



**99th National
Cancer Advisory
Board Meeting**

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**NATIONAL CANCER INSTITUTE
NATIONAL CANCER ADVISORY BOARD
BETHESDA, MARYLAND**

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September 10-11, 1996

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The National Cancer Advisory Board (NCAB) convened for its 99th regular meeting at 8:00 a.m., September 10, 1996, in Building 31, C Wing, 6th Floor, Conference Room 10, National Institutes of Health.

LIST OF ATTENDEES

NCAB Members

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

President's Cancer Panel

Dr. Harold P. Freeman (Chairperson)
Dr. Paul Calabresi
Ms. Frances M. Visco

Alternate Ex Officio NCAB Members

Dr. Alison Martin, FDA
Ms. Lynn Jenkins, NIOSH
Dr. Marilyn A. Fingerhut, NIOSH
Capt. Bimal C. Ghosh, DOD
Dr. Hugh McKinnon, EPA
Ms. Rachel Levinson, OSTP
Dr. Lakisma C. Mishra, CPSC
Dr. Kenneth Olden, NIEHS
Dr. Paul Hoffman, DVA
Dr. P. C. Srivastava, DOE
Dr. Ralph E. Yodaiken, DOL

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. George Vande Woude, External Advisor, Division of Basic Sciences; Director, Advanced
BioScience Laboratories, Inc., NCI-Frederick Cancer Research and Development Center
Dr. Claude Klee, Chairperson, Intramural Advisory Board, Board of Scientific Counselors
Dr. Martin Abeloff, External Advisor and Co-Chair Clinical Sciences Subcommittee A of the
NCI Intramural Board of Scientific Counselors; Professor and Director, Johns Hopkins Oncology
Center
Dr. David Livingston, External Advisor, Chairperson of the NCI Extramural Board of
Scientific Advisors; Professor of Medicine, Dana-Farber Cancer Institute
Dr. Edward Harlow, External Advisor, Special Advisor, Office of Science Policy, Co-Chair,
Basic Sciences Subcommittee B of the NCI Intramural Board of Scientific Counselors; Member,
Massachusetts General Hospital
Dr. Alfred Knudson, External Advisor, Special Advisor to the NCI Division of Cancer
Epidemiology and Genetics, Acting Director Intramural Genetics Program; Senior Member, The
Institute for Cancer Research, Fox Chase Cancer Center
Dr. Maureen O. Wilson, Executive Secretary of the President's Cancer Panel

Liaison Representatives

Dr. John Currie, American Association for Cancer Education, Inc.
Dr. Marc E. Lippmann, American Association for Cancer Research

Dr. Robert Martuza, American Association of Neurological Surgeons
Dr. John Laszlo, American Cancer Society
Ms. Kerrie B. Wilson, American Cancer Society
Ms. Elaine Locke, American College of Obstetricians and Gynecologists
Dr. Stanley Zinberg, American College of Obstetricians and Gynecologists
Dr. Bernard Levin, American Gastroenterological Association
Dr. Edward P. Gelmann, American Society of Clinical Oncology
Dr. John Glick, American Society of Clinical Oncology
Ms. Julie Taylor, American Society of Clinical Oncology
Dr. Stanley Order, American Society of Therapeutic Radiologists
Dr. Edwin A. Mirand, Association of American Cancer Institutes
Dr. Robert W. Frelick, Association of Community Cancer Centers
Mr. James Kitterman, Candlelighters Childhood Cancer Foundation
Mr. Thomas Brandt, Intercultural Cancer Council
Dr. Ronald Jones, Intercultural Cancer Council
Ms. Jean Whalen, Leukemia Society of America, Inc.
Ms. Dorothy J. Lamont, National Cancer Institute of Canada
Dr. J. David Beatty, National Cancer Institute of Canada
Dr. Margaret Foti, National Coalition for Cancer Research
Dr. Tracy Walton, National Medical Association
Dr. Eve I. Barak, National Science Foundation
Dr. James Brown, National Science Foundation
Dr. Kathi Mooney, Oncology Nursing Society
Ms. Roberta Strohl, Oncology Nursing Society
Dr. Jeffrey Norton, Society of Surgical Oncology, Inc.
Dr. Marston W. Linehan, Society of Urologic Oncology

CALL TO ORDER, OPENING REMARKS, INTRODUCTION OF NEW MEMBERS—DR. BARBARA RIMER

Dr. Barbara Rimer called to order the 99th meeting of the National Cancer Advisory Board (NCAB). She acknowledged the recent passing of Ms. Iris Schneider, former NCI Assistant Director and executive secretary of the NCAB Planning and Budget Subcommittee. She also noted a recent car accident involving Ms. Amy Langer, a member of the NCI Board of Scientific Advisors.

She then introduced the new board members: Dr. Ivor Royston, president and Chief Executive Officer of the Sidney Kimmel Cancer Center; Ellen Stovall, executive director of the National Coalition for Cancer Survivorship (NCCS); Dr. Sandra Millon-Underwood, associate professor at the University of Wisconsin School of Nursing; and Dr. Fred Li, professor at Harvard University and physician at the Dana Farber Cancer Institute. The reappointment of Dr. Richard Boxer to the Board for a full 6-year term was noted.

Dr. Rimer also introduced Dr. Phillip Sharp, professor and head of the Department of Biology at Massachusetts Institute of Technology, a consultant to the Board, and several guests representing numerous cancer education and research associations and institutions. She invited members of the public to submit in writing, within 10 days, any comments regarding items discussed during the meeting.

Dr. Rimer made a motion to approve the minutes of the previous May meeting. They were approved by the Board unanimously.

FUTURE BOARD MEETING DATES—DR. BARBARA RIMER

In discussing upcoming NCAB meeting dates, Dr. Royston informed the Board that the May 18-20, 1998, meeting overlapped with the American Society of Clinical Oncology (ASCO) national meeting. Dr. Rimer noted that this would be investigated for a possible change of date.

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

In recalling his first meeting with the NCAB 1 year ago, Dr. Klausner reaffirmed that investigator-initiated research was the number one priority of the NCI. He then presented statistics related to NCI research funding. He stated that the research projects grants pool was set at \$1.022B out of a total budget of \$2.25B. Next, he reminded the Board that the R01 payline for individual investigator-initiated research was set at the 23rd percentile—up from the 15th percentile the previous year. One-third of P01 applications received were funded. Dr. Klausner felt that maintaining the payline at the 23rd percentile, even with an uncertain budget, was a high priority. He informed the Board that accelerated executive review (AER) had been introduced to decrease the unpredictability of the study section process and the difficulty of dealing with a strict payline. To help address the needs of patient-oriented research, AER's zone of consideration was set at 10 percentile points from the payline and everything else at 4 percentile points from the payline. For FY 1996 to date, 51 AER applications were received; 24 were patient-oriented and 27 nonpatient-oriented grants. Twenty-six were approved for funding (51% approval). The Executive Committee (EC) was pleased with this and is expected to increase the allocations from \$6M to \$9M in FY 1997.

Dr. Klausner reviewed exception funding, which was budgeted at \$18M, or 6% of available research project grants (RPG). These were reviewed by the EC on a case-by-case basis. Bridge support (interim funding) was allocated at \$2.8M. Twenty-two R01s and 10 P01s were funded with the remaining monies. Most of these R01s were not eligible for AER.

Within the RPG funding line, \$12M (4%) of available funds were distributed to the extramural divisions for use as administrative supplements, \$5.6M of which funded the Division of Extramural Activities (DEA), Comprehensive Minority Biomedical Program Minority Investigation Supplement Awards.

Dr. Klausner expressed his excitement regarding an October retreat for the EC to establish written operating procedures for the soon-to-be-implemented cyclical (every 4 years) review policy within the Institute. These reviews will allow for a coupling of planning and review processes for presentation to the NCAB and other boards.

Dr. Klausner then highlighted several initiatives within the Cancer Centers Program and the Clinical Trials Program Cooperative Groups. These initiatives represent the use of one-time supplemental funds to help facilitate programs that have been identified as high priority by the advisory planning working group, the review processes, and the NCI staff. In addition, funds from Dr. Varmus' 1% transfer authority (\$6-7M) were also used. The one-time supplemental monies can be as much as \$500,000.

Dr. Klausner summarized initiatives in the two areas identified for the Cancer Centers Program: cancer genetics and AIDS malignancies. For cancer genetics, the largest initiative was aimed at understanding heritable factors involved in human cancer, coupled with the identification and establishment of risk. Applications for funding in this area came overwhelmingly from the clinical and comprehensive cancer centers. There was also an interest in genetic counseling and education, for which a variety of applications were received.

Regarding AIDS malignancies, Dr. Klausner acknowledged that considerable emphasis was needed on training programs for oncologists as part of extensive research programs. He further commented that the quality of the applications received for the two initiatives was impressive.

Dr. Klausner summarized the Clinical Trials Cooperative Group Program, which currently has about 9,000 active affiliated investigators located in at least 1,500 institutions. There are currently 530 trials, 400 of which are therapeutic. About 15% are Phase I, 50% Phase II, and the rest Phase III. Activity was expected to remain high in these trials.

Dr. Klausner briefly noted some of the problems associated with the Clinical Trials Evaluation Program (CTEP). This program, which exists to support, coordinate, and evaluate anticancer therapies, had inefficient data collection methods (primarily due to independent CTEP databases), which resulted in delayed communication and difficulties with data analysis. This problem led to an internal CTEP information systems initiative that involved improvements in communication and staff access to CTEP databases, establishment of a common database infrastructure, and a linking of existing CTEP databases. A detailed report will be presented at a future NCAB meeting.

Dr. Klausner turned his discussion to the Intramural Research Program (IRP). During the previous year, three individuals had been recruited to lead the three intramural divisions of the NCI: Dr. George Vande Woude, Division of Basic Sciences (DBS); Dr. Joseph Fraumeni, Division of Cancer Epidemiology and Genetics (DCEG); and Dr. Edison Liu, Division of Clinical Sciences (DCS). They helped the NCI carry out some changes, such as setting up new labs, completely closing others, and increasing resources. Dr. Vande Woude, in his capacity as advisor to the Director, NCI, will report on this at the November Board meeting.

Dr. Klausner then highlighted several significant findings from the IRP over the past year. First, in the DBS, researchers identified the gene responsible for Gorlin's syndrome, which was determined to be the human homolog of a well-studied drosophila gene called Patch, which is involved in pattern development.

Next, regarding cervical cancer and human papillomavirus (HPV), significant progress was made towards developing effective HPV-protective vaccines using insect cells to produce immunogenic viral particles, called virus-like particles (VLPs). An internal meeting will soon be held to promote the development of an HPV vaccine.

Also, researchers identified and mapped 2,100 mouse genes. This map is being coordinated with a microsatellite map to improve the usefulness of mouse genetics for all biomedical research, including cancer. Using this map, researchers have already discovered the mouse gene responsible for some forms of acute myelogenous leukemia—a disease that occurs in both mice and humans. These findings illustrate how the progress of human genetics benefits from research in simple model systems.

Next, Dr. Klausner highlighted some of the progress in HIV research, which includes detailing the active site of the third of the three known enzymes encoded by HIV and the use of protease inhibitors against the virus. Dr. Klausner stressed that research must continue to identify other HIV structural and functional components.

Dr. Klausner then moved to an update of DCS. A new laser capture microdissection technology has been developed as a nondestructive, easy-to-use methodology for the isolation of clonal populations of cells. He regarded this technology as essential for doing molecular science and hailed this technology as a great breakthrough.

Next, he described an intriguing clinical trial involving children and adult patients with noncleaved, small-cell lymphoma (a non-Hodgkin's lymphoma), in which a 90% response rate was seen by using an intensive two-component chemotherapy regimen, mixing a CHOP-like regimen with three additional drugs—ifosfamide, VP-16, and high-dose ARA-C. Dr. Klausner explained that CHOP-like regimen relapse cases require more aggressive chemotherapy because of p53 mutations.

Moving on to the DCEG, Dr. Klausner mentioned that the Washington Breast Cancer Susceptibility Study—an evaluation of the prevalence of BRCA1 and BRCA2 mutations in the metropolitan area Jewish community—had been completed and results might be available for the next NCAB meeting.

**REPORT OF THE DIRECTOR, NATIONAL CANCER INSTITUTE
QUESTIONS AND ANSWERS**

Following several questions about these research updates, a discussion ensued regarding the initiative to improve communications. Dr. Schein commented that, considering the NCI's potential as the largest pharmaceutical company in the world, he believes that the ability to harmonize communication among the NCI, its cooperative groups, and ultimately the potential drug sponsors, is a vitally important step.

NCI OFFICE OF SCIENCE POLICY—DR. EDWARD HARLOW

Dr. Klausner opened the presentation by introducing Dr. Edward Harlow as the new Associate Director for Science Policy and Associate Director for Planning. Dr. Klausner briefly discussed some of the challenges of "planning" for science, which he acknowledged was an interesting and challenging task.

Dr. Harlow stated that his Office was in its early stages of development. In general, the Office was looking at scientific initiatives that would not fit clearly within single existing individual divisions. The Office comprises four major program areas, including Evaluation, Special Populations, Institutional Planning, and Technology Development.

The Evaluation Group is primarily responsible for analyzing organizational structures within the NCI. The approach to these analyses is to look at a problem as a subject-oriented event, rather than in an organizational setting. Another major operation within the Evaluation Group is setting up the Progress Review Groups. A third operation is establishing and maintaining a Science Information System. This is a mechanism to keep track of what is happening at the NCI with regard to the organizational structure of the NCI, scientific advances, and the tasks of its staff. It will enable the Evaluation Group to identify the key goals and science information details that need to be addressed. The Evaluation Group is also responsible for the production of the NCI's Bypass Budget.

A second program within the Planning Office involves Special Populations; it provides a clear definition of the boundaries in special populations and establishes a survey of activities related to special populations throughout the NCI's divisions.

The third program involves establishment oversight of Institutional Planning Groups. To date, groups have been established which focus on cancer genetics, development diagnostics, preclinical models of cancer, and early detection. Dr. Harlow described these Groups as the NCI's approach to develop "think tanks" on specific research issues. These ideas, in turn, are converted by NCI leadership into implementation plans that come back to the EC, who then determine what actions need to be carried out.

The Cancer Genetics Working Group was the first of these think tanks formed. Dr. Harlow's Office believed that, because of the development of the kinds of research advances that Dr. Klausner previously highlighted, researchers should be able to identify most of the major inherited predisposition genes within a short period—perhaps 5 years. The Working Group's task is to take information such as this and translate it into possible alternatives that would lead to real advances in diagnostics and care.

The Developmental Diagnostics Working Group, also newly formed, is responsible for helping cancer researchers to understand the potential of advances in molecular genetics and technology. Dr. Harlow suggested that they also improve our ability to perform highly throughout diagnostic tests to reveal the full range of subtle differences in cancer cells.

A third working group that is just getting started is the Preclinical Models of Cancer Working Group. The two main goals of this group are to identify genes in the mouse that could be used to identify models of cancer development and to consider the advantages of looking at organisms that are very simple genetically to help understand human cancer cells.

Finally, an Early Detection Working Group may be started by January 1997 that will be primarily responsible for image technologies and will look for tumor markers that can be detected in easily accessible samples.

The fourth program within the Planning Office is devoted to Technology Development. Primary responsibilities include looking for developing technologies, along with conduits for these ideas to reach the NCI, and detecting technology problems that might be addressed by new developments. These strategies are implemented in the IRP, the ERP, and in worldwide industry.

NCI OFFICE OF SCIENCE POLICY QUESTIONS AND ANSWERS

Dr. Harlow explained the integration of extramural and intramural activities in the Planning Office's processes. As an example, he used the Cancer Genetics and Developmental Diagnostics Working Groups. These have representation from individual divisions, as well as representation from other NIH institutes and the extramural community. People from the Genome Center, for example, have been very important members of these Working Groups. Recruiting both intramural and extramural scientists to collaborate in these Working Groups has proven to be a fairly clear and easy way in which to integrate intramural and extramural activities and move forward.

Board members asked for further explanations of the logistics of the institutional planning processes, the timing of the site review groups, and the methods for looking into the scientific, research, and clinical programs at the NCI without looking at the changing community health care system. To address these concerns, Dr. Harlow responded that his Office was more structured to look at the scientifically based questions rather than the sociologically based issues. He welcomed suggestions as to how he could get his Office to expand to this dual structure.

Dr. Freeman elaborated on the point that discovery must be connected to "real people" if it is to help accomplish the aim of wiping out cancer. In further stressing his point, he suggested extending the "plan" to include this valuable component.

NCAB: 25TH ANNIVERSARY INITIATIVES—DR. ELLEN SIGAL

Dr. Sigal updated the Board on the progress of the Friends of Cancer Research (FOCR) 25th anniversary initiatives. The mission was clear: present an appreciation of what has been accomplished in the past 25 years in the war on cancer and, most importantly, introduce the tasks that lie ahead. To communicate to the public the need for continuing cancer research, FOCR will emphasize the importance of continuing research and hope to excite the general public about the opportunities ahead.

FOCR has an extensive media-based education plan that includes op-eds, editorial boards, talk shows, information packets, celebrity and congressional support, and a launching by President Clinton. Many of these events are scheduled for October and November of this year, with additional heavy emphasis in 1997 from January through April.

To involve the lay communities, Dr. Sigal stated that using the American Cancer Society (ACS), the NCCS, the other cancer centers, and the survivor networks should help to encourage large public involvement. Dr. Sigal stressed the importance of not only highlighting the physicians and the research that is going on in the community, but also survivors and other people who have benefitted from treatment.

Dr. Royston gave a recent example from his center in San Diego that involved patients who benefitted from experimental therapy. He felt that many people in the lay public were more profoundly moved by what these patients said than by what professionals such as he or Dr. Klausner could have said. He urged the inclusion of patients in the Friends' campaign. Dr. Sigal confirmed this.

NEW BUSINESS: SESSION I—DR. BARBARA RIMER

Dr. Rimer briefly discussed two topics in the new business session. The first was in reference to a letter that the NCAB had recently written supporting tobacco control measures (part of the Health Plan Employer Data and Information Set-3 [HEDIS-3]). One of the measures proposed, which asked patients about smoking and monitored smoking within managed care organizations, had been put forward. Dr. Rimer stated that the NCAB correspondence may have influenced this action.

The second topic was a reference to a Healthy People 2000 session on the Hill. Dr. Rimer had worked on this as part of the Subcommittee on Cancer Control and Information. She hoped that this session would bring some attention to the issue of smoking in young women.

ONCOLOGY NURSING SOCIETY--DR. KATHI MOONEY

Dr. Rimer introduced Dr. Kathi Mooney, the president of the Oncology Nursing Society (ONS). Dr. Mooney has conducted extensive research on the behavioral aspects of cancer.

The ONS was founded in 1975 and is the largest professional society devoted to cancer world wide and currently has over 24,000 members. The mission of ONS includes a commitment to achieve quality cancer care, as well as to promote the role of nurses in cancer care. A new strategic plan, adopted by ONS, will directly focus activities on the impact of health care reform, outcomes research, new opportunities for nurses in cancer care, and external partnerships. ONS supports efforts to involve nurses in activities that will reduce cancer incidence, mortality, and morbidity and will improve the lives of those who experience cancer and its aftermath. ONS strives to assure the contributions of registered nurses' to cancer care. ONS supports activities that prepare nurses for new roles in cancer, such as cancer genetic testing.

ONS supports research through a small grants program that addresses clinical problems in cancer care such as symptom management, survivorship, end-of-life care, and quality-of-life. ONS is also concerned about the potential impact of changes through health care reform and managed care that may threaten the quality of care that has been achieved. Access to care—particularly for the underserved—and the safe delivery of treatment are issues of concern. These include the delivery of clinical trials, access to supportive care, psychosocial support, survivor needs, and end-of-life care. And, finally, ONS is concerned about who would provide that care. Dr. Mooney stated that access to oncology expertise was broader than simply access to oncology physicians—it must also include access to nursing and other health care providers.

Dr. Mooney believes that recent changes in health care have already had an impact on the nursing industry. Primarily, this includes what she referred to as the "de-skilling" of nurses. This takes the registered nurse away from direct patient care and uses cost-saving, unlicensed personnel to provide direct line care to individuals with cancer and their families. The nurse, in turn, provides a supervisory role. As a result, initiatives are forthcoming from ONS to address these concerns and to promote nurse's roles and contributions to quality cancer care. Also, ONS will continue to emphasize and promote issues of importance to nurses, namely cancer pain relief, cancer fatigue, and end-of-life care.

Dr. Mooney hopes that an increase in collaborative relationships between ONS and outside partners, including the NCI, will be achieved.

ONCOLOGY NURSING SOCIETY QUESTIONS AND ANSWERS

Dr. Freeman asked Dr. Mooney if she had any nonanecdotal evidence to support her comments about the impact on cancer care by the "de-skilling" of nursing. Dr. Mooney agreed that evidence was necessary to support this and mentioned that there were a couple of "loose" surveys that reported this type of activity. Dr. Mooney reiterated that a goal of ONS was to support this supposition with data.

INTERIM REPORT ON THE TASK FORCE ON GENETIC TESTING—DR. NEIL HOLTZMAN

Dr. Rimer then turned the meeting over to Dr. Neil Holtzman for a presentation on genetic testing. The many related legal, policy, scientific, and behavioral issues have been a concern for the Board and the Task Force on Genetic Testing.

Dr. Holtzman began by discussing the implications of the discovery of a new human gene. Because an initial, practical application of such a discovery is the ability to test individuals for a variety of inherited mutations, two questions immediately come up in the development of these tests. The first is: How strong is the association between mutations and disease? The second question, which was the focus of the presentation, is: What can be done to reduce risks in apparently healthy individuals? This situation is frequently encountered in genetic testing for cancer predispositions. Unfortunately, Dr. Holtzman said, there is no systemic means for answering these two questions and, at the rate at which our ability to predict future disease is accelerating—due in part to the Human Genome Project—what will happen in the interim is unknown. Dr. Holtzman informed the Board that commercial interest in developing tests for genetic disorders is increasing and, not surprisingly, this interest is directed largely at relatively common disorders, such as various types of cancer, Alzheimer's disease, heart disease, and hypertension.

Input from several organizations, such as the National Center for Human Genome Research (NCHGR), the NCI, and the National Institute of Nursing Research (NINR), aided in the decision for the Ethical, Legal, Social Issues Working Group (ELSI) to set up a task force on genetic testing. This group is working closely with the Genome Project and the Secretary of the Department of Health and Human Services (DHHS), Donna Shalala. The Task Force's goals are to make recommendations to ensure 1) the development of safe and effective genetic tests, 2) the delivery of these tests in high-quality laboratories, and 3) their appropriate use by health care providers and consumers.

The Task Force is currently examining the background and current state of genetic testing. After a full consideration of all factors, they will make recommendations to ensure the development of safe, high-quality testing. So far, about 30 "interim principles" have been laid out to govern genetic testing without getting involved in how the principles can be implemented. These principles deal with: scientific validation of genetic tests; assurance of laboratory quality; education, counseling and delivery of genetic tests; and oversight and support for test development.

Dr. Holtzman then detailed the scientific validation of genetic tests, citing that it was most relevant to the current state of genetic testing. The Task Force states that "the genotypes to be detected by a genetic test must be shown by scientifically valid methods to be associated with the occurrence of a disease. The observations must be independently replicated and subject to peer review." This will help to protect against unconfirmed associations between a gene and a disease. This principle is relevant for dealing with diseases that exhibit very complex heterogeneous etiologies where it is difficult to establish associations beyond reasonable doubt, such as has been done for colon and breast cancer.

To clarify this concept of the association between particular mutations and disease, Dr. Holtzman presented the three parameters that are examined when determining clinical validity. These are sensitivity, specificity, and positive predictive value—all extremely important factors when conceptualizing guidelines for genetic testing.

Dr. Holtzman also discussed the Task Force's Principle I-7, which states: "before a genetic test can be generally accepted in clinical practice, data must be collected to demonstrate the benefits and risks that accrue from those positive and negative results." He admitted that this would be difficult to assure before a specific test actually came on line. Dr. Holtzman mentioned three approaches. First, randomized, controlled trials which compare the safety and efficacy of different interventions are a concern as many women and/or physicians choose to not participate in these—although there may be increasing recognition that such trials are the best way to collect information.

In the second approach, patients choose their own interventions and follow protocols as are used in randomized, controlled trials. This less-systematized method may help in determining whether interventions are truly beneficial and of minimal risk. But, as Dr. Holtzman asserted, when people—both providers and patients—are allowed to choose their own interventions, biases exist that make it difficult to interpret the results of the study. This further adds to the complexity of the genetic testing issue.

The final approach involves tracking participants to help make correlations between the interventions and the ultimate outcome. Dr. Holtzman felt that continuing to do nothing would slow the progress of scientific knowledge and inquiry.

INTERIM REPORT ON THE TASK FORCE ON GENETIC TESTING QUESTIONS AND ANSWERS

Dr. Li inquired about the need for an ELSI-like committee for the NCI. Dr. Klausner didn't think that it would be needed, as the Cancer Genetics Working Group overlapped the activities of the ELSI Working Group.

Dr. Sigal conveyed to the Board the concerns of people having the choice to participate or not participate in randomized, clinical trials. She felt that consumers and physicians would understandably be reluctant to participate. Dr. Holtzman agreed but commented that, until good answers were provided as to how to deal with the various followups of a positive test result, many people will be in the dark about how to proceed.

Next, Ms. Stovall asked Dr. Holtzman what he was doing to ensure that the intersection of the public/private marketplace for treating people for genetic predispositions was being addressed. Dr. Holtzman explained the differences between the Food and Drug Administration (FDA) regulation for commercial companies that manufacture test kits (e.g., home pregnancy or HIV test kits) and those that offer services. Currently, laboratories offering genetic testing for cancer only offer services. FDA has the authority to regulate both and the former are actually well-regulated, but the latter, perhaps because of lack of resources, have little FDA regulation. A model considered by the Task Force and Institute of Medicine (IOM) involves the use of "conditional approval" by the FDA. This would put some of the responsibility for data collection and monitoring in the hands of test developers. If problems with the test arose, the application could be withdrawn or approval denied. If the test looked good and demonstrated real benefits, then the "conditional approval" would be removed and the test would become fully approved. During the period of "conditional approval," the lab could include a profit in its price.

Dr. Freeman asked Dr. Holtzman if he believed that it would be ethical for a company to own a human gene. Dr. Holtzman responded by first noting that, regardless of the ethics involved, such situations were occurring. He also noted that there was a movement in the United States to outlaw this. Beyond this, Dr. Holtzman preferred not to respond because the Task Force has not considered patenting. He felt that one of the concerns about patenting, which might be related to ethics, was the idea of a company owning a gene or an analytical process and exerting a monopoly on the market—driving up the costs for consumers and/or insurers.

In response to Dr. Rimer's inquiry about a timeline for a final Task Force report, Dr. Holtzman informed the Board that the completion date had recently been set for the end of March 1997. Recommendations will be available in January through both the Federal Register and the Internet.

Ms. Levinson then brought another advisory commission—which the President had established—to the attention of the Board. Members of the advisory commission represent a very broad range of people including, public community representatives, ethicists, philosophers, clinical and basic scientists, and lawyers. The President charged the commission to deal with the rights and welfare of human subjects, as well as the use and management of genetic information, including human gene patenting.

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

Dr. Harold Freeman opened his presentation by asking the Board to consider that an estimated 58 million Americans are covered under managed care. Predicting that this number would continue to increase, or perhaps even "explode," Dr. Freeman speculated that managed care might end up as the major mechanism for health care coverage for Americans. This, then, would become a special concern for the research community and those concerned about cancer care. For this reason, the President's Cancer Panel has made managed care the major issue for its meetings this year. The first meeting, which approached the issue of the effect of managed care on the war against cancer, was inconclusive as to whether this system of care was "friend or foe."

The Panel continued to be concerned that the market-driven aspect of managed care, with its emphasis on cost containment, might reduce access to quality medical care and, ultimately, could impede the ability of the research community to translate results for the public's benefit.

At the first meeting, the Panel explored the capacity of clinical investigators to conduct research, outreach activities, and research dissemination. The Panel also attempted to collect information on the availability of quality health care to all segments of society. A recurrent theme was that access by patients to trials or to studies at institutions of their choice was being limited by economic considerations of third-party payers. There is increased hesitation among researchers at undertaking complex experimental therapies because patient reimbursement may be difficult to obtain. Delays in treatment due to lengthy preapproval are resulting in patient ineligibility. These two issues, as well as other factors, affect the type and the number of patients that are recruited into clinical trials. The testimony also suggested that higher-income patients were being favored over lower-income patients with regard to participation in cancer research trials.

On the positive side of managed care, Dr. Freeman mentioned some of the opportunities it offered. Regarding cost, there was some perceived benefit of managed care's emphasis on reducing cost for some clinical trials by streamlining study protocols and eliminating certain costly tests for protocol patients. Additionally, partnerships among cancer centers, insurers, physicians, and drug and biotechnology companies have been formed to help reduce duplicative studies and resource depletion.

Dr. Freeman reported that the Panel believed that every approved clinical trial had the opportunity to advance the quality of cancer care. These trials ultimately benefit health plans and patients. He continued by stating that advancing cancer knowledge would make good economic sense. The public, he felt, tended to want to choose the lowest cost plan when healthy, but demanded the latest treatments and the newest technologies when faced with cancer. It will be a challenge for researchers to convince managed care providers that each clinical trial has been well thought out, is informative and cost effective, and will provide society with benefits that go beyond the marketplace.

Another challenge will be to provide hard—rather than anecdotal—data regarding the cost of clinical trials and impact of managed care on the accrual to trials. This will be necessary to help the cancer community educate the public, patients, insurers, providers, and lawmakers about the value of supporting clinical research. Other concerns included decreasing the time between research results and their "bedside" implementation; the need to at least rearticulate, if not redefine and reclarify, the definition of "clinical research" and its various phases—to clarify the differences between "experimental therapy" and "clinical trial"; and to define what "managed care" really is.

Some issues that the Panel wished to bring to the attention of the Board included whether or not patient access to a defined category of clinical trials should be mandated and become standard care for the American public; the impact on quality of care of increasing outpatient care versus inpatient care; and who should assume responsibility for payment of patients on clinical trials.

Dr. Freeman elaborated on the last issue with some testimony from the first Panel meeting. The managed care insurance companies contend, for example, that payment for patients on clinical trials should come from sponsors, such as pharmaceutical companies or the NCI. This is based on their views that academic medical centers are expensive and inefficient, and that Phase IV outcomes of effectiveness research are more justifiable than Phases I, II, or III. Sponsorship from pharmaceutical companies or the NCI creates a dilemma for researchers, as they feel that

these funds rarely cover the full costs of clinical care of patients who are on trials.

The second Panel meeting, scheduled for September 24, will address the impact of managed care on clinical trials as it relates to the issue of patient care. The final two meetings will be held on October 25 and November 22. At these two meetings, the focus will be on changes in translational research affecting the Northeast and Southeast part of this country. Broader issues regarding outreach and information dissemination, education, and training will also be addressed.

Based on what the Panel has heard thus far, Dr. Freeman stated that the Panel believes managed care is clearly having an impact on clinical research and cancer care in general. What is not yet clear is the real extent to which managed care is interfering with research. The Panel hopes to reach some conclusions about this point later in its deliberations. Furthermore, Dr. Freeman stated that clinical research on prevention, diagnosis, and treatment of cancer, as well as the translation of research findings to the public, must continue to be supported to provide the best quality of care to cancer patients. The war against cancer cannot be won in laboratories alone.

Dr. Freeman acknowledged that managed care is succeeding in controlling costs, but he believes that, in so doing, it has brought about the rise of certain other problems. He stressed that a medical care system driven by the marketplace raises significant social, moral, and ethical concerns and questions about the problems of advancing research and providing quality care.

In closing, Dr. Freeman proposed the question of who will pay for research under this new system. In the final analysis, he speculated, perhaps the outcry from sick patients who are experiencing the actions of the managed care company will determine the ultimate fate of managed care.

REPORT OF THE PRESIDENT'S CANCER PANEL QUESTIONS AND ANSWERS

Dr. Sigal opened the question and answer session by asking Dr. Freeman if he thought that anything of significance, in terms of clinical trials or clinical research in a managed care environment, was going to happen with a nonregulatory approach. Dr. Freeman responded that, to avoid failure, all managed care companies would have to abide by a certain set standard that would neutralize the marketplace considerations.

Next, Dr. Royston commented that, at his institute in San Diego, he sees the effects of managed care mentioned by Dr. Freeman. His second comment addressed the issue of payment of sponsored research. He felt that some of the pharmaceutical companies do pay the full cost of doing clinical research; yet complaints are continually voiced that the NCI, in its Cooperative Trials Program, does not. He suggested that the NCAB and the NCI really needed to attack that very important issue.

LEGISLATIVE UPDATE—MS. DOROTHY TISEVICH

Ms. Dorothy Tisevich opened with comments regarding an amendment to the Agriculture and Appropriation Bill (FY 1997) by Congressman Durbin (D-IL), which would shift \$25M out of a tobacco subsidy line and into rural economic development and safe drinking water loan programs. This amendment was defeated on the House floor in June 1996 by two votes. Ms. Tisevich promised more information about the amendment to the Board.

She then updated the Board on the FY 1997 appropriations for the Labor/HHS bill. For the NCI, the House mark is \$2.386B, which is about \$138M over the FY 1996 level. Ms. Tisevich noted that indications were that the Senate's proposal would be less than that of the House but greater than that of the President.

She proceeded with details on the Department of Defense (DoD) appropriation bill, which this year will include funding for breast cancer and prostate cancer research programs. In the House, the DoD bill proposed providing \$125M for breast cancer research; there was not a major increase for prostate cancer research. The Senate proposed \$150M for breast cancer research and a \$100M increase for prostate cancer research.

Ms. Tisevich gave a final update on the NIH Revitalization Bill, which she said would not be acted on during the 104th Congress. Clearly, the current plan was to get the appropriation bills out. The House had finished all 13 of their bills, all of which had been reported. The Senate still had 8 bills to go, with little time left.

Ms. Tisevich discussed two other bills. One was related to the need for consumers to have access to information in a more streamlined fashion. The second was the Rockefeller-Johnson bill, which would require that the Health Care Financing Administration (HCFA) undertake a demonstration project to cover cancer patients, that is, beneficiaries who are entering clinical trials. Though this bill had tremendous support and a tremendous amount of pressure behind it—which may prompt some greater degree of responsiveness by HCFA to undertake such a demonstration project—it was unclear whether this bill itself would go anywhere.

RECOMMENDATIONS BY THE COMMISSION ON RESEARCH INTEGRITY: SCIENTIFIC MISCONDUCT—DR. WILLIAM RAUB

Dr. William Raub familiarized the Board with the background and the progress of the Commission on Research Integrity (CRI) recommendations regarding scientific misconduct. The Implementation Group on Research Integrity and Misconduct (IGRIM) was established to propose to Secretary Shalala which of these recommendations warranted implementation. Thirty-three recommendations were made. This Group was also to suggest steps to be taken for effecting these implementations. Of the 33 recommendations, the IGRIM found 23 suitable for implementation. In response to these recommendations, the National Academy of Sciences (NAS) wrote a letter to Dr. Raub indicating that they did not support the IGRIM report and made suggestions for amendments. A concern for the Board at this NCAB meeting was to endorse either the IGRIM report or the NAS letter.

Dr. Raub stated that, from the beginning, the first principle of DHHS' dealings with instances of real or apparent misconduct has been to view the research institutions as the first line for both prevention and response. Many of the Commission's recommendations tended to reinforce that idea.

In endorsing the concept of more ORI site visits to awardee institution, IGRIM did not agree with the recommendation that site visits should be opportunities for "whistle-blowers" to meet independently with site visit groups to voice a grievance. And although they thought they understood the motivations of the Commission with respect to giving whistle-blowers an opportunity, it seemed that the opportunity would, in such instances, contradict other principles of the Commission. In making their generally concurring proposal on this recommendation, the IGRIM specifically noted an area of disagreement and a more narrow implementation than a literal reading of the commission report would have indicated.

One of the other four recommendations upon which the IGRIM disagreed was the proposal that the investigation and adjudication functions be separated organizationally. Dr. Raub summarized this by saying that the Group believed an organizational change would not add value and, if anything, might incur expenses without dealing with the very fundamental questions. Therefore, they believed that the current organizational arrangement was a satisfactory framework.

The second disagreement involved a proposed "special layer" of the process review overseeing the Office of Research Integrity (ORI), in addition to what already was in place with the Office of the Inspector General, the Office of the Secretary, and special oversight. Again, they did not believe that additional resource expenditures would be appropriate.

Third, the Commission recommended that, upon completion of investigations, the ORI should publish a full disclosure of the information, including the names of individuals, even in those instances where the individual was cleared of the suggestion of wrong-doing. The current practice, Dr. Raub reminded the Board, included an extensive information disclosure, but without the names of cleared individuals. Once again, they reaffirmed the current practice.

In the last of the four dissensions, the Commission recommended that the NIH, because of its flagship position in the research community, be held to some higher level of requirements. Dr. Raub's group disagreed with this. First, they believed that the Commission did not fully consider that NIH was already under different restrictions than academic institutions; and, second, they did not see any value added by this new recommendation. Consequently, they chose to reaffirm the current set of practices.

One of the most controversial elements of the report was its focus on "whistle-blowers." The IGRIM report challenged the Commission on what was perceived as an apparent imbalance in the way the Commission approached this issue. The Group felt that, although a careful reading of the Commission's whistle-blower bill of rights demonstrated their attempts to grapple with the rights and responsibilities of all parties, a quick interpretation could be that the focus was much more on the rights of whistle-blowers and the responsibilities of others than on the responsibilities of whistle-blowers and the rights of others. So, they recommended that, as the DHHS moved to develop regulations in this area, it should weigh not only the Commission's observations and findings, but also the concerns expressed by the IGRIM and others about issues of balance from these many perspectives.

Dr. Raub stated that since other factors governed the situation for this particular recommendation, in reality, the DHHS had a statutory requirement in this area. Dr. Raub believes that the implementation of this recommendation was deferred with the creation of the Commission and with the full understanding and support of the Congress. Now that the Commission report has been submitted, the DHHS has the responsibility to proceed with the statutory requirement of having a whistle-blower protection regulation. Dr. Raub informed the Board that a working group has been activated to address this set of issues. Many institutions have already pointed out that they have mechanisms in place such as faculty grievance procedures and would like the opportunity to build upon these mechanisms, rather than either create wholly new systems.

Another controversial feature of the Commission report had to do with its proposed definition of what constituted misconduct. Dr. Raub felt that recognizing similarities to or differences from what was currently in place depended on the reader. Because the IGRIM felt strongly about the importance of government-wide uniformity on the definition of misconduct, Dr. Raub visited with the staff in the Office of Science and Technology Policy and called the Commission's report to their attention—especially the recommendation about government-wide uniformity. As a result, an interagency group has been at work trying to define an approach that all of the major science agencies in the government might endorse.

Dr. Raub noted that underneath some of the controversial issues are also some important points, one of which is structuring the definition to try to reconcile the concerns of scientists, lawyers, and others who might deal with its investigative and adjudicative aspects. A second issue is that "falsification" should include the failure to disclose important pieces of information, as well as the overt misrepresentation of information.

Dr. Raub said that further work is needed on some fundamental questions regarding the proper delineation of roles among the federal government, universities, and the scientific societies. Also, there are questions as to the proper role of the federal government, if any, with respect to some of the so-called "lesser sins," such as authorship practices, selective reporting, and certain publication practices.

Dr. Raub closed his presentation by informing the Board that Secretary Shalala had received this report and would be making a final decision about the implementation steps once the report of the interagency group is in hand.

RECOMMENDATIONS BY THE COMMISSION ON RESEARCH INTEGRITY: SCIENTIFIC MISCONDUCT QUESTIONS AND ANSWERS

In response to two questions from Dr. Robert Day concerning the NAS letter, Dr. Raub commented that the letter, which was receiving a good deal of attention, was one of the clearest and least equivocal expositions of the limits of the definition of misconduct. He proceeded by saying that whatever steps the DHHS chose to take on the major issues would be subject to a broad solicitation of public comment. The final decision would come from Secretary Shalala after comments had been analyzed and weighed.

Dr. Klausner asked if there is a set of issues that would be addressed regarding the rights of the accused as related to the issue of the whistle-blower. He emphasized this as he sensed that the rights of the accused in the scientific community have been lost. Dr. Raub confirmed that part of the thrust of the commentary was to ensure that they address the rights and responsibilities of the whistle-blower, the accused individuals, and the institutions. He noted the importance of being able to cross-examine under conditions in which evidence was presented. He felt that this needed to be put in place very early in the process, particularly before it moved beyond an institution.

Dr. Sigal had several concerns. First, she felt that the issue of the government-wide definition of misconduct was problematic. She was particularly concerned that it may "go too far." In reply, Dr. Raub reiterated the concerns expressed by many in the research community, especially university leaders. They felt that if a situation was misconduct for one department but not another, the confidence in the whole system could be eroded and money wasted.

Dr. Sigal also felt that the report did not stress the rights of the accused enough, since those who willfully have misappropriated differ substantially from those who get audited by accident.

Dr. Day indicated that strong misconduct issues could only appropriately be handled by the courts and no administrative process would be sufficient. In agreeing that the courts could be viewed as the legal venue, Dr. Raub indicated that their implementation report was virtually silent at that level of process. Dr. Day explicitly stated that he did not believe that either the recent or proposed administrative processes are comparable in any way to what is available through the courts.

Conversely, Dr. Michael Bishop stated that he would fully endorse the NAS criticisms as he felt that the words "fabrication, falsification, and plagiarism" were clear, precise, and had well-defined meanings. Dr. Royston, however, questioned whether these words were truly all-inclusive of ethical misconduct. They briefly debated over specifics related to actions included in the definition of "plagiarism."

Dr. Raub's final observation was that, although arguing the issues was important and appreciated, what was basically at stake was describing the covenant between the agencies of the federal government and the scientific community-at-large regarding these issues and, particularly, the scope of the federal government's role.

As a final thought, Dr. Klausner felt that pursuing comments from the interested public may be very valuable for DHHS, to be aware of the disparity between the public perception of science and reality regarding the ability of science to police itself in these issues.

CANCER CENTERS REVIEW GROUP UPDATE—DR. ROBERT DAY

Dr. Day's update was very brief, stating only that the Cancer Centers Review Group Report was due to be presented to Dr. Klausner on October 14. The report will be released after that date and will be discussed at the November NCAB meeting.

HOW THE NCI SETS ITS R01 PAYLINE—MR. STEPHEN HAZEN

Mr. Stephen Hazen stated that some clarification is necessary as to the decision-making process involved in setting the R01 payline—a process that he feels is unfamiliar to the extramural community.

Mr. Hazen gave some working definitions. The first was "setting the payline." This phrase describes the process used to select which grant applications the NCI will fund based on "peer-review results." These are priority scores for P01s and derived percentiles for R01s. "Payline" refers to the least well-regarded percentile ranking or priority score that will be funded within the budget for a given fiscal year.

Mr. Hazen informed the Board that the process of setting the payline includes a consideration of the NIH "cost management principles." These principles stipulate that the average cost of the competing cohort in one fiscal year can be no more than the average cost of the preceding fiscal year plus 4 percent. The cost management principles were articulated several years ago by the NIH director as a means of addressing some concerns Congress had about the increase of the average cost of research grants.

The NCI also considers how much it wants to set aside for exceptions, that is, funding grants that are outside the payline, which should be paid even though the score is not within the percentile.

When setting the R01 payline for the year, the NCI looks at the prior fiscal year as a model, and also at how the grant applications come in for the three review rounds. When setting the initial payline, some projections are necessary as the total number of grants and the costs for each percentile point for the end of the year are still unknown.

Dr. Sharp asked if, when doing these analyses, they consider the numbers of investigators already in the system, coming into the system, leaving the system, etc. Mr. Hazen responded that, although they are unable to analyze demographics this way, they do make attempts to ensure that the R29s (the First Awards) represent that population. Adding to this, Dr. Klausner informed the Board that they also routinely move money from one line to another.

Dr. Klausner notified the Board that the EC recently decided that they will move monies as needed to make sure that the payline does not drop below the 23rd percentile. To assure this, they prioritized so that the payline came first, AER second, and exceptions third. Exceptions, he continued, are very valuable for addressing the issue of stability, because they can fund individuals who would otherwise lose their grants.

HOW THE NCI SETS ITS R01 PAYLINE QUESTIONS AND ANSWERS

Dr. Li, Dr. Klausner, and Dr. Kalt discussed percentiling and setting rigid paylines. Dr. Li felt that if they set the payline by percent, and all the proposals were poor, somebody would still get the best score. Dr. Kalt clarified this by saying that, although percentiling was used, they still had the raw score numbers, where "outstanding" still meant "outstanding", "excellent" was the second tier, etc.

BEHAVIORAL SCIENCES RESEARCH MEETING REPORT—DR. THOMAS GLYNN

Dr. Thomas Glynn, Chief of Prevention and Control, Extramural Branch, in the Division of Cancer Prevention and Control (DCPC), presented the recommendations from the Working Group on Behavioral Research, which met April 11-12, 1996, to define priorities in behavioral research in cancer prevention and control. The recommendations of this group will be combined with those of the Prevention Working Group and the Cancer Control Working Group to set priorities about needs and opportunities in behavioral research.

Dr. Glynn stated that the three main areas where behavior research could affect cancer prevention and control are tobacco, diet, and screening. He reviewed the progress in each of these areas, including reductions in smoking rates, successes in improving dietary consumption of vegetables and fruits, and dramatic increases in mammography screening rates. He also highlighted the shortcomings in each of these areas, such as the consistently high rates of high school smoking, the small percentage (23%) of Americans eating 5 or more servings of vegetables and fruits per day, and the unsatisfactory screening rates for male colon cancer.

The working Group defined six priorities for behavioral and communications research. The number one priority is preventing tobacco use in children and teenagers. The second is enhancing risk communication and decision-making. The Group felt that people still tended to either under- or overestimate their cancer risk, and also to under- or overvalue what they see as the value of treatment. The third priority is integrating preventive and early detection services into changing health care delivery systems. Great opportunities exist, Dr. Glynn believes, to incorporate dietary counseling, treatment for nicotine dependence, and increased screening into managed care.

Improving the outcomes of genetic testing for cancer susceptibility was noted as a priority by the Working Group. As these tests become available, health care professionals and counselors will need to be able to help people deal with the information that they receive and interpret it correctly.

The final two priorities include enhancing the quality-of-life for the increasing numbers of cancer survivors, and promoting healthy diets and physical activity to help prevent and control cancer. Both basic and applied research in the lab, the clinic, and the community are needed to address these six priorities.

Dr. Glynn stated that, in addition to identifying specific research needs, the NCI needs to communicate these ideas to investigators, funding agencies, and potential partners. He said that there has been a feeling among the behavioral research community that the NCI either didn't care or wasn't able to review their proposals. The biggest challenge now is applying and using the available research and supplying it to those who can use it.

In terms of evaluation, the Working Group discussed several possibilities. The Group is interested in seeing changes in grant submission and funding patterns. Measuring the progress of the Healthy People 2000 cancer objectives should be another important evaluation component.

Dr. Glynn discussed several approaches to increase behavioral research. First, the Working Group will be bringing specific research proposals to the Board of Scientific Advisers (BSA) and, ultimately, to the NCAB. A Program Announcement, aimed at the six priority areas, will be one of their first strategies and will be followed with a joint request coming through the Office of Behavioral and Social Science Research. They will be trying to carry out a joint activity among the institutes. Finally, they will try to bring several very targeted RFAs concerning behavioral research to the BSA.

BEHAVIORAL SCIENCES RESEARCH MEETING REPORT QUESTIONS AND ANSWERS

Dr. Klausner stated that it was important to reiterate that this Group is working on articulating real plans and initiatives in this important area. He stated that this could be considered an opportunity within managed care. He then mentioned that the NCI is interested in expanding the model of the DoD/NCI clinical trials agreement to prevention in the broadest sense, with medical delivery in payer systems. The NCI is also very close to signing a Memorandum of Understanding with the Veteran's Administration (VA) system, under which there would be an agreement to include prevention and behavioral research, as well as treatment research in Phases I-IV.

Dr. Calabresi discussed some data on smoking prevalence in white and black teenagers. Apparently, there are considerable differences between these groups, with whites smoking at much higher rates than blacks. Dr. Sherry Mills, Program Director, Prevention and Control Extramural Research Branch, DCPC, further addressed this topic. She informed the Board that, although there is a three-fold difference between the groups, the gap is getting smaller, because black teen smoking rates are increasing. She commented that the differences could at least partially be attributed to parents' prioritization of undesirable behaviors. Dr. Alfred Goldson said that this combination of risk communication and family decision-making is truly an exciting field, and he looks forward to future followup.

Dr. Klausner reiterated the importance of these two areas and informed the Board that he had asked the Office of Cancer Communications (OCC) to produce a set of publications aimed at trying to find better ways to communicate risk, especially aimed at the health provider community.

SUBCOMMITTEE REPORT: CLINICAL INVESTIGATIONS—DR. PHILIP SCHEIN

Dr. Schein discussed the potential new initiatives to be incorporated into the 1999 Bypass Budget. The first initiative is related to general concerns about the problems of translating new discoveries into clinical trials. The Subcommittee thinks that the new Bypass Budget might provide an opportunity to expand the current activities of the NCI program in this area to ensure that well-trained physicians/clinicians are working with their basic science colleagues.

The Subcommittee also thinks that money put aside to support applications that aim to validate laboratories' observations would be a major asset to the overall program, particularly compared with the current speed at which technology is validated clinically through the more traditional Phase I through Phase III testing programs.

The second area discussed related to the issue of patient care costs serving as a barrier to the future generation of clinical data. The Subcommittee noted that, unfortunately, this trend was increasing. It was assumed that these trends would begin to affect institutionally based research grants, as denials of coverage increased. Short of enactment of new legislation that would obligate third-party payers to participate in clinical trials, the NCI might have to consider providing some share of patient care costs. Dr. Schein informed the Board that there was already some precedent for this. He stated that the place to include those costs is perhaps in the Bypass Budget—perhaps focusing principally on Phase I testing. Phase II and Phase III testing could probably find other ways to be covered. Dr. Schein said that, if nothing else, the inclusion of a very strong statement regarding the need to provide patient care costs to ensure clinical investigations might send important messages to Congress. But, he emphasized, the best approach to this problem is to force, through legislation, third-party payers to recognize their obligations to participate in this process.

Dr. Calabresi reaffirmed some of Dr. Schein's comments and suggested three alternative approaches to the one suggested by Dr. Schein. First, money could be acquired from the managed care companies. He explained that this would ultimately be providing new therapies for the future. The second possibility is to enlarge the clinical center program of the NIH, so that these studies could be done in a clinical center setting, but not only at those institutions that are lucky enough or prestigious enough to have the facilities. These studies could therefore be extended to reach more patients, such as in community hospitals. Dr. Calabresi thought that the third alternative—a hybrid of Dr. Schein's approach and the first two alternatives he proposed—might be the most palatable way to get the job done.

SUBCOMMITTEE REPORT: CLINICAL INVESTIGATIONS QUESTIONS AND ANSWERS

Dr. Royston brought to the attention of the Board the bill pending in Congress that would require Medicare to pay for clinical trial expenses. If this passed, Dr. Royston thought there would be a ripple effect throughout the HMO industry. He suggested to Dr. Klausner that, if it failed, Dr. Klausner should very strongly consider putting something like it in the Bypass Budget and should ask the President and Congress to pay for those expenses that are required, as Dr. Schein suggested.

Dr. Wilson suggested that, in addition to talking about the opportunities for the future, the 25th Anniversary initiatives should discuss the barriers that exist, such as those that are financial and time-oriented, related to doing clinical trials.

Dr. Rimer then made a motion to approve the minutes of the subcommittee. The minutes were approved unanimously by the Board.

SUBCOMMITTEE REPORT: PLANNING AND BUDGET—DR. ELLEN SIGAL

This subcommittee discussed the mission of the Bypass Budget and was very pleased that the document was readable and user friendly. The discussion mainly centered around the document being a three-year-cycle budget. Changes will be made on an annual basis in terms of yearly updates and accomplishments, and immediate opportunities that could translate to immediate progress.

Dr. Sigal suggested that making this document available to groups other than the Congress is very important for educating the public and constituent organizations about the importance of the Bypass Budget.

Dr. Rimer then made a motion to approve the minutes of the subcommittee. The minutes were approved unanimously by the Board.

PEER REVIEW INITIATIVES: RGA PROGRESS REPORT—DR. MARVIN KALT

The stated purpose of Dr. Kalt's presentation was to inform the Board about study section behavior to enable the Board to interpret scores better. He discussed changes in scoring behavior in the Division of Research Grants (DRG). One change was related to the situation where reviewers rescored applications that they previously approved for funding, but which were not funded at the end of the review process. This led to compressed and perhaps meaningless percentiles because of the reviewers' attempts to "inflate" scores so as to ensure funding after the second round. As a consequence, reviewers were asked to refrain from "grade inflations."

When a study section reviews applications from a single discipline assigned to the same NIH institute, this inflated score effect is essentially lost because of analogous judging criteria. However, study sections often exhibit uneven objectivity when reviewing applications from different disciplines and different institutes. A disproportionate effect may arise—either positive or negative—in terms of being afforded an opportunity for funding.

A number of experiments have been going on regarding the use of scores for funding decisions. Dr. Kalt stated that AER, practiced by the NCI's EC, has led to an experiment in DRG called accelerated peer review. This experiment involves DRG asking their study section members to include some straightforward pieces of information for quick amendment if they feel that an application is competitive but not certain to fall within the payline. When the initial review group identifies such an application, the DRG will bring that application back to the next meeting, 4 months later—together with additional or amended documents from the applicant—as a one-round deferral reconsideration of an amended application, cutting the turnaround time in half. This approach, although ideal for some, will not accelerate the process for all, as review groups often do not know the payline for the applications they review. Dr. Kalt acknowledged that this approach has not yet been evaluated. The principal intent is to start to think about whether or not there are ways NIH can expedite final funding decisions.

Dr. Kalt discussed additional concerns about grant applications. First, the obligations the NIH has to previously funded research—that comes back for continuing funds and falls short of the payline—must be considered. The NCI, he explained, has had interim funding for Type 2 applicants (i.e., already funded) for a number of years, to help support their activities at a core level, while a final decision can be made either through the amendment process or through AER. Case-by-case financial status consideration of individuals who find themselves in this predicament is also practiced.

Considering that funding previously established projects decreases the amount of money for new projects, Dr. Kalt suggested that one of the policies that the NCAB might wish to discuss is the balance of support for new versus continuing investigators. The consequences of missing the results of a continuing research project that is closed out must be considered. Phase-out funding is established to help finalize projects in order to complete and publish the data. Dr. Kalt suggested that the interest in interim support and bridge funding had been reopened at NIH due to the attention of Congress, which may lead to such funding becoming legislated.

Next, Dr. Kalt addressed the ways in which new investigators are supported and brought into the grants process at the NIH. He explained that the First Award, or the R29 award, has been maintained a differential payline relative to R01s, historically between 5 and 10 percentile points. However, because of the budget constraints put on the First Award, two-thirds of new investigators choose to use RPG mechanisms over the R29. As a result, a trans-NIH committee is being formed to review the best application format and the best award mechanism to support and encourage careers of new investigators in an RPG environment.

Dr. Kalt's final topic was the Review of Grant Applications (RGA) Report for the RGA initiative. This report was prepared by an internal NIH working group that determined a series of questions about how grants are evaluated, how review is structured, and what the possible alternatives are to the current scoring system. Dr. Kalt said that it is the intention of NIH, if possible, to implement a new fundamental review scoring paradigm for FY 1998. This would include application evaluation and scoring in completely different ways than what is presently being done.

The DRG will soon start a series of experiments to evaluate some of the factors discussed in the RGA report. For example, some of the original recommendations that were examined by the Peer Review Oversight Group—a group

that was set up to try to achieve some kind of global, generic consensus of how peer review should be modified.

Dr. Kalt informed the Board that, within the original text of the RGA report, three criteria are proposed—significance, approach, and feasibility. These criteria are evaluated and commented upon and scored independently. The Peer Review Oversight Group was initially unsatisfied with the RGA report and suggested adding a criterion for innovation/creativity as another dimension for evaluation and review.

A second recommendation in the RGA report is that there should be a separate review section for each criterion. The Group felt that more information would be helpful to the applicant and the program staff's decision-making.

It is further recommended in the RGA report that reviewers should score the various dimensions; that is, they should not assign an overall global score. The Peer Review Oversight Group, in contrast, has a very strong leaning to a global score. This is still under active discussion.

Other recommendations include changes to the scale, such as using a 1 to 10 system, with 10 being the best and 1 the worst. Also, the number of points along the scale was considered. The report recommends that the scale should be anchored at the ends with criteria for the best and worst applications.

The report suggests that scores be normalized for each reviewer, that is, peer reviewers essentially would have to rank their votes. This idea was the focus of significant discussion by the Peer Review Oversight Group and was not strongly supported.

In conclusion, Dr. Kalt informed the Board that the progress of the RGA report recommendations could be followed on the NIH home page. He will also be reporting back to the NCAB as these experiments start to take place in DRG.

REPORT ON THE NCAB RETREAT—DR. BARBARA RIMER

The goals of the retreat were to examine the workings of the Board to determine how they could be improved to become more effective in helping the NCI to achieve its mission. The NCAB examined how to structure the agenda better and raised questions about the subcommittees. During the retreat, Board members discussed their visions of the Board's role as an advisory committee to the NCI. Individual Board members were in agreement with regard to the role of the NCAB. Dr. Rimer stated that the Board felt it needed to identify Board priorities in the area of policy.

Board members determined that the process used by the Board to carry out secondary review had improved over the years, but could get better. In terms of stewardship and advisory oversight, Board members questioned how they could ensure that they help the NCI to identify problems before they become crises. Dr. Rimer stated that tremendous progress had been made over the previous year-and-a-half in the area of budget and planning. Despite its strengths, the Board felt that it needed to focus its efforts more definitively when looking at investments and opportunities.

Dr. Rimer promised further discussion of the NCAB retreat at the November Board meeting.

PEER REVIEW INITIATIVES: RGA PROGRESS REPORT QUESTIONS AND ANSWERS

In response to Dr. Klausner's suggestion to comment on the EC discussion of the original recommendations, Dr. Kalt replied that he recognized that the EC had strong outside influence, and so he believed that they followed the traditional belief that there ought to be an overall unlinked score. Though there was some skepticism about certain other issues, he did not believe that anybody had problems with a revision of the scaling, in terms of the increments of the scale, the anchoring, and the number of units.

Dr. Sigal questioned the rationale behind the many changes in the scoring. She thinks that the critical issue is the composition of the peer review committees. Dr. Kalt replied that there have been two kinds of discussions regarding this issue. The first was a fundamental restructuring of the concept of a study section. What DRG essentially did, Dr. Kalt explained, was to aggregate study sections into larger groups of subcommittees. This allows for more flexible reviewer assignments across study sections and more flexible assignment of applications to some aggregation of members from across that larger pool.

In response to Dr. Rimer's inquiry about a timeline for these recommendations, Dr. Kalt informed the Board that the majority of evaluation results for the recommendations would be reported at the May Board meeting. Incorporated into this report would be a parallel review, so as to not disadvantage those who are part of the experimental arm of the study.

NEW BUSINESS: SESSION II—DR. BARBARA RIMER

The first topic to be revisited from the previous day's discussions was the Congressional legislation on the tobacco subsidy amendment, which was defeated by two votes. Dr. Kay Dickersin was interested in getting a list detailing how each person voted so that individuals might contact them with opinions. Dr. Rimer suggested that Ms. Tisevich would be of assistance in that area. Dr. Rimer and Dr. Bishop thought that knowing when such votes were to happen in advance would be better than an "ad hoc cleanup."

The second topic on the agenda was a continued discussion of the CRI report. Dr. Bishop moved to endorse the position of the NAS, and the motion was quickly seconded, followed by considerable discussion. A member indicated that he was not in total agreement with the NAS letter and hence had a hard time supporting the motion. Although he was sympathetic to the NAS letter in terms of the rights of the accused, he felt that the definitions in the CRI report were much clearer and inclusive.

Dr. Day addressed the serious questions he had about the validity of the ORI and about handling accusations such as these through administrative procedures. His personal preference was for Congress to pursue this so as to provide the court system's full protections. A first step in remedying this matter, he felt, would be to concur with the NAS' pronouncement.

Dr. Sharp agreed with the NAS letter and further explained that misconduct in science is dealt with in a variety of ways. It is dealt with among peers, at the institutional level, and now at the NIH or federal level. He felt that to have misconduct of such importance being investigated outside the community of peers, the institution, and the federal level, required a delineation of significance.

Dr. Klausner echoed Dr. Sharp's point that misconduct covers a wide range of activities, from those that are quite severe to those that are marginally illicit. He added that trying to implement a single structured policy across these varying degrees of wrongdoing might result in judicial difficulties.

Dr. Royston expressed his concern for limiting oneself to "plagiarism, fabrication, and falsification," as this would basically convey that these are the only things that one needs to worry about and be on guard against. The other behaviors would then be perceived as less serious. Furthermore, he thought that it is not necessary to send a message to scientists that these other kinds of misconduct are important, but what is needed is a message indicating that more types of misconduct exist than just those three items.

In response, Dr. Rimer commented that there are many other avenues for sending those messages, including universities, mentors, and professional organizations. Her concern was that the most profound and the most significant types of misconduct be reserved for this definition. She further felt that the CRI definition is really open to hearsay, innuendo, and witch hunts, and that it is not verifiable by the scientific method. She believes that this definition could have enormous impacts and is a huge mistake. She urged the Board to endorse the NAS statement.

Dr. Calabresi further supported the views of Dr. Day and Dr. Rimer, and stated that the CRI report would constitute an obstacle to cancer research and cancer science.

Dr. Rimer called for a vote. All members present voted to endorse the NAS letter with Dr. Dickersin and Dr. Royston abstaining, because they had not had time to read the related documents completely.

Dr. Rimer volunteered to write a letter to Secretary Shalala that reflected the Board's point-of-view with a copy to Dr. Varmus. At Dr. Rimer's request, Dr. Freeman said he would write a separate letter from the President's Cancer Panel, supporting the NAS letter.

ADJOURNMENT—DR. BARBARA RIMER

There being no further business, Dr. Rimer adjourned the open session of the 99th meeting of the NCAB at 10:35 a.m.