCRR), demonstrated the microdissection technology for the Board. The NCRR is associated with the components of CGAP having to do with tissue samples, microdissected samples, cDNA libraries and associated sequences, and tumor- or tissue-specific arrays.

One important goal is to transfer this material into the CGAP cDNA library bank; the

microdissected library sequences go onto the Web page as soon as the sequences come back. Dr. Liotta reported that he and colleagues have successfully made microdissected libraries of premalignant prostatic intraepithelial neoplasia (PIN) lesions of prostate, normal prostate epitheliums, and invasive prostate cancer. The thousands of sequences from the prostate libraries have proven to be rich in content, with interesting correlations between the normal prostate epitheliums and the PIN lesions, compared with the invasive prostate carcinoma. One of the first papers related to this research has been published in *Cancer Research*.

CGAP Web Page Demonstration—Dr. Kenneth Katz

Dr. Klausner introduced Drs. Kenneth Katz and Gregory Schuler, CGAP collaborators on the NLM team headed by Dr. David Lipman. Dr. Katz reported that the National Center of Biotechnology Information (NCBI) has as its first task for CGAP the design of a tracking database for the TGI. The NCI will be the central management point of this relational database.

Dr. Katz explained the process for entering data and the relationships that occur in the database. Each tissue procured by the NCI for the TGI database receives a unique CGAP identification number (ID), which is generated automatically by the database. Microdissected samples of that tissue receive unique sample IDs, which maintain the information of the tissue's CGAP ID. This process continues as the tissue flows through the phases of library construction, library samples, arraying, cloning, and sequencing. By querying for this unique identifier, it is possible to assess the status of a tissue and all of the samples that derive from that tissue. Dr. Katz noted that the number of libraries to date exceeds the 45 that were projected to be available in the database by the end of the first year.

Dr. Katz explained that, to be useful to scientists and the public, it is necessary to decide whether a particular sequence is showing that an already-known gene or a new and unique gene has been cloned. Thus, each sequence received is compared with a collection of sequences called the UniGene dataset, an innovation of great importance to the generation of the TGI. Because one gene could be represented in the NCBI database by multiple sequences, it was difficult to determine the number of unique genes in the database. Therefore, Drs. Mark Boguski and Gregory Schuler organized all of the sequences in the NLM database to generate the UniGene dataset, in which each known human-expressed gene and its multiple sequences become a single UniGene cluster. When a new gene is cloned or a sequence is generated in the CGAP project, it can be compared to all known UniGene clusters.

Dr. Katz then demonstrated how the home page of the CGAP Web site can be used to extract information associated with reagents, clones, and sequences from the tracking database. The TGI relational database will also support data analysis using tools that have already been developed. Dr. Katz emphasized that the CGAP team at the NCBI would respond to the need for new and better tools for analysis as dictated by the new information that will be generated in the project. He projected that the Web site would be operational within the next few months and its availability would be publicized through established channels of communication.

Questions and Answers

Dr. Rimer asked how the TGI might promote understanding of diseases like ductal carcinoma in situ (DCIS). Dr. Klausner replied that the CGAP approach promises to be critical to the issues that surround carcinoma in situ whether it is for prostate, breast, or elsewhere. As the ability to detect disease improves, so must the ability to interpret what has been detected to arrive at the correct diagnosis and correlate that with prognosis. A question was asked about the status of the proposal for archival tissue isolation. Dr. Klausner responded that one technology being developed addresses the assessment of archival stored tissue, and NCI investigators have made progress in isolating DNA, RNA, and protein from archival tissue.

Dr. Kay Dickersin asked how the number of samples of each tissue type would be decided and how issues of diversity of tumor types and patient population sources would be addressed. Dr. Liotta answered that the structure of the first libraries will be based on histopathology, with no identifiers back to the patient. Dr. Klausner added that, in the first phase, discovery of genes for the index is immediately being coupled with the ability to array the index genes so that they can be used for discovery. Phase II will focus on questions similar to those on polymorphism variations, which cannot yet be answered; the process is continuous.

**REPORT AND DISCUSSION: AMERICAN ASSOCIATION FOR CANCER
RESEARCH (AACR)
Dr. Louise Strong**

Dr. Louise Strong, President, AACR, presented a review of AACR origins and current status as part of the NCAB's liaison with key cancer-related organizations. Founded in 1907, AACR is the oldest and largest cancer research association in the world, with more than 13,000 members internationally. The broad and diverse membership bridges research from the laboratory to the clinic and beyond, to epidemiology and prevention, and provides the AACR with strong representation from virtually all aspects of cancer research. The AACR's primary missions have been to facilitate communication and knowledge among scientists and to foster cancer research. This mission has been carried out primarily through dissemination of information among scientists through the AACR's four scientific journals, the annual meeting, 8-10 small yearly meetings, workshops, and outreach activities such as career mentoring, public education, and international collaborations. Communication, education, and training within the scientific community have traditionally been areas of AACR strength.

Over the past year, the AACR as an organization has been considering the need to reposition and redefine itself in areas of public outreach, public education, and public policy. A strategic plan was developed with the objectives of increasing AACR's role in fostering cancer research, using the strength of its membership to identify and set national priorities, developing a more proactive public education strategy, and strengthening communication with members of the cancer research community, the lay public, Congress, advocacy groups, and the NCI. Primary goals were to provide an authoritative voice for cancer research and public policy and effect a dramatic increase in funding for cancer and biomedical research.

The AACR's priority agenda issues for 1997 are: stable and flexible funding for cancer and biomedical research; support for clinical investigations; revitalization of the NIH Health Research Trust Fund; Food and Drug Administration (FDA) reform; health care delivery and managed health care; Medicare reform, particularly as it focuses on funding for cancer detection and prevention activities; genetics legislation; and tobacco regulation, with emphasis on limiting access to children. The AACR is also interested in the public policy issue surrounding legislation relating to genetic testing for cancer susceptibility. AACR's proactive outreach includes the new Clinical Investigations Committee; working for third-party reimbursement for NCI-sponsored clinical trials is a priority for this committee. Other AACR priorities include increasing support both for clinical and translational research and training for clinician scientists. AACR's public policy initiatives in recent months have included recommendations and statements to Congressional committees and testimony to the NCI Cancer Prevention Working Group. In addition, the AACR annual meeting in April will feature a report to the public on progress in cancer research. Finally, the AACR is establishing a task force on genetics and cancer legislation.

Regarding future directions, Dr. Strong noted that AACR is convinced of the importance of working as an organization in the areas of public policy and adopting a proactive approach to participation. *Ad hoc* task forces are being established to provide input for some of the public policy issues specific to the AACR mission of fostering cancer research. Efforts are being made

to increase interactions with other cancer organizations, patient advocates, survivors, and the NCI. In conclusion, Dr. Strong strongly endorsed many of the NCI's ongoing initiatives on behalf of the AACR and looked forward to maintaining an active dialogue and a positive, ongoing relationship.

MAMMOGRAPHY FOR WOMEN UNDER AGE 50

Dr. Richard Klausner, Dr. Donald Berry, Dr. Otis Brawley, Dr. Barbara Rimer

To introduce this discussion, Dr. Rimer noted that the NCAB was beginning a deliberative process consistent with its mandate as a presidentially appointed Board to advise, assist, and consult with the Director, NCI, with respect to NCI activities and policies. In this instance, the product will be recommendations about possible next steps in the process to define the NCI's position on mammography screening for women aged 40 to 49. Presentations that preceded NCAB deliberations included introductory comments from Dr. Klausner; an overview of data from the randomized trials on mammography screening presented by Dr. Donald Berry, Professor of Statistics at Duke University and a member of the 1997 NIH independent consensus panel; a presentation by Dr. Otis Brawley, Director, Office of Special Populations, on the shortcomings of the data on minority women; and a brief presentation on informed decisionmaking by Dr. Rimer. Questions to be addressed related to the message the NCI should send to women and providers, plans to craft the message, possible needs in the area of data monitoring, strategies for gaining access to individual data, and whether the NCI might invest in a Eurotrial along with the American Cancer Society (ACS).

Dr. Klausner affirmed that the discussion by the NCAB of possible actions by the NCI concerning mammography screening before the age of 50 is part of an orderly process by which the NCAB provides advice, oversight, and guidance for the NCI on matters of public importance. Dr. Klausner emphasized that communication about the issue of mammography screening and the age at which all women begin receiving benefit from regular screening will be anchored to the available evidence. The discussion, therefore, would focus on what the NCI can contribute and what research questions should be addressed now and in the future. The need to find better prevention approaches and curative therapies for breast cancer also must be considered.

Overview of Randomized Trials in Mammography-Dr. Donald Berry

Dr. Berry summarized some of the information presented at the recent NIH consensus conference together with various analyses of that information. Dr. Berry first reviewed the incidence of breast cancer by age for women in the United States. Using a line graph, he demonstrated that incidence increases with age with no significant increase at age 50. The average annual incidence between ages 40 and 49 is about 60 percent as large as the incidence between ages 50 and 69. Dr. Berry pointed out that an average percentage reduction over all ages translates into a smaller absolute reduction in the group aged 40-49, because of the lower incidence in this age group.

Dr. Berry pointed out that the standard and most appropriate outcome measure to consider in analyzing randomized trials is total breast cancer mortality regardless of age and regardless of the age of detection. Data from the eight (and only) randomized trials in existence were reviewed by the NIH consensus panel; five trials were Swedish, and the others were Canadian, Scottish, and U.S. (New York Health Insurance Plan [HIP]). Five of these studies showed a decrease in mortality and three showed an increase. Over all studies, the mortality reduction ranged from -14 percent to 44 percent; the average reduction indicated a 17 percent benefit for mammography screening between ages 40 and 49. Dr. Berry pointed out that these data change daily, and his attempt to obtain the trials data tapes was not successful. He advised that an effort should be made to obtain and use the raw data as a basis for establishing national policy.

Trial Characteristics. Two of the trials considered only women aged 45-49. Only the Canadian trial expressly addressed the 40-49 age group as part of the design. In the other trials, women between the ages of 40 and 49 were accrued as part of a larger cohort. The mammographic interval in the various trials ranged from 12 to 28 months, and the number of views was either 1 or 2. Dr. Berry pointed out that the major issue with regard to trial results is the uncertainty or variability in the estimated benefit. Using a graph that combined all participants from the eight trials, Dr. Berry showed that the variability is substantial within and across trials. With other graphs, he compared the curve that results when homogeneity is assumed (the Mantel-Haenszel "fixed effects" model) with the curve obtained when heterogeneity is considered (different reductions in each of the groups). Dr. Berry stated that both extremes are wrong, because there are differences and similarities among the studies. The main differences include the populations, technicians, mammographic schedules, numbers of views, types of controls, and lengths of followup. But there are similarities; the major similarity is that all studies addressed the same question. If differences and similarities are recognized and combined using a random effects (Bayesian hierarchical) model, a curve is produced that fits the data better than the Mantel-Haenszel assumption. The estimated benefit is the same, 17 percent, and the probability of a benefit based on this analysis is 80 percent.

Quantifying the assumed 17 percent benefit implies that 4 women per 10,000 will have their lives extended by regular screening, but the amount of extension is unknown. In a cohort of 1,000 women, based on a 17 percent reduction, Dr. Berry's estimate was that between 2,000 and 5,000 days would be saved for all women screened over a 10-year period. Reduction in mortality may be delayed up to 7 years as shown by comparing breast cancer mortality per 1,000 women in the control versus the mammography groups in the 5 Swedish studies.

Reservations. Because of the design of the studies, emphasis was on women in their later forties. The average age at mammography was 48 in these studies, and 30 percent of women were over age 49. In the Edinburgh and Malmo studies, the average age was greater than 50. An estimated 30-40 percent reduction in breast cancer mortality was a result of mammograms after age 49. Dr. Berry noted that the Eurotrial will consider only women who enter at age 40, which will give a better picture of the early forties. Another reservation was that some women (usually fewer than 20%) assigned to mammograms did not get them, and it is not known whether these women had a higher mortality rate. Conversely, some control women got mammograms, but that number also is not known. Only the Canadian study reported on mammograms in the control arm, and most of those were reported to be diagnostic. Findings suggest that if there is a benefit in the forties, it is concentrated in the late forties.

Another reservation was that Gothenburg, the Swedish study with the greatest reduction in mortality, had 8 percent more cancer in the control group. Dr. Berry also pointed out differences in data presented at various conferences, as well as differences in calculations of mortality reduction percentages when the same datasets were used.

Other Considerations. In arriving at a decision about mortality reduction benefit as shown in the eight studies, one consideration was that the studies included little information about the effect of the schedule for mammography and no obvious correlation of schedule with benefit. The studies also did not address the question of when to start mammography. Comparing ages 40-49 with 50-69, the absolute reduction in mortality for ages 40-49 was about 15 percent that of the older groups—that is, 4/100,000 (younger women) compared with 26/100,000 (older women). Moreover, benefit may be delayed in younger women. Dr. Berry analyzed the criticism of the Canadian study, which showed no benefit from mammography in the age 40-49 group. The NIH consensus conference panel had agreed unanimously that this study was important, and Dr. Berry concurred that it was well designed and should not be ignored.

Risks of Regular Screening. Dr. Berry listed the following risks of regular screening: the ~20

percent increase in number of cancers detected per 1,000 women; false positives estimated at 30 percent; and inconvenience, pain, and anxiety. Radiation-induced breast cancer mortality and false negatives, estimated at 25 percent, should not be counted as risks per se and they would be reflected in breast cancer mortality comparisons. With respect to the question of whether finding DCIS is a benefit or a risk, Dr. Berry argued that it is probably both because DCIS should be excised in some women and does not matter in others.

Dr. Berry concluded with the personal opinion that controlled trials provide some evidence of a small reduction in breast cancer mortality for women screened in their forties, but the evidence is not robust. Mammography has not yet been proven to be an imperative health measure for women in their forties. Women should be informed of the benefits and risks of screening. Some may reasonably choose periodic screening in their forties. They should be encouraged and supported, and the screening should be covered by third-party payers and health maintenance organizations (HMOs). Other women may reasonably defer screening and should not feel guilty even if cancer is eventually diagnosed.

Special Populations and Breast Cancer Screening—Dr. Otis Brawley

Dr. Brawley stated that his principal responsibility as Director of the NCI Office of Special Populations is to ensure that all people are included in the Institute's agenda. He said that his presentation would address some of the difficulties in special populations as they relate to breast cancer screening for women in their forties. Dr. Brawley urged that this discussion should not overshadow the fact that many more lives would be saved by extending screening to the half of women aged 50-70 in this country who are not receiving mammograms at this time.

Dr. Brawley showed data indicating that Asian American and Hispanic American women have breast cancer death rates that are slightly lower than those of white women. Hawaiian and African-American women have death rates that are greater than white women in the United States. Dr. Brawley pointed out that the higher mortality for African-American women in their forties has given rise to the theory that breast cancer screening recommendations for African-American women should differ from those for white women. He noted also that, of the eight studies reviewed, only the HIP study had enrolled a high number of minority women. There were no data in that trial for Hispanic women or other minorities. Because very few data exist on women of color in their forties. Dr. Brawley and NCI colleagues have planned a meeting with a group of people interested in screening in all minority populations. Included are cancer survivors, at-risk individuals, and representatives of appropriate scientific disciplines. Some of the issues to be discussed are: What are the questions that should be asked? What are the questions that can be asked? What questions are currently being addressed in the NCI portfolio of trials? What are the ethical limits in terms of what should be asked? These issues are important to address now because the Eurotrial planned for women in their forties will include about 97 percent Caucasian women. Thus, data needs for nonwhite minorities still will not be met.

Promoting Informed Decisionmaking about Mammography-Dr. Barbara Rimer

Dr. Rimer emphasized the importance of developing the necessary tools if future movement is toward patient and consumer participation and away from prescription of treatment, regardless of the exact nature of the NCAB recommendation. As a guideline, she proposed the definition adapted from Geller & Kass (1991), that an informed decision is one that is made intentionally and in the absence of control, with substantial understanding of the purpose, risks, and benefits. The kinds of information women need are: (1) risk of getting breast cancer for women of their age and race and personal estimated lifetime probability of breast cancer; (2) risk of dying of breast cancer ever and by a given age, and the reduction in chances of dying as a consequence of getting regular mammograms in terms of both relative and absolute risk; (3) possible

limitations of mammograms; and (4) potential benefits. Other relevant information would be a description of the procedure, the cost, and quality control. Women should understand the voluntary nature of the decision and be provided the opportunity to obtain further information either from their providers or from other sources in the community.

Dr. Rimer concluded that the ideal communication would tailor the information to a woman's age, race, and personal risk; correct misperceptions about risk, benefits, and limitations of mammograms; provide an opportunity to ask questions; and be delivered in a manner most appropriate for that individual. She challenged members of the Board to commit to helping each woman weigh the personal pros and cons as a critical part of her health care decisionmaking.

Questions and Answers

Mrs. Zora Brown asked about percentages of false positives in the 40-49 group versus the older group. Dr. Rimer noted current estimates that suggest a woman in her forties who has a yearly mammogram would have a 20-30 percent chance of having a false positive; the number would be half that for the older group. Dr. Berry explained that his figures addressed abnormal mammograms as a function of age, and most abnormal mammograms in both age groups are false positives. In the older age group, however, the ratio is 10-15 abnormal mammograms per 1 cancer detection; in the younger group, the ratio is 40-45:1.

Dr. Philip Schein pointed out that a previous meta-analysis calculated a benefit of 14 percent using the same eight studies and included the Canadian study. This was not considered statistically significant at the time. He asked whether the data were static or whether the current estimate of 17 percent benefit with statistical significance suggested that the data were moving in an increasingly positive direction. Dr. Berry noted that the main difference in the numbers was a result of adding the second Malmo study of women aged 45-49, which was highly positive. There is a suggestion that the data are not static, but the question of extent of change is difficult to answer. Dr. Rimer pointed out that the later figures also represent more years of followup and more cases of cancer, which allow a greater chance of detecting a difference.

Dr. Ivor Royston asked for clarification of a comment in the letter from Dr. A. B. Miller, Canadian National Breast Screening Study (CNBSS), which stated that "In the HIP Study, there was a suggestion of benefit for women enrolled at ages 40-44, but less for women ages 40-49, and in the CNBSS there was also a suggestion of benefit for women enrolled at ages 40-44, but the reverse for women ages 40-49." Dr. Berry commented on the difficulty of assessing benefit depending on age and suggested that the differences could be random.

Mrs. Brown expressed a preference for discussing mammography in conjunction with treatment issues. Dr. Harold Freeman pointed out that many women who have mammograms in time are lost to followup, particularly in poor populations, and this should also be addressed. Ms. Frances Visco proposed that the focus should shift to women over 50 who have no access to mammograms and to women who are diagnosed with breast cancer but have no access to treatment.

Dr. Alfred Goldson and Dr. Dickersin asked how reliable the 17 percent reduction is as a real number, what the confidence intervals are, and whether one model fits the data better than others. Dr. Berry stated that the probability of a benefit is 80 percent and the best estimate of the benefit is 17 percent. He favored the confidence interval 0 percent to 35 percent based on the model that takes both heterogeneity and homogeneity into account.

Dr. Schein commented on the importance of refining understanding of how mammogram screening can be used in this specific age group, because this modality has a potential to make an impact on survival, whereas advanced-disease treatment at this time does not. Dr. Vainutis Vaitkevicius noted that the information available at this point will not support recommendation

of any specific interval at which every patient needs to be tested. He suggested devising guidelines that communicate to patients a method for making these decisions. Dr. Frederick Li suggested that a monitoring committee should be established to keep the Board informed on an ongoing basis.

Dr. Goldson commented that his group at Howard University Hospital has new information relating to the diagnosis of breast cancer in the African-American population treated at the hospital. Thirty percent of Howard's patients with breast cancer were found to be in the 40-49 age group. The data will be published soon. He suggested that these are representative studies to consider as the Board makes its guidelines and recommendations.

Dr. Rimer summarized the discussion on screening mammography for women in their forties. She stated that a subcommittee of the Board is needed to develop recommendations related to screening mammography and to consider how to improve the data monitoring process. The Board must make recommendations about the message to be communicated and what communication products are needed to enhance informed decisionmaking. The Board should consider Dr. Berry's analysis and other materials that were provided. The message should reflect that mammography is only one part of a process that includes followup and treatment. The recommendations should be completed in 1 or 2 months.

**SUBCOMMITTEE REPORT: THE NCI CANCER CENTERS PROGRAM AND
REVISED CANCER CENTER GUIDELINES
Dr. Robert Day, Dr. Robert Wittes**

Dr. Robert Day presented the report of the Subcommittee meeting for Board consideration. Issues concerning the restructuring of the Cancer Centers Program submitted by NCAB members after the previous meeting had been organized and sent to Dr. Robert Wittes, Director, Division of Cancer Treatment, Diagnosis, and Centers (DCTDC), at the end of January. The comments fell into several broad categories: (1) lack of a "clinical" designation for centers that were neither comprehensive nor basic centers—the word "research" was not included as part of the designation; (2) de-emphasis of training, education, outreach, and information dissemination in the comprehensive center guidelines; (3) emphasis on scientific excellence (for planning grants) that could more narrowly draw from the pool of potential applicants; and (4) inadequate geographical distribution of centers.

Dr. Wittes summarized the NCI responses that have been incorporated in the revised guidelines for the Cancer Centers Program. "Clinical cancer center" was added as one of three designated types; "comprehensive cancer centers" and "cancer centers" are the other two types. The guidelines were revised to provide greater flexibility in writing, interpretation, and peer review of applications to encourage research agendas that address the needs of special populations and the opportunities presented by special populations. To remove barriers to attaining cancer center status, planning grants were marked for modification and will probably take the form of a standing program announcement (PA) with somewhat higher standards for applicant approval than in the past. This would provide institutional funding for a period of approximately 5 years to develop programs and critical masses of personnel that would ensure strong P30 applications at the end of that time. Moreover, scientific excellence would continue to be the bedrock of the Cancer Centers Program.

For outreach and education issues, the NCI plans to establish a centralized compendium of activities (on paper at first and in an electronic format later) in these areas and award the comprehensiveness designation partly on a center's willingness to submit their activities for entry into this database. Further, the NCI proposes establishing a competitive program to stimulate the development of improved strategies for outreach and provision of information and education, in ways that relate to cancer. On the issue of the geographical distribution of centers,

Dr. Wittes proposed a continuing dialogue with the NCAB as one approach to identifying strategies that lie within the scope of a scientifically driven organization such as the NCI. Finally, the word "research" was not made part of the cancer center designation in the absence of a Board consensus in this regard.

Dr. Wittes concluded that the current draft of the guidelines incorporates the substantial input of the cancer center community and the NCI's advisory boards, including the NCAB. He asked for the Board's approval of this draft as an interim document, to be labeled as such. The interim guidelines would begin the process of restructuring the Cancer Centers Program by enabling the NCI to complete a year or two of recompetitions and reviews and return to the Board for an interim assessment.

Questions and Answers

Dr. Li suggested that outreach and educational research should be supported by additional core support analogous to that provided for biostatistics, because of the difficulty of establishing credibility in the surrounding community without steady support. Dr. Wittes stated that biostatistics is included in the Cancer Center Support Grant (CCSG) because it directly serves the clinical research, laboratory research to some extent, and population research of the institution. An applicable criterion is whether the outreach, education, and provision of information is being done in a service or research mode.

On the issue of geographical distribution, Dr. Ellen Sigal suggested that the Board should have a mechanism for determining whether areas are grossly underserved and should be the focus for a center of excellence, research center, or clinical center. Dr. Pelayo Correa added that lowering the rates of cancer incidence will require reviewing which groups have the highest rates and providing the opportunity for the scientific development of talented young people across the United States to solve the problems of the underserved. Dr. Wittes agreed that this was an appropriate agenda item for the NCAB Subcommittee on Cancer Centers to address.

Ms. Ellen Stovall asked what the plan was for integrating recommendations of the Cancer Control Program Review Group (CCPRG) that could have an impact on the Cancer Centers Program. Dr. Wittes replied that the Guidelines would acknowledge the CCPRG and would include the part of the CCPRG text that defines prevention, control, and population areas. The process would involve monitoring CCPRG communication with the Institute for further definition of the area of cancer control and modifying the Guidelines as appropriate. Modifications would be submitted for Board review.

Dr. Rimer raised the issue about provisions for establishing the infrastructure for outreach as well as other cores needed in support of research. Dr. Wittes pointed out that the shared resources section is written to incorporate complete flexibility in the centers' ability to propose any cores that they can justify to the peer review as serving a research function in the center. In response to a question about the timeline for the planning grant initiative, Dr. Wittes proposed formulating the concept for discussion at the June Board meeting.

Dr. Day moved adoption of the revised document as the Interim Guidelines. Dr. Schein reminded the Board that the Subcommittee on Cancer Centers had agreed to monitor the Interim Guidelines to determine their impact in fulfilling the public perception of a comprehensive cancer center, and would be prepared to revisit the guidelines if a negative impact was discernable. Dr. Day amended his motion to include a revisitation of the Guidelines within 1 to 2 years, with monitoring by the Subcommittee on Cancer Centers. The motion was seconded and adopted by unanimous vote.

REPORT OF THE DIRECTOR, DIVISION OF RESEARCH GRANTS Dr. Elvera Ehrenfeld

Dr. Elvera Ehrenfeld stated that the mission of the Division of Research Grants (DRG) is to provide an efficient, high-quality, and fair review for all grants that the NIH receives, in a manner such that the institutes can make funding decisions to advance their fields most effectively. Because today's science requires a multidisciplinary approach to problems, accommodation and change in the NIH review process became necessary. Issues to be addressed in changing the review process fell into two categories. One category was a series of process initiatives aimed at shortening the time between submission and award, simplifying the paperwork required for submitting amendments, and improving the process for rating grant applications. Many changes to the review process had already begun as part of the NIH reinvention activities and involved the application of information technology to bring about automation. The second category of issues was scientific and involved the overall organization of NIH study sections. Issues centered around the distribution of science to the study sections in an era when many experts are needed to evaluate biological problems. There are two questions to address: (1) Can the DRG accommodate the programmatic needs of the institutes, if there are areas in the portfolios of individual institutes that need to be developed or stimulated? (2) Is the structure of the review process able to accommodate programmatic needs that can change rapidly? Dr. Ehrenfeld emphasized that the goal of any changes will be to have the science drive the review process.

Dr. Ehrenfeld stated that the first initiative in this regard is to evaluate the need for, and then implement, a major reorganization of the NIH study sections on the basis of how scientific research is conducted today. The DRG is administering small trials and general rules are being articulated. In approaching this task, Dr. Ehrenfeld noted, the DRG's intent is to engage the entire scientific community in a dialogue by maintaining a high level of communication with the institutes, centers, and divisions (ICDs) at NIH and with the extramural community. Dr. Ehrenfeld identified the following concerns that have already been articulated to the DRG: (1) the issues relating to low-volume applications and whether to consider forming temporary study sections to review applications in a small field or to assign those small numbers of applications to existing study sections where they represent a minority of the total that are reviewed; (2) the issue of choosing reviewers who do clinical research; and (3) the issue of aggregating the evaluation of clinical oncology applications. She opened the floor for a discussion of these and other concerns related to the review process and for questions from the Board.

Questions and Answers

Ms. Stovall pointed out that recommendations about convening a clinical study section have been submitted by several different bodies with minimal effect. Dr. Ehrenfeld replied that several committees have been addressing these issues, including the current NIH Director's Committee on Clinical Research, which has presented some interim recommendations. In the long term, some of those issues will be absorbed if the study sections are reorganized in a manner that defines how science should be approached today. One immediate plan is to recruit extramural experts with stature and credibility in clinical research and behavioral science areas for short-term appointments to the NIH to establish liaisons with the extramural research community, make recommendations, and help with the implementation of recommendations. Dr. Ehrenfeld emphasized the experimental nature of this plan and the possibility for failure; other experiments will be undertaken until the biomedical research community perceives that the system is working. The focus of the reorganization will be to observe how applications in the different science areas are being reviewed and to ensure that the mechanisms are in place and are flexible enough.

Dr. Rimer asked how to change the constrictive practice that develops in study sections and drives people towards a particular norm, for example, towards using a particular theoretical model in the behavioral area or risk receiving a lower score. Dr. Ehrenfeld stressed the need to

communicate the message to the research community that safe science is not necessarily good science and that different approaches to communicating this message will probably be needed. One message has to do with the reviewer population and the possibility for creatively and innovatively expanding the participation of reviewers. To overcome problems relating to limitations in the types and the numbers of reviewers at certain stages in their careers, alternative roles could be considered, such as being present at specific study section meetings as discussion moderators. Dr. Ehrenfeld underscored the fundamental importance of the review process to the conduct of the Nation's biomedical research enterprise and the need to recruit people with vision and perspective who are capable of helping to move their fields of science forward. Among other potentially helpful issues currently under discussion is the development of criteria for rating grant applications.

Dr. Sigal commended the creative and flexible approaches to the important problem of recruiting new and more representative individuals to the grant review process. Dr. Ehrenfeld commented on the need to recognize that the context in which people function has changed in recent years, especially for clinical researchers who face the pressures of managed care and the situation in academic medical and research centers. At the same time, the research community shares in the responsibility for and the benefit derived from ensuring that study sections have the right reviewers.

Dr. Royston asked if the new review system would consider alternatives to the current prospective review for researchers in the Extramural Program, and whether creativity can be favored over feasibility in obtaining funding. Dr. Ehrenfeld commented that the current discussion about the development of criteria for evaluating or rating grant applications is focused on that particular issue. Part of the solution will probably lie in structural changes and part in an education process to stimulate a larger number of grant applications of that type.

Dr. Dickersin asked whether consumers are considered for participation in review groups. Dr. Ehrenfeld replied that the issue is under discussion. Dr. Dickersin raised the issue that many projects in her field appear to be spinoffs on the same basic dataset and asked which NIH component had responsibility for ensuring a better balance in the portfolios. Dr. Ehrenfeld advised that this issue is appropriate for consideration by the new Peer Review Oversight Group (PROG). Dr. Dickersin asked what kind of mechanisms would be used for transmitting messages from peer-review groups to council-type reviewers to improve the effectiveness of the latter. Dr. Ehrenfeld noted that discussions with Dr. Klausner on this problem have focused on the possibility of establishing a formal liaison function that conforms to the NIH requirement for separation between review and program. The DRG is also working on structural changes to pair program and review staff, as appropriate, for a better exchange of information.

Dr. Klausner emphasized the importance of the role played by the DRG and the complexity of the many issues to be addressed. He called for a concerted effort by all parties to enlist a wider range of individuals who can contribute to the review process. Dr. Rimer suggested that the Board should be considering where Dr. Ehrenfeld's presence at the meetings of some of the working groups might be helpful.

LEGISLATIVE UPDATE

Ms. Dorothy Tisevich

Ms. Dorothy Tisevich presented an update of Congressional activities that relate to the NCI and the National Cancer Program. With the opening of the 105th Congress, some committees that have jurisdiction over NCI programs have changed significantly and others less significantly. The Senate Subcommittee on Public Health and Safety was reestablished and has assumed jurisdiction over Health and Human Services (HHS) programs; Senator Bill Frist (R-TN), a physician, is chair and Senator Edward Kennedy (D-MA) is the ranking minority member. The

membership includes strong supporters of biomedical research. In the House of Representatives, few changes have occurred in the full Committee on Appropriations and the Subcommittee on Labor, HHS, and Education, which have jurisdiction over NCI programs. Membership of the latter includes one new member who is a strong antismoking advocate and another who is an ovarian cancer survivor, as well as other strong advocates from both parties. Representative Rick Lazio (R-NY), who has been active in the Long Island Breast Cancer Study Project and heads an interest group on cancer in the House, is a member of the Subcommittee on Health and the Environment.

Legislation of interest included a resolution on mammography screening introduced by Senator Olympia Snowe (R-ME), which called for the NCAB to discuss the issue of mammography screening for women in their forties and provide guidance to the NCI on what the next steps should be. Another resolution introduced by Senator Connie Mack (R-FL) proposes that the federal commitment to biomedical research should be increased substantially over the next 5 years. Several breast cancer screening and genetic discrimination bills have been introduced. In the latter category, one by Senator Pete Domenici (R-NM), which would have allowed patients access to certain information related to research, is being revised with regard to informed consent and access to clinical records to make the bill less disruptive of research. The One-Stop Shopping Bill, introduced originally in the 104th Congress, has been reintroduced. This bill would amend the Public Health Service Act to provide a centralized information resource for patients with life-threatening diseases. In the area of women's health, the Breast Cancer Patient Protection Act of 1997 (the Drive-Thru Mastectomy Bill) has been introduced in both the House and the Senate. This bill would require that women and their doctors have the option of insurance coverage for a minimum hospital stay of 48 hours. Several bills have been introduced establishing biomedical research trust funds. Legislation on the reauthorization or revitalization of NIH programs will be considered by the 105th Congress.

**NIH ANNUAL REPORT: IMPLEMENTATION OF NIH POLICY ON THE
INCLUSION OF WOMEN AND MINORITIES AS SUBJECTS IN CLINICAL
RESEARCH
Dr. Marvin Kalt**

In introducing this topic, Dr. Marvin Kalt, Director, DEA, stated that one new oversight duty of the Board in the closed sessions will be to review grant summary statements where concerns have been identified in terms of the accrual of women and minorities in clinical trials. This is one aspect of the NCI's implementation of procedures in response to the NIH Revitalization Act of 1993. The Act mandates that women and members of minority groups be included as subjects in each research project, and pertains primarily to Phase III clinical trials in broad categories that include behavioral, therapeutic, and prevention interventions. An evidence-based component in relation to exclusions in Phase III trials is included, but the appropriate inclusion of both genders and minorities is strongly encouraged. The Act made the Director, NIH, responsible for ensuring compliance with this mandate and requires that the advisory council of each national institute shall prepare a biannual report describing the manner in which the institute has complied with this section. In response, the NIH put forward guidelines that were science driven and represented a partnership with the research community. The process for reporting has been standardized across the NIH, and responsibility for preparing the overall report for NIH resides in the Office of Research on Women's Health (ORWH). Data from the annual report for each study are now collected in a special information system based on awards and then reduced to a series of standard tables. The oversight process, on a day-to-day level, is in the hands of program directors who monitor the grant portfolios, noncompeting continuation reports, and annual progress reports from grantees. Each grantee is required to fill in a simple chart with the number of accrued subjects in each mandated category. The data from the individual sources are combined in an institute-wide version and reported in the aggregate format to the NIH. The summary report is prepared by the ORWH and requires a statement that

the NCAB has reviewed NCI procedures for implementation of the policy, as well as the results of that policy, and has determined compliance.

Dr. Kalt explained that compliance entails providing the Board and the NIH with data on the trials in a timely way, as requested. Data from individual divisions or programs can now be supplied to the Board upon request because of the systemized process for collecting data, which became operational in 1996.

Dr. Kalt then reviewed the target distributions for NCI clinical studies active in FY95, the first year that aggregated and sorted data were available, to demonstrate the percentages that would apply in large population-based studies. He compared the target distributions, which presented the standard view of the population across the United States if absolutely proportional representation were achieved, with the actual data in aggregated format from the NCI clinical studies to show that the actual data were better in virtually every category in terms of accrual of both genders and minorities. Based on the raw numbers of people enrolled in NCI clinical studies active in FY95, females were overrepresented due to large-scale studies similar to the Breast Cancer Prevention Trial involving tamoxifen. To give a sense of their impact, Dr. Kalt noted that more than 3 million people were enrolled in NCI clinical studies in 1995. Estimated prevalence of cancer for all sites in the U.S. population was about 7.5 million people. The high total enrollment in relation to estimated cancer prevalence is the function of counting both cancer patients and controls, study subjects in the large-scale prevention trials, and Surveillance Epidemiology and End Results (SEER) Program populations used for special studies. In addition, a person can be enrolled in several clinical investigations and counted for each one; also, each entry onto a funded grant is counted as a separate entry. Dr. Kalt reminded the Board that previous presentations by the Division of Cancer Prevention and Control (DCPC), the Cancer Therapy Evaluation Program (CTEP), and SEER staff have highlighted the extent to which the NCI has been successful in recruiting subjects for therapeutic trials and ensuring appropriate gender representation. Recruiting the appropriate number of subjects from minority groups for prevention trials has been difficult; the numbers are not proportional, but they are substantive and fulfill the requirements for compliance.

Dr. Kalt asked for a motion from the Board to concur with the NCI's compliance in implementing the NIH guidelines on inclusion of women and minorities in clinical studies and the results of that implementation. A motion to that effect was made, seconded, and adopted unanimously.

Questions and Answers

Dr. Dickersin expressed uncertainty about the meaning of the aggregated data, for example, the number, gender, and race of the people in multiple studies who are counted more than once. Dr. Kalt explained that the tables represent a manageable summary of an overwhelming quantity of aggregated numbers from each study. Information on individual trials or aggregate data can be provided on an individual basis. Congressional intent in the mandate was to ensure that inclusive representation in clinical trials was not systematically neglected. The NCI summary tables indicate a systematic effort to assure the highest possible representation. Dr. Rimer concurred that the data presented in the summary report clearly fulfills the requirement for compliance. The Board's task will be to begin to focus on the specific areas and questions over time as the NCI program is developed.

Dr. Freeman commended the summary report as a good beginning, but raised the issue that it does not answer questions about the effect of other factors such as poverty and cultural differences. Dr. Kalt suggested that these were valid topics for further research. Dr. Rimer noted that the Board will look to the leadership of Dr. Brawley in its further discussions of this topic.

ANNUAL REVIEW OF DELEGATED AUTHORITIES/INTRAMURAL TRAINING INITIATIVES

Dr. Marvin Kalt, Ms. Maryann Guerra

Dr. Kalt requested review and renewal by the NCAB of authorities delegated to the Director, NCI, as provided for in the Public Health Service Act. The first permits the Director to appoint 151 special experts or consultants who have scientific and professional qualifications to assist in accomplishing the mission of the Institute; the second permits the Director to exercise authority to appoint one or more advisory committees of private citizens and officials of federal, state, and local governments for oversight activities; and the third defines administrative actions that can be taken without consulting the Board to make minor budgetary adjustments between Board meetings in noncompeting continuation applications and competing applications (new, renewal, or supplemental) before issuing a grant award.

Dr. Sigal asked for clarification of the size of cost adjustment that could be made without Board review. Dr. Kalt explained that these would be administrative adjustments and generally would be under the 1 percent total budget limit that would be brought forward to the Board. He suggested that a list could be generated of applications that were over a certain dollar limit and would be shown in closed session.

A motion was requested to continue the delegated authorities. A motion was made, seconded, and adopted by unanimous vote.

Intramural Training Initiatives

Ms. MaryAnn Guerra, Associate Director, Office of Intramural Management, stated that under the Public Health Service Act the NCI is also granted the authority to establish its own training programs. She then reported on the NCI's intramural training and career development programs. Currently, the NCI has nine fellowship programs, with three new ones under consideration. In addition, the NCI uses eight NIH domestic training programs. The NCI's first training program, the Health Communication Internship, began in 1975, and the most recent, the Cancer Genetics and Epidemiology Fellowship, was added in January 1997. Each program has its own recruitment requirements, qualifications, benefits, and appointment processes. The number of positions and related fellowship funding is provided by each division from the annual fiscal year appropriation. Technology transfer fellowships are generally supported using NCI royalty income.

For information purposes, Ms. Guerra briefly summarized the date established, purpose, number of trainees, and costs in FY96 under the Biotechnology Training General Fellowship Program and the Student Research Training Program, as well as fellowship awards in the areas of Health Communications, Cancer Epidemiology and Biostatistics, Cancer Prevention, Technology Transfer, Cancer Genetics and Epidemiology, and Cancer Nursing. Two programs are scheduled for termination. The General Fellowship Program will end when trainees conclude their assignments. The Cancer Nurse Training Program will terminate in 1997; six fellows were funded in FY96 at the cost of \$191,000. Ms. Guerra reported that both of these will be subsumed under the new Center Training Program, to be discussed next. In summary, the NCI's fellowship programs provided training for 320 fellows at the cost of approximately \$5.5M. Under the NIH domestic programs, NCI trained 396 fellows at the cost of approximately \$9.9M. In the NCI's Visiting Fellow Program, 373 fellows were funded at the cost of approximately \$10M. In response to a question, Ms. Guerra explained that each program has a separate recruitment process for application and internal review, and the processes are usually division-specific. She agreed to provide the Board with additional information on the ratio of total applicants to successful appointments.

Ms. Guerra then presented for Board review a description of the proposed cancer training award, a streamlining initiative that, if adopted, would be one of only two fellowship mechanisms used in the future by the NCI. Currently, about 20 different award mechanisms are used to recruit fellows and provide benefits and, therefore, the streamlining benefits are substantial. The CTA would be established as the universal domestic training fellowship. The existing fellowship programs described above would be used as recruitment mechanisms, but the CTA would be the appointing mechanism for those individuals identified under the separate programs. The NIH Visiting Fellow Program would continue to be used for foreign recruitment because of visa issues that require interactions with the Fogarty International Center. Ms. Guerra stated that the CTA proposal has undergone review by most NCI bodies and several at the NIH level and is proceeding through the review process toward approval by the Office of General Counsel. If approved, the next steps would be to establish the administrative processes and stipend levels and then to identify fellows who would be affected by the changes. The estimated project initiation date is October 1997.

Questions and Answers

Dr. Boxer raised the issue that a disproportionately low number of slots in the \$25M fellowship program are currently being used for oncology nursing, yet that is the area being reduced and, in the future, fewer than 6 oncology nurses could be trained through the NCI programs. Ms. Guerra explained that the divisions can access these training programs and fund as many trainees in a particular discipline as needed. Moreover, the nurse practitioner group that exists at the NIH level and within the NCI is revising the old program to update the training competencies and credentialing processes. Recruitment would then continue and probably expand in scope under the new program. The CTA would be used to make the actual appointment of individuals to that program. Dr. Sandra Millon-Underwood asked for data on the gender, racial composition, and professional backgrounds of the 1,089 fellows currently involved in the NCI programs. Ms. Guerra agreed to provide this information, if available. Dr. Rimer added monitoring of the number of oncology nurse and nurse practitioner positions to the list of agenda items to be revisited in the next year.

Dr. Kalt asked for a motion to continue the delegation of authority to the NCI for intramural training. A motion was made, seconded, and adopted by unanimous vote.

REPORT AND DISCUSSION: ASSOCIATION OF COMMUNITY CANCER CENTERS (ACCC)

Dr. James L. Wade III

Dr. James Wade, President-elect of the Association of Community Cancer Centers (ACCC), announced that the focus of his presentation would be a 1996 ACCC study entitled "The Impact of Managed Care on Medical Oncology." A summary of this study has been submitted for publication to *Health Affairs* and is expected to be available in the next few months. Dr. Wade described the ACCC as a national interdisciplinary organization that represents those who promote the continuum of cancer care in the community. ACCC membership incorporates 500 hospital and free-standing community cancer programs throughout the United States, representing all 50 states, and 14 state chapter Medical Oncology Societies as full delegate members, as well as 300 general members. The ACCC has a longstanding interest in clinical research, having been a proponent of the development of the Community Cancer Oncology Program (CCOP). ACCC membership includes 237 institutions that are either CCOPs or Community Group Outreach Program (CGOPs) and 5 that are NCI-designated comprehensive cancer centers. The 14 state affiliates include investigators from leading U.S. academic cancer centers.

ACCC's decision to conduct a formal study followed its 1990 Clinical Trial Denial Survey of

members who were participating in CCOPs. This small study revealed that between 3 and 5 percent of patients who would be eligible for a trial could not be enrolled because of fear about insurance coverage, and the locations of these patients seemed to correspond to centers for the development of managed care programs. Other deciding factors were reports from oncologists at regional meetings about difficulties in coping with the changes imposed by managed care, as well as the increasing proliferation of managed care plans as the dominant source of payment for health care.

Dr. Wade stated that the ACCC adopted a well recognized terminology in naming its survey instrument the Hassle Factor Survey. The purpose was to measure the perceived impact of managed care on medical oncologists' ability to deliver care, determine whether denied payments affected the clinical judgement of medical oncologists, and determine if types of treatment were no longer offered in managed care practices. Forms were sent to 2,000 adult medical oncologists randomly selected from the nationwide mailing list of 5,000, with representation from each state. Results are based on 322 responses. Of the types of practices that responded, 40 percent represented single-specialty group oncology practices, 18 percent were in solo practice, and 18 percent were part of multispecialty groups or clinics. Of the total, 72 percent of the practices reported active managed care contracts for the survey year of 1995. Managed care contributed less than 12 percent of total revenue in the lowest quartile of practices and more than 35 percent in the highest quartile. In 80 percent of the managed care contracts that physicians signed in 1995, prior authorization was required for services. The mean contribution of managed care contracts to total revenue across all the practices was 24.9 percent.

In terms of effects on patient access, Dr. Wade stated that 66 percent of the contracts imposed a gatekeeper, 29 percent of the practices reported that patients regularly had to switch oncologists due to contract changes, and 33 percent of the practices reported that patients had prolonged travel for services due to contracts. The impact on clinical trials varied, depending on the types of questions asked and where the practice was in its evolution of accepting managed care as the mechanism to deliver care to patients. Of the total group, 37 percent reported that insurers would deny patient participation when a clinical trial question was asked, about 77 percent of oncologists hesitated to place a patient in a managed care plan on a clinical trial because of previous denials and the possibility for economic measurements, and about 33.9 percent of oncologists in a capitated plan hesitated to place a patient on a clinical trial. Specifically, the percentages of oncologists were 41.8 percent for Medicare, a similar percentage for Medicaid, and 32.2 percent for commercial insurance. Dr. Wade offered to provide Board members with a larger set of raw data for a more detailed review. He explained that in this particular question, the survey did not differentiate between NCI-sponsored clinical trials that may cover only the data management costs and those sponsored by pharmaceutical companies where all costs might or might not be included in the budget. Dr. Wade indicated that a statistical analysis of managed care versus capitated plans produced a p value less than 0.01, indicating a statistically significant difference. This was regarded as an important piece of information in support of the general perception that managed care is adversely affecting enrollment to clinical trials.

Responses to a question about referring a patient for a high-cost procedure such as bone marrow therapy, based on payer type, indicated that oncologists would be more reluctant if the patient was in a managed care plan (87.4%) than with other payer types (38.5% for capitated plans). Disease was not specified in the survey. When the same question was asked in reference to prescribing an expensive chemotherapeutic regimen as a standard of care, responses were 28.9 percent for patients in a capitated plan and 53.7 percent for managed care patients. Other observations made in the course of the study were: (1) 56 percent of practices had to add staff for the increased paperwork and communication requirements for the managed care plan; (2) 55 percent of practices had difficulty in contacting the managed care plans to clarify coverage; and (3) 43 percent of physicians personally handled managed care appeals because of the complexity of the information to be transmitted.

Dr. Wade stated that information on oncologists' adaptation to this new environment was sorted into quartiles of 80 responses each, based on the degree of managed care penetration into the practices. Those practices in the first and fourth quartiles—which averaged 12 percent and 35 percent, respectively, of their revenue from managed care—reported few difficulties. Practices in the second and third quartiles experienced the greatest impact from managed care, reporting a greater hassle factor and increasing difficulty in reaching plans. Practice difficulties varied in an inverted "u" curve when plotted on a horizontal axis of increasing percentage of revenue from managed care plans and a vertical axis of increasing hassles as reported by physicians.

Questions and Answers

Dr. Freeman asked if the survey produced information on the amount of clinical or other research that is being done in the fourth quartile position compared with the other groups. Dr. Wade stated that this was deemed beyond the scope of the study. Col. Louis Diehl suggested that, having explored the perspectives of patients and physicians, the NCAB in its advisory capacity could recommend that the NCI conduct a study to determine what actually is happening. Dr. Wittes pointed out the complexity of the study that would be required to determine whether health care decisions by providers are being inappropriately constrained by managed care, and whether quality suffers as a result of certain ways of organizing the system. This issue was to be revisited during the managed care discussion.

Ms. Stovall expressed concern at the 15 percent return on the survey and the potential difficulty for advocacy groups to convince people of the significance of the results that are published in *Health Affairs*. She asked for comment on disincentives to putting patients on clinical trials. Dr. Wade explained that the survey was designed to look more at the effects of the payer mechanism on physicians than at the many other barriers to clinical trial access.

NEW BUSINESS AND SUBCOMMITTEE REPORTS

Dr. Barbara Rimer

As a first item of new business, Dr. Rimer announced that Dr. Robert Hutter, editor of *Cancer*, had offered her an opportunity to write a regular column for the journal concerning Board issues or to report on Board activities. Dr. Rimer stated that she accepted the offer on behalf of all Board members and further information would be forthcoming. This offer came about as a result of her letter to the editor in response to a commentary on the Board written by Walter Lawrence and published in the December issue of *Cancer*. The letter will be published in full in an upcoming issue.

As a followup of the previous day's discussion, Dr. Rimer announced that a new NCAB subcommittee on mammography had been organized, with Drs. Day and Li as co-chairs. Other members are Dr. Rimer, Dr. Michael Bishop, Dr. Dickersin, Ms. Barbara Gimbel, Ms. Stovall, and Dr. Millon-Underwood, all of them representing different points of view and backgrounds. A draft statement of points to be addressed by the Subcommittee was circulated for review. The main issues have to do with the message, the communication products, and the need for a formal data monitoring structure. Deliberations of the subcommittee will be brought before the full Board, beginning with a draft report prepared by Dr. Li and the development of a decisionmaking guide.

Dr. Royston suggested the issues surrounding prostate-specific antigen (PSA) screening as a future agenda item. Dr. Peter Greenwald, Director, DCPC, commented that any communication and guidance would necessarily be based on the evidence, and more research is needed on PSA screening as part of the larger area. He agreed that it would be possible to track prostate funding for the Board and report, periodically, on the large-scale prostate, lung, colon, and ovary (PLCO) screening trial.

Subcommittee on Planning and Budget—Dr. Ellen Sigal

Dr. Sigal referred members to the written minutes of the Subcommittee meeting and reminded them to indicate preferences for oversight committee membership and to comment on the presentation of budget numbers. She then briefly described public education events in observance of the 25th anniversary of the National Cancer Program held in Philadelphia, Arkansas, New York City, and Hollywood. Plans are under way for meetings in Vermont, Connecticut, and St. Louis. Dr. Sigal gave an account of the invitation-only Hollywood event that was attended by Vice President Albert Gore, Dr. Klausner, and 40 leaders of the entertainment industry. A Hollywood task force was created to communicate key messages about cancer research and prevention to the public. Dr. Rimer thanked Dr. Sigal and all Board members for their participation in these events. She particularly recognized Ms. Helene Brown, former NCAB member, for her pivotal role in the Hollywood event and her commitment to work with the task force.

***Ad Hoc* Subcommittee on Policy/Advocacy—Dr. Kay Dickersin**

Dr. Kalt, substituting for Dr. Dickersin, reported that, in a discussion to identify the distinction between the NCAB's role as it relates to advocacy and the process of advocacy, it became apparent that the Subcommittee should assume the task of defining these and related terms, such as education, to clarify the possible NCAB roles. In discussing how to raise policy issues, the Subcommittee concluded that the relationship between policy and advocacy was less than apparent, and that these two areas might be more effectively addressed in separate subcommittees. The Subcommittee recognized the necessary communication linkage between setting general policies about how the Board wishes to deal with certain issues and the subset of issues that the Board might advocate, as well as what advocacy might mean to the Board.

In discussion, Dr. Sigal asked how the separation of advocacy and planning functions would be implemented. Dr. Rimer explained that work on those issues had not been completed at the Board retreat and the task of defining advocacy was assigned to the Subcommittee. Ms. Stovall indicated that the Subcommittee was having difficulty reaching a consensus and was moving toward linking it to communication and the work of the Subcommittee on Information and Cancer Control. Dr. Rimer agreed to work with the Subcommittee to formulate this issue as an agenda item for the June meeting.

A motion was requested for acceptance of the written minutes of the *Ad Hoc* Subcommittee on Policy/Advocacy. The motion was seconded and adopted.

Future NCAB Agenda Items

Proposed agenda items for June were as follows: a minisymposium on managed care featuring a presentation on the legislative perspective by a Congressional representative; a presentation on RFAs; consideration of and response to the reports of the Prevention Program Review Group and the Clinical Trials Program Review Group; a presentation by Dr. Joseph Simone on the National Cancer Policy Board (NCPB) and deliberation as to what issues the NCAB would like the NCPB to address; and a discussion on training issues raised during the presentation on the CTA.

PRESIDENT'S CANCER PANEL/NCAB: DISCUSSION OF MANAGED HEALTH CARE AND PANEL REPORT TO THE PRESIDENT Dr. Harold Freeman, Dr. Barbara Rimer

On behalf of the President's Cancer Panel, Dr. Freeman presented an update on some findings of the Panel's inquiry in 1996 on managed care and its effect on the war against cancer, and

particularly on the National Cancer Program. The Panel views the National Cancer Program in a broad sense, as a program that includes basic research and discovery, translation of the research in the clinical and epidemiologic arenas, and access to health care. In addition to the four regional hearings held from July through November, the Panel met at the White House with the President's advisors on domestic policy to discuss this issue. The Panel also held a closed meeting with representatives of managed care companies to understand their perspective.

The Panel has attempted to determine how these changes in health care delivery have affected the National Cancer Program and the reduction of the burden of cancer on the American people. Testimony was heard from representatives of managed care organizations (MCOs), physicians and health care providers, patients, academic medical centers, government officials, and pharmaceutical and biotechnical industry representatives. Preliminary findings fell into six categories: (1) the impact of managed care on the funding of clinical cancer research studies; (2) how managed care penetration is affecting patients' access to clinical trials and clinical care; (3) the impact of managed care policies on physicians who participate in clinical research; (4) the impact of managed care policies on institutions that conduct clinical research; (5) the impact on the education and training of future clinical researchers; and (6) the relationship between biotechnical industries and clinical research.

Funding. The Panel believes that sources of funding for clinical research are disappearing. Dr. Freeman noted that, despite decreased patient care income, many institutions testified to having been able to maintain some level of cancer clinical research effort, and some said there was no decline. This has been possible through the adoption of cost-effectiveness as a standard of success and the reengineering of key research processes to enhance efficiency. The Panel also found that pharmaceutical and biotechnical companies are funding more clinical trials, creating a potential risk over time of limiting investigator-stimulated research. To compensate for lost income, many providers are increasing the number of patients they see at the expense of time spent with each patient. Other institutions reported curtailment of nonpatient associated costs, including training and education. The Panel heard concern over insufficient participation by MCOs, particularly the for-profit MCOs, in clinical research efforts. Dr. Freeman noted virtually unanimous support among the people who testified for policies that would require all beneficiaries of cancer clinical research to share in paying for research and education costs.

Access. The Panel heard testimony that MCOs are impeding access to trials. Testimony indicated a consensus that MCOs rarely approve reimbursement for Phase I and Phase II clinical trials, but frequently approve Phase III trials, although more documentation is needed for the latter. In addition, patients appeared more likely to have limited entry onto a study by insurers if the experimental therapy required additional treatment steps, such as a second hospitalization for a distinct standard of care. The Panel believed these issues could significantly affect not only whether patients are receiving the best and the most appropriate types of care, but also the validity of clinical study outcomes. Concern was also expressed that trials may become skewed toward those that are easier to finance, opening the way for a possible bias in the populations that would be included in future research.

A principal barrier to broader clinical trial participation on the part of MCOs appeared to be the perception that trial-related patient care costs are higher than costs of conventional therapy. Research is needed to provide adequate cost data. MCOs indicated a willingness to embrace well-designed, efficiently run Phase III trials that address important research questions. They believe, however, that Phase I and II trials should be funded from a source other than premium dollars, because efficacy has not yet been established. The Panel believes that the failure to support Phase I and II trials may translate into major delays in bringing potentially important new therapeutics to a broad spectrum of patients.

The Panel believes that access to pediatric clinical trials should be standard for children with

cancer, but managed care appears to be affecting access. The Panel also heard testimony that managed care is limiting the standard of pediatric care by applying guidelines for adults to children with cancer, not providing ready access to pediatric subspecialists for consultation in certain cases, and controlling continuity of care through referral to multiple-participating or low-cost service sites.

On a positive note, the Panel encountered managed care plans, such as several in Oregon, that are committed to research and are working well in relation to research. In an effort to address the concerns of managed care providers, some institutions are developing clinical pathways for treatment of selected malignancies. Evidence-based algorithms are provided that would curtail continuation of nonbeneficial therapies. At the same time, payers are assured that clinical procedures are being provided in settings designed to help answer important questions. To the extent that this is occurring, these are positives.

Access issues extend beyond clinical trials to concern that managed care is negatively affecting patient access to supportive cancer care services, such as pain relief, symptom control, and psychosocial and hospice care. Considerable discussion focused on the need for access legislation, such as the Rhode Island legislation that requires coverage of new therapies in specified Phase III and IV trials. After 2 years, two major HMOs in Rhode Island have reported no adverse financial impact. The NCI-Department of Defense (DoD) Cancer Treatment Clinical Trials Demonstration Project is another example of innovative programs that are being implemented to improve clinical research opportunities and access to patients.

Provider Issues. The Panel heard testimony in western states, where managed care penetration is the greatest, that compensation in 1996 depended largely on productivity compared with the situation in 1983 when physician compensation depended in equal proportions on productivity, participation in clinical research, and publication. Similarly, other providers reported less time for research participation and patient education due to the volume of activity that is required. From an ethical perspective, this raises the issue that physicians may be facing an increasing challenge to maintaining their roles as patient advocates.

Research Institutions. The Panel heard testimony about changes in the conduct of clinical research at the institutional level. Academic medical centers, in particular, are experiencing shifting alliances and changing infrastructures, increases in overhead costs, higher levels of nonreimbursed patient care costs, and decreased patient referrals. This was a concern to the Panel, because the major institutions are tending to confirm these particular issues.

Training and Education. Although evidence of the adverse impact of managed care on the training and education of future researchers is anecdotal, the Panel believes that failure to act promptly could cause significant problems for future researchers. Presenters speculated that attracting young investigators into research careers will be increasingly difficult. At the institutional level, the Panel heard that academic physicians face difficulties in striving to excel as clinicians, researchers, and teachers, because of both the pressure to generate revenue through direct patient care and the increased paperwork.

Industry. The Panel heard testimony that biotechnology and pharmaceutical companies are assuming a greater role in funding clinical trials and are viewed as important partners for developing cancer therapeutics in a managed care system. At several institutions, the total number of clinical studies has remained stable only because of increased industry sponsorship. According to its own representatives, however, industry studies cannot replace academic research, because the necessary focus on rapid drug approval results in a narrower approach to conducting research. The Panel believes that further reductions in investigator-initiated research could result in important questions not being asked and answered.

Conclusions. The Panel concluded that, despite concerns heard in the testimonies, on a system-wide basis, managed care—not managed cost—could ultimately lead to some system-wide benefit in a balanced system. Benefits could include a greater emphasis on prevention; development of better research guidelines, protocols, and outcome measurements; greater consistency across health care delivery systems; and improved affordability. The Panel believes, however, that problems do exist and that strategies must be developed for operating in this new environment. Access, cost containment, and quality of care are currently the competing priorities in the struggle to achieve a balance. Without high-quality, accessible clinical research, progress in the war on cancer will be undermined. In the debate on productivity and payment, the focus must remain on the American public.

Questions and Answers

Dr. Sigal asked if the Panel considered working with groups that do not have the same constraints in terms of advocacy as those of the NCAB and the Panel. Dr. Freeman characterized the role of the Panel as organizing the information collected in the testimony to produce a set of conclusions and develop appropriate recommendations. This is in accord with the mandate to the Panel to report barriers to progress in the National Cancer Program. At this time, plans have not been made to include other organizations in the Panel report. Ms. Visco added that the Panel has identified problems and has either supported or recommended some general strategies. Legislation is being introduced regarding these issues, and many organizations are advocating the enactment of these pieces of legislation. Ms. Stovall stated that qualitative evidence becomes a body of evidence at some point, with the same urgency and weight as the quantitative evidence presented earlier, and emphasized that advocacy must begin.

Dr. Boxer asked whether the Panel considered recommending that preparations for clinical trials include input from a specialist from the managed care industry. Dr. Freeman noted that the effect of such a strategy would not be universal if it were conducted on a company-by-company basis, and the Panel must focus on what will happen to the country as a whole. Whatever approach is adopted must include the whole managed care industry. Ms. Visco agreed that strategies were needed that would engage the entire industry in helping to fund clinical research, such as the legislation that is being discussed.

Dr. Schein suggested that the Panel's final report will carry a message that should be taken nationwide, and he asked if there were plans in that regard. Dr. Freeman welcomed suggestions from the Board. Ms. Visco agreed that a number of strategies could be developed to highlight the recommendations of the Panel, but she urged recognition that the Panel report is but one piece of information in a complex issue.

Dr. Royston suggested that an increase in the amount of the per-person reimbursement for NCI clinical studies is needed. Dr. Day identified two areas where additional data are needed: (1) the kinds of trials being sponsored by the NCI and the number of people enrolled on an annual basis; and (2) the actual cost per patient for treatment on a clinical trial. Dr. Kalt stated that the data on types of trials and patient enrollment would be provided insofar as it is possible to extract it from the new reporting dataset. Dr. Wittes added that the presentation on the NCI-DoD clinical trials project would discuss initiatives to obtain that type of information. In addition, two cancer centers are gathering cost data for sharing patient-care costs in trials, and one cooperative group has concentrated economic expertise on determining costs as an ongoing research program. Dr. Wittes agreed that the issue of clinical research costs affects the entire insurance industry, and DCTDC has been attempting to engage in a dialogue with individual companies and with the American Association of Health Plans. In addition, the Clinical Trials Program Review Group (CTPRG) was asked to address the economics of clinical trials.

Dr. Day suggested that the NCAB Subcommittee on Clinical Investigations be asked to develop

a several-point plan of action that the Board can endorse and support, and Dr. Rimer agreed. Dr. Schein reminded the Board that the Subcommittee had brought forward a recommendation for the Bypass Budget that included supplemental funding for clinical research for patient-related costs. He also suggested that a data collection instrument could be added to the protocols for new NCI-sponsored trials to produce quantitative data on participation and the extent to which managed care is a major problem among the many barriers to physicians' participation in clinical research. He endorsed the Panel report as a valuable survey of a serious situation in clinical research and called for action to get the message out to the public and Congress.

Col. Diehl questioned whether solving the managed care part of the problem would help to enroll more of the 97 persons out of 100 who do not participate in clinical trials at the present time. He pointed out the need to know how deeply other factors, such as the time and effort required to enroll a patient, are involved in the problem. Dr. Wittes agreed that the question is important, but he emphasized the need to act on what is already known with the tools at hand. Dr. Faye Austin, Director, Division of Cancer Biology (DCB), pointed out that these complex issues have been reviewed by the NCPB, and that interaction with the NCAB is possible. Dr. Rimer emphasized that the long-range collection of quantitative data and the short-term initiation of action are not mutually exclusive events. Dr. Schein agreed that the Subcommittee at the next meeting would be able to supplement the valuable information presented by Dr. Freeman and Dr. Wade and would be prepared to craft a policy statement for Board review and approval. In the longer term, he would consult with Dr. Day on the text of a data collection instrument that could be added to new studies to produce the quantitative data on enrollment and costs.

UPDATE ON DoD/VA AGREEMENTS **Ms. Mary McCabe**

Ms. Mary McCabe, Assistant Director, DCTDC, announced that she would try to relate the update on the DoD/VA agreements to the preceding discussions. The two agreements represent cooperation and coverage for clinical trials with a large single-payer system—the DoD—and a large provider system—the Department of Veterans Affairs (VA). Both agreements have the goal of assuring a healthy future for clinical research. In her presentation, Ms. McCabe focused first on NCI resources and efforts in regard to these agreements, and then on the challenges to be overcome in trying to assure success. She noted that these agreements are not independent and not outside of the managed care discussion.

According to the Memo of Understanding signed in early 1996, the purpose of the NCI-DoD Clinical Trials Demonstration Project was to support and expand the clinical trials activities conducted at the military treatment facilities and to provide Civilian Health and Medical Plan of the Uniformed Services (CHAMPUS) beneficiaries with new access to NCI clinical trials at civilian institutions. The agreement covers Phase II and Phase III clinical treatment trials. The NCI is working to extend coverage to include Phase I and prevention trials. Part of the terms of the agreement include expanding the Physician Data Query (PDQ) database and a 3-year duration for the demonstration project, to be renewed annually.

This demonstration project provides opportunities to maintain a strong group of clinical investigators and increase accrual to NCI clinical trials. Important sidelights are the two economic evaluations that are ongoing, to answer frequent questions from managed care companies and self-insured corporations concerning the cost of coverage for cancer clinical trials. The first is a pilot study to measure the costs of CHAMPUS-eligible participants in the Southwest Oncology Group (SWOG) cancer treatment trials from 1988-1995. By linking the SWOG and the CHAMPUS databases, more than 1,000 CHAMPUS-eligible patients have been identified as enrolled on breast, prostate, colon, leukemia, and lymphoma trials during this period. The next step is to establish a retrospective evaluation to produce data on the costs of

clinical trials compared with the cost of standard care for those patients. In the second economic evaluation, the NCI is working with the Rand Corporation to develop a prospective study for estimating the cost of treating CHAMPUS patients in Phase II and Phase III NCI-sponsored treatment studies.

Because the *Federal Register* notice announcing the demonstration project and the activation of the NCI-DoD agreement made it retroactive to January 1, 1996, DCTDC worked quickly to offer patients and their physicians the opportunity to have access to NCI-sponsored trials. Immediate implementation activities included establishing an office and a case management system so that each patient could be given the opportunity, even before the protocols were listed in PDQ, to become aware of potential clinical trials and to be enrolled. This case management system continues and customized PDQ searches for clinical trials have been added to facilitate the matching of patients to trials.

CHAMPUS/TRICARE training was immediately activated to inform CHAMPUS staff about the NCI clinical trials program and equip them to discuss the program with physicians and beneficiaries. The PDQ expansion project was invaluable because of the need to provide broad access to physician and patient versions of treatment protocols covered under the DoD agreement. To publicize this opportunity to military audiences, the civilian community, managed care contractors, and beneficiary organizations, a joint promotion plan has been developed by the NCI Office of Cancer Communications (OCC) and the DoD and is being implemented. One barrier to participation expressed by clinical researchers within the military treatment facilities was the lack of data management support. This is being addressed within the DCTDC by Drs. Richard Ungerleider and Leslie Ford, DCPC, who are working with the cooperative group chairs on a mechanism for per capita reimbursement over and above the current accrual to cooperative group studies.

Ms. McCabe reviewed low accrual figures for the demonstration project, which indicate that much effort and more time will be needed for knowledge about the demonstration project to be widespread in the community, for patterns of behavior to change, and for people to see clinical trials as one avenue to quality cancer care. Of the 59 cases reviewed, 51 were approved and 8 denied. The patients, mostly adults, have been enrolled in cooperative group trials, cancer center trials, and NCI grantee studies for a variety of cancers. Thirty-two patients have been enrolled on Phase II studies, and 19 on Phase III studies. The majority of patients have been enrolled on bone marrow transplant studies, indicating that the DoD agreement so far has been a vehicle for providing access to high technology. The goal will be to change this mindset over time so that the NCI-DoD agreement is seen as a broader opportunity.

In addition to the challenge of promoting this agreement, the NCI will need to coordinate with the new configuration of health care delivery within the DoD. The organization, called TRICARE, places all military treatment facilities and CHAMPUS areas under an umbrella divided into 12 regions, which will be overseen by 4 managed care contracts. The challenge faced by the NCI is to integrate the clinical trials agreement into the evolving CHAMPUS/TRICARE health care system.

Ms. McCabe then described the purpose and terms of the 3-year VA-NCI Clinical Trials Demonstration Project, which was initiated January 1, 1997. In this case, the purpose is to expand an already productive relationship between the VA and the NCI, which includes 21 cancer centers, 51 cooperative group affiliations, and 6 CCOPs and Minority-Based CCOP affiliations. The terms of the agreement cover all phases of NCI-sponsored clinical trials for treatment, prevention, and diagnosis. Implementation activities are similar to those under the DoD agreement. The joint promotion plan will focus on beneficiary and advocate organizations for assistance in publicizing this opportunity. Although it is not moving to managed care contracts, the VA is reconfiguring its health care delivery system into 22 integrated service

networks (VISNs) around the country. The VISN directors will decide independently how the integrated networks look, how they focus on cost, and how they centralize specialty care. This reconfiguration will require extensive NCI effort and involvement as the changes occur, because the activities appear to be much the same as those occurring under managed care.

In summary, Ms. McCabe pointed out that these agreements present opportunities for the future of clinical research. They are prototypes for integrating clinical trials into managed care systems and assure that military and VA physicians remain committed to participating in NCI-sponsored clinical research. Ongoing attention will be needed to achieve NCI goals as the provider system (VA) and payer system (DoD) in the agreements undergo the same reorganization that is occurring in the private sector with the same focus on cost and centralization of specialty care. The key to the success of these agreements is to increase patient and public awareness of clinical trials as an option in cancer care.

**ANNUAL DIVISION OF EXTRAMURAL ACTIVITIES (DEA) DIRECTOR'S REPORT:
FY96 SUMMARY
Dr. Marvin Kalt**

Dr. Kalt reviewed the current advisory organization of the NCI, beginning with the extramural groups instituted to advise the Director. These include the President's Cancer Panel, which reports directly to the President; the NCAB which reports to the President and the Secretary, HHS; the Board of Scientific Advisors (BSA), the Board of Scientific Counselors (BSC), and, most recently, the Advisory Committee to the Director (ACD). In addition to the advisory groups, he reviewed the divisions responsible for NCI intramural and extramural program activities—DCTDC, DCS, Division of Basic Sciences (DBS), Division of Cancer Epidemiology and Genetics (DCEG), and DEA.

The organization of DEA was described. The Comprehensive Minority Biomedical Program (CMBP) and the new Office of Advisory Activities (OAA) are within the OD, DEA. The branches that constitute the DEA are the Research Analysis and Evaluation Branch (RAEB), which tracks the funding in each category of research; the Grants Review Branch (GRB); and the Special Review, Referral and Resources Branch (SRRRB), a combination of the former Contracts Review Branch (CRB) and the Review Logistics Branch (RLB). The new SRRRB receives all grant and contract applications to the NCI, directs the applications to the appropriate program, conducts contract and RFA review, and supports much of the information resource management within the NCI.

RFA usage was briefly summarized. RFAs not funded through the RPG pool are primarily either clinical cooperative group activities or cancer control activities. A comparison of the relative use of RFAs in FY95 and FY96, across various institutes at the NIH, indicates that the NCI's 16 percent of total awards was below the NIH average of 17 percent.

Having assumed the information resource management functions of the former RLB, this new branch is also responsible for the DEA's section of the NIH/NCI WWW site. The now-unified extramural research entry page, which is still on a test server, can be accessed through the NCI Home Page with DEA's temporary address. Information is provided on Boards and groups, DEA personnel, and grant guidelines and descriptions.

Dr. Kalt reviewed the organization of the OAA. The diversity of OAA functions includes oversight of the newly independent process for peer review of the IRP and responsibility for the NCI committee management function. The OAA also facilitates linkages among the many advisory and oversight groups and their activities to assure synthesis and integration of overall activities and serves in an advisory capacity to the staff and units of the Institute responsible for conducting similar advisory and oversight functions.

Dr. Kalt gave a brief description of other advisory and oversight groups and their function, noting that they assure the broadest possible input from the broadest possible community. The BSA focuses on the activities of the extramural divisions and reviews the concepts for all RFAs and contracts before they are advertised. The two BSA subcommittees—Cancer Biology, Epidemiology, and Genetics (CBEG) and Prevention, Clinical and Therapeutic (PCT)—are newly formed and in the process of defining their roles. The Cancer Centers, Cancer Control, Prevention, Clinical Trials, and Developmental Therapeutics Program Review Groups operate under the auspices of the BSA. Program Review Group reports are submitted for review to the NCAB. The BSC, which was consolidated from all of the previous independent Boards of Scientific Counselors, assists the directors of the intramural divisions and Deputy Director, NCI, on a wide variety of matters concerning the IRP. The BSC subcommittees are the Clinical Sciences Subcommittee and the Basic Sciences Subcommittee. The BSC evaluates the site visit reports of the intramural program and provides the core of the site visit teams. Site visits are now administered out of the DEA and are independent of the IRP. The newly formed ACD is an aggregation of the chairs and cochairs of all the other advisory boards that have oversight function for the programs. The ACD ensures communication across these bodies for NCI issues.

Another series of groups have been constituted, which either report to one of the boards or are *ad hoc* and have independent status. In the first category, the NCI Director's Working Groups relate to the Bypass Budget and the extraordinary investment opportunities list. The Prostate and Breast Progress Review Groups, both of which are currently under development, make up the second category. A third series of working groups have been created, with both intramural and extramural representation. They are the AIDS-Related Malignancies Working Group (in progress), DCLG (under development), Information/Communication Task Force (under development), and the NCI Initial Review Group.

Finally, the DEA has the responsibility of tracking scientific misconduct. Dr. Kalt reviewed the statistics reported in 1996 by the Office of Research Integrity (ORI), a unit of the Public Health Service. NCI grantees were involved in 7 of 39 open cases, 10 of 49 closed cases, and 7 of the 48 that remain active in one stage or another of investigation. Findings of no misconduct were returned in 8 of the 10 NCI cases that were investigated and closed. Under the current process, the ORI reviews allegations as they are received and determines whether an investigation is warranted. If an investigation is warranted, the institution that holds the award conducts the first investigation. In 1996, the ORI received 196 allegations, of which 20 could be identified as involving NCI applicants and might be transferred to the NCI for action within the next year. Because of the low level of activity and the fact that most of the issues raised did not result in a finding of misconduct, no discussion was necessary.

ADJOURNMENT

Dr. Barbara Rimer

There being no further business, the 101st meeting of the National Cancer Advisory Board was adjourned at 1:08 P.M. on Tuesday, February 26.

Advisory Home
Funding Opportunities

created: 27sep95 [Lorrie Smith](#) revised: 28jan00