

## NATIONAL CANCER ADVISORY BOARD

convened on May 12-13, 1998, at the:  
National Institutes of Health  
Building 31-C, Conference Room 6  
Bethesda, Maryland 20892

### ATTENDEES

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**The National Cancer Advisory Board (NCAB) convened for its 106th regular meeting at 9:00 a.m., May 12, 1998, in Conference Room 6, C Wing, Building 31, National Institutes of Health.**

**NCAB MEMBERS**

Dr. J. Michael Bishop (Chairperson)  
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  
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 Visco

**Alternate Ex Officio NCAB Members**

Dr. Gwen Collman, NIEHS  
Col. Louis F. Diehl, DoD  
Ms. Lynn Jenkins, NIOSH  
Dr. Kenneth Kizer, DVA (absent)  
Ms. Rachel Levinson, OSTP  
Dr. Alison Martin, FDA  
Dr. Hugh McKinnon, EPA  
Dr. Lakshmi C. Mishra, CPSC (absent)  
Dr. Gerald Poje, NIEHS (absent)  
Dr. Prem C. Srivastava, DOE (absent)  
Dr. Ralph Yodaiken, DOL (absent)

**Members, Executive Committee, National Cancer Institute, NIH**

Dr. Richard Klausner, Director, National Cancer Institute  
Dr. Alan Rabson, Deputy Director, National Cancer Institute  
Ms. MaryAnn Guerra, Deputy Director for Management  
Dr. Robert Wittes, Deputy Director for Extramural Science; Director,  
Division of Cancer Treatment and Diagnosis  
Dr. Faye Austin, Director, Division of Cancer Biology; Chairperson,  
Extramural Advisory Board  
Dr. Joseph Fraumeni, Director, Division of Cancer Epidemiology and  
Genetics  
Dr. Peter Greenwald, Acting Director, Division of Cancer Prevention  
Dr. Marvin Kalt, Director, Division of Extramural Activities  
Dr. Edison Liu, Director, Division of Clinical Sciences  
Dr. Barbara Rimer, Director, Division of Cancer Control and Population  
Sciences

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

#### **Liaison Representatives**

Dr. John Currie, American Association for Cancer Education, Inc.  
Dr. Margaret Foti, American Association for Cancer Research  
Dr. Marc E. Lippman, American Association for Cancer Research  
Dr. Robert Martuzza, American Association of Neurological Surgeons  
Ms. Kerrie B. Wilson, American Cancer Society  
Dr. John Stevens, American Cancer Society  
Dr. Stanley Zinberg, American College of Obstetricians and Gynecologists  
Dr. Bernard Levin, American Gastroenterological Association  
Dr. Edward P. Gelmann, American Society of Clinical Oncology, Inc.  
Dr. Eli Glatstein, American Society of Therapeutic Radiologists  
Dr. Edwin A. Mirand, Association of American Cancer Institutes  
Dr. Robert W. Frelick, Association of Community Cancer Centers  
Ms. Laura Liebermann, Candlelighters Childhood Cancer Foundation  
Dr. Lovell A. Jones, Intercultural Cancer Council  
Dr. Armin D. Weinberg, Intercultural Cancer Council  
Ms. Katharine R. Boyce, Intercultural Cancer Council  
Ms. Martha M. Kendrick, Intercultural Cancer Council  
Ms. Jean Ard, Leukemia Society of America  
Ms. Dorothy J. Lamont, National Cancer Institute of Canada  
Dr. Robert A. Phillips, National Cancer Institute of Canada  
Dr. Tracy M. Walton, Jr., National Medical Association  
Dr. Eve I. Barak, National Science Foundation  
Ms. Pamela Haylock, Oncology Nursing Society

Dr. Linda U. Krebs, Oncology Nursing Society  
Dr. Jeffrey Norton, Society of Surgical Oncology, Inc.  
Dr. Marston Linehan, Society of Urologic Oncology

### CALL TO ORDER, OPENING REMARKS AND CONSIDERATION OF MINUTES OF PREVIOUS MEETINGS

Dr. J. Michael Bishop

Dr. J. Michael Bishop called to order the 106th meeting of the National Cancer Advisory Board (NCAB), and introduced guests representing cancer education and research associations and advocacy organizations. He welcomed members of the public and the press and invited them to submit in writing, within 10 days, any comments regarding items discussed during the meeting. A motion was requested and made to approve the minutes of the February 1998 meeting. They were approved by the Board unanimously.

### FUTURE BOARD MEETING DATES

Dr. J. Michael Bishop

Dr. Bishop called Board members' attention to the meeting dates listed in the agenda. NCAB meeting dates have been confirmed through 2000.

### REPORT OF THE DIRECTOR, NATIONAL CANCER INSTITUTE

Dr. Richard Klausner

Dr. Richard Klausner, Director, NCI, reported that NCI staff activity since the February NCAB meeting included extensive communication to the public about progress being made in the science underlying the National Cancer Program (NCP). These communications included the results of a variety of clinical trials (e.g., the Breast Cancer Prevention Trial), basic studies, and epidemiology studies, as well as the annual cancer statistics, which were announced in conjunction with the American Cancer Society (ACS), Centers for Disease Control and Prevention (CDC), and National Center for Health Statistics (NCHS). In this regard, Dr. Klausner drew attention to the NCI question and answer sheet developed and circulated by the NCI Office of Cancer Communications (OCC) in response to inquiries raised by the recent *New York Times* article on anti-angiogenesis therapeutics. He next addressed the issue of NCI priorities, the oversight of which is the responsibility of the NCAB, emphasizing that the top priority has been to capture promising new areas of science (such as angiogenesis) and to facilitate rapid translation of that new science to testing in the clinic.

**NCI Organizational Update and Staffing Changes.** Dr. Klausner reported on the significant structural changes effected in the NCI over recent years and the new administrative structure that underlies the management across the Institute. As recommended by the Bishop-Calabresi report, extramural functions were separated from the intramural functions, and two interacting but parallel management structures were developed—the Office of Intramural and the Office of Extramural Administrative

Management. Dr. Klausner announced that with the retirement of Mr. Philip D. Amoruso, Associate Director for Extramural Administrative Management, the scientific programs will remain separate but administrative management structure is being reorganized to form a single integrated structure under the new Deputy Director for Management, Ms. MaryAnn Guerra. The reorganization is expected to be completed by early summer and will be reported on at the September NCAB meeting. Dr. Klausner acknowledged Mr. Amoruso's contributions to the NCI in his 31 years of government service.

Dr. Klausner announced two recent staff appointments. Dr. George Vande Woude was appointed Director, Division of Basic Sciences (DBS), and Dr. Susan Sieber was appointed Associate Director for Special Projects in the Office of the Director (OD), NCI. Among her responsibilities, Dr. Sieber will have the task of assembling teams to address the many issues that require a response from the OD, NCI. Dr. Klausner called attention to Dr. Vande Woude's recently published findings from studies in his laboratory on the MAP kinase pathway, an important signaling pathway downstream of the ras pathway, and its relevance to blocking the toxic effects of anthrax lethal factor.

Dr. Klausner next described NCI strategies to ensure coordination of program activities across the Institute. Intramural Research Program (IRP) and Extramural Research Program (ERP) division directors meet every 2 weeks with the Director, NCI, and the Deputy Director for Extramural Science (ODDES), respectively. A new set of mechanisms to promote trans-divisional collaboration involves the implementation of recommendations made in the reports of the Program Review Groups and Working Groups. Dr. Klausner reminded the Board that, in addition, the Working Groups are linked to enacting and implementing the planning processes laid out in the Bypass Budget and stated that a review of this trans-institute process would be presented at the September NCAB meeting. As a model of how future cross-divisional/trans-institute collaborations could work, Dr. Klausner described the NCI's new scientific and proactive approach to the analysis and annual communication to the public of the nation's cancer statistics, which are based both on the national data on cancer mortality and on the cancer incidence data that emerge from the Surveillance, Epidemiology, and End Results (SEER) program. Working groups were organized with staff from throughout the Institute to analyze the statistics relating to the different cancers—childhood, breast, prostate, colorectal, lung, brain, lymphoma, and melanoma. In a series of seminars, models were developed for analyzing these numbers to determine their meaning, the level of confidence in them, and areas where additional numbers are needed.

**Cancer Centers and the New Guidelines.** Dr. Klausner reported on progress in implementing the new Cancer Center Guidelines, which were developed according to recommendations in the report of the Cancer Centers Program Review Group (CCPRG). Two review and funding rounds have been completed under the new guidelines, and the perception is that they are providing flexibility and satisfactory peer review to the cancer centers. Dr. Klausner stated that the NCI plans to engage the cancer centers' directors and the NCAB—through its Subcommittee on Cancer Centers—in discussions on a methodology for evaluating and re-evaluating the guidelines, particularly those that relate to the issues of comprehensiveness designation and planning grants. The new guidelines have incorporated comprehensiveness as an integral part of the scientific evaluation of cancer centers. The scientific evaluation is followed by an Executive Committee (EC)

review of the centers in the areas of cancer information, outreach, and education. As a result of the new review guidelines, the number of cancer centers (59) designated as comprehensive has increased from 26 to 33. Two new cancer centers have been funded in FY98 from the 10 applications that were received—the Moffitt Cancer Center in Florida and the University of Minnesota Cancer Center. Dr. Klausner noted that the NCI is interested in determining whether new institutions with new models for centers would be attracted by P20 the planning grant, which was opened to all potential applications as an investigator-initiated mechanism. One issue to be addressed is related to the review process and how to evaluate applications at both ends of the spectrum—the smaller, more scientifically defined concepts for centers and the concepts for large, multi-institutional consortium-designated centers with their potentially complex geographic and institutional considerations. Dr. Klausner reported that, as a result of the new guidelines, four or five other institutions are interested in applying for either a P20 planning or a full P30 core grant. In addition, the NCI cancer centers are working collaboratively with the National Institute for Allergy and Infectious Diseases (NIAID) to co-fund eight Centers for AIDS Research (CFARs). The Cancer Centers Program is continuing to help implement the survivorship initiatives through supplemental funding and has initiated a letter-request for application (RFA), in collaboration with the Division of Cancer Control and Population Sciences (DCCPS), to fund pilot projects in this area.

**Clinical Trials Review.** Dr. Klausner reported that three areas of clinical trials review are being addressed. The first two involve the redesign of the Physician Data Query (PDQ) database and the Clinical Trials Information System. The third will seek to develop a strategy to formally market clinical trials to the public, as part of new and important NCI activities to educate and inform the public about clinical trials and other NCI initiatives, as recommended by NCI's advisory groups. A June working meeting with marketing executives from major national corporations is planned to develop approaches to communicating more effectively the concept and value of clinical trials and the opportunities they represent. Dr. Klausner noted that the implementation process for recommendations of the Clinical Trials Program Review Group (CTPRG) continues and will be presented at the September NCAB meeting. He reported that the President's proposed budget for FY99 includes an increase in funding for the Clinical Trials Program closer to peer-review recommended levels. As budget deliberations stand, the NCI expects the clinical trials line to increase by about 20 percent in FY99 over FY98 levels. Dr. Klausner informed the Board that a new group based in the American College of Surgery has been added to the NCI-funded clinical trials infrastructure to expand the ability to conduct trials that involve clinical surgical procedures.

**Chemistry Biology Centers.** Dr. Klausner described the newly funded Chemistry/Biology Centers as an effort to bring together chemists, biologists, and technology developers to focus on the area of genetic or Darwinian chemistry. Detailed knowledge is emerging about the circuitry within the cancer cell, each point of which is a potential target for the development of drugs and therapy targeted specifically to the mechanisms that underlie the disease. Because the percentage of known circuitry within a cell that has been related directly to cancer is expected to accelerate rapidly, the challenge will be to accelerate the pace of identification and selection of drugs aimed at the specific

interactions whose alterations are responsible for the behavior of cancer. One anticipated result of this initiative is to move toward the identification of specific molecules of all types (e.g., the anti-HER-2 neu antibodies), so that the precise action of those molecules can be placed on the cell circuit diagrams. Dr. Klausner noted that the technology exists to develop in the laboratory extensive collections of small-molecule combinatorial libraries, and the goal of the new centers is to link the development of these chemical technologies directly to the biology and to the development of cell-based screening assays (so-called smart assays). The centers will work together with the NCI to share reagents and technologies toward the end of making these sorts of technologies exportable into academic laboratories where proof-of-principle interactions can best take place. Dr. Klausner noted that discussions with the pharmaceutical industry have begun in anticipation that the NCI will be able to work together with industry. The four centers funded in the first round of grants are located at Harvard Medical School, The Scripps Research Institute, University of Pittsburgh, and Torrey Pines Institute for Molecular Studies, and each institution has brought together a group of eminent scientists. Because of the interest expressed by other groups and the importance attached to stimulating this new type of multidisciplinary center, the NCI has decided to re-release this RFA.

**Director's Consumer Liaison Group (DCLG).** Dr. Klausner reported on the activities of the DCLG, which he described as a model of how advocacy groups with diverse agendas can work together toward a common goal. At a recent meeting, the DCLG proposed a set of gateway criteria for selecting consumer advocates for peer review. Dr. Klausner noted that the NCI's goal is to have consumers participate in all NCI review processes, and the DCLG is working with Dr. Marvin Kalt, Director, Division of Extramural Activities (DEA), to develop the criteria and a process for evaluation and training to achieve that goal. Orientation and ongoing educational tools for consumer advocates, as well as evaluative tools for the review process, are being developed. In another meeting, the DCLG focused on issues and the interface between the Institute and its constituencies, particularly issues of informed consent and confidentiality in areas such as genetic research. The national need for educational materials in these areas was identified, and the DCLG is working with the NCI to develop those materials. Dr. Klausner noted that the DCLG is particularly interested in addressing the public issues of informed consent and confidentiality in the area of clinical trials and will sponsor, as its first meeting, a forum on patient–public issues in clinical trials. The DCLG also has expressed interest in working on other aspects of the community-scientific research interface, such as developing effective approaches to engaging specific special populations in cancer research.

**Staff Recognition.** Dr. Klausner reported that NCI scientist, Dr. Susan Gottesman, Laboratory of Molecular Biology, DBS, was recently duly honored and recognized by her peers in science with election to the National Academy of Sciences (NAS). He remarked that Dr. Gottesman has been instrumental, over the past 20 years, in demonstrating the importance of protein degradation in the regulation of gene expression, and in identifying and characterizing a new class of proteases called the Clp proteases. The critical role of regulated proteolysis in movement through the cell cycle has placed it at the forefront of cancer research, and many of the insights guiding that research come from studies in



simple organisms in Dr. Gottesman's laboratory. Dr. Klausner congratulated Dr. Gottesman for her election to the NAS and for the many honors she has received, and he introduced her to present a brief discussion of her work.

Dr. Gottesman described prokaryotic studies in her laboratory conducted in *E. coli* that demonstrated protease remodeling by ClpATPases or degradation by ClpATPases and peptidases. She then pointed out similarities in the architecture of the major protease complex in eukaryotic cells and noted that although the details of the biochemistry of that system are more complex and difficult to obtain, the belief is that the rules will be similar. Dr. Gottesman expressed the view that the biochemistry of the eukaryotic protease and what one can do to modify its activity under various conditions will be forthcoming in the next few years, and that studies in ClpAP will have led the way. Dr. Bishop commended Dr. Gottesman's work as an example of a study best started and fostered within the IRP, particularly when all of the budgetary vicissitudes that have occurred in recent years are taken into account.

**Art for Recovery Breast Cancer Quilts Project.** Dr. Klausner called Board members' attention to the NCI breast cancer quilt on display outside the conference room. The quilt was created by 26 women living with breast cancer and participating in clinical trials at the NIH Clinical Center, each of whom designed a patch to express what it is like to cope with breast cancer. The Art for Recovery project is based on the use of creativity as a means of healing, recovering, and allowing for a richer understanding of each woman's journey through breast cancer. It is a collaboration of the NCI Breast Cancer Think Tank and the University of California, San Francisco/Mount Zion Medical Center.

### Questions and Answers

Dr. Ellen Sigal noted that only 2 of the 10 planning grants applications had been funded and asked whether this low rate was due to the review process or to the quality of the applications. Dr. Klausner replied that the NCI's intention is to encourage planning grants and was heartened at the size of the response. He reiterated, however, that there may be issues related to applications for both consortial and very specialized centers that are not easily demonstrated in applications, so may be confounding to the review process. Dr. Robert Wittes, DDES, agreed with Dr. Sigal's concern and noted that his office is considering strategies to address that concern.

### LEGISLATIVE UPDATE

#### Ms. Dorothy Foellmer

Ms. Dorothy Foellmer, Director, Office of Legislation and Congressional Activities (OCLA), described activities to improve the way OCLA updates the status of bills and provides information to the NCAB and to the public. The NCAB meeting books will display a Legislative Scorecard that provides an overview and updates the status of the more than 236 bills being tracked by the OCLA. In addition, the OCLA has a new web site that can be accessed directly through the address <http://www.nci.nih.gov/legis/index.html> or from the NCI main page by selecting "Legislative." Information that is available at that web site includes brief descriptions of the bills, hearings, and testimony by Dr. Klausner, Dr. Harold Varmus, Director, NIH,

and other staff; legislative history (statutes creating the NCI and NCP as well as special authorities and programs); and committees of interest. The OCLA web site also provides a link to THOMAS, the Congressional web page, that is the entry to a database that gives the full text of legislation.

Ms. Foellmer next reviewed other OCLA activities, including visits, hearings, and briefings during which NCI staff convey information about NCI programs. Topics of interest in recent months have been in the areas of new scientific advances, minority issues, and particular diseases, namely, breast, colon, lung, and cervical cancer. Eight visits, five briefings, and four hearings have been held since mid-February, which in previous years would have been the workload for the whole year. Ms. Foellmer concluded her presentation with a review of legislation in the areas of comprehensive tobacco settlement and medical records confidentiality. In regard to the latter, she stated that although the level of interest in this topic remains high, the progress of the bills through Congress has slowed considerably. She noted that a trans-NIH committee is considering ethical and medical confidentiality issues related to protecting personal medical information and it is expected that the NIH position and recommendations resulting from these deliberations would help form the basis for Congressional action.

#### **Questions and Answers**

Dr. Sigal asked if a hearing on the angiogenesis research might be held and whether members of Congress understood the importance of NCI's role in sponsoring the research. Ms. Foellmer replied in the affirmative to the latter question and noted that the OCC's Question and Answer document had helped greatly in clarifying what was happening and the status of angiogenesis research. She added that the Senate Cancer Coalition is in the conceptual stages of considering a hearing on new approaches to cancer therapy in a broader sense, including tamoxifen, angiostatin, endostatin, and others.

#### **REPORT OF THE PRESIDENT'S CANCER PANEL**

##### **Dr. Harold Freeman**

Dr. Harold Freeman, Chair, President's Cancer Panel, presented the written statement of the Panel's meeting at the Jonsson Comprehensive Cancer Center in Los Angeles on "Defining Quality for Cancer Care." This was the first of three meetings planned for 1998 on the overall topic "Quality of Cancer Care/Quality of Life." At the meeting, the issue of quality for cancer care was addressed from the perspectives of the patient, physician, and insurer. Dr. Freeman recalled for the Board the current Panel's history as champions of equitable access and appropriate delivery of quality care. He stated that the Panel initiated the series of meetings because of the need for a comprehensive examination of what "quality" means in the context of cancer care and in the NCP context. The Panel at these meetings is considering what expectations are associated with the deliver of quality cancer care from prevention through palliation. The Panel is coordinating activities with the National Cancer Policy Board (NCPB) in order to consider fully how the quality of cancer care services in the United States can be evaluated. The NCPB's research-based review of quality issues will complement the Panel's public exploration of these issues,

which will take into account the quality of life considerations and the human perception of quality.

Dr. Freeman discussed the varied definitions of quality cancer care expressed in the expert testimonies heard. Similarly, the Panel found that cultural, geographical, economic, and other factors can influence perceptions of what constitutes quality cancer care and must be considered to be sensitive to the total set of issues. The Panel recognized that defining standards for diagnostic quality is essential because the precision and quality of screening technologies determine a patient's diagnosis and influence choices regarding treatment and care. The Panel heard, overall, that better systems are needed to capture information related to measuring quality of care. The role of investigational therapy in cancer care was discussed and found to be a source of controversy, even though most people agreed that new is better and no cost must be spared in treating life-threatening illness. These conflicts must be taken into account, as well as the knowledge that investigational therapies provided in the context of determining efficacy and therapeutic value are the ones most likely to be supported by third-party payers.

Dr. Freeman reported that many speakers emphasized the importance of communication between patient and physician and believed that patients and families must become active participants in health care decisions. The Panel heard that although knowledge about cancer is growing, little is known about the process of communicating this information in ways that will affect behavior change, particularly in diverse populations. It was stated that cognitive information regarding health care options may not be as effective as approaches that identify and capitalize on personal, cultural, and community values. The Panel heard that quality-of-life issues must be considered when evaluating quality of cancer care, and, for survivors, important considerations include preventing disease recurrence, minimizing future treatment and disease-associated complications, and maintaining or improving function from diagnosis until time of death.

Dr. Freeman stated that the Panel believes that defining quality cancer care is a crucial issue for the NCP as the number of cancer survivors grows. The Panel notes the interplay of understanding what standards of care should exist, when they should apply, and how they should impact the delivery of care. Equally important, the Panel believes that quality cancer care must be made available and accessible to all populations. Dr. Freeman noted that the Panel has accepted the challenge of bringing the various perspectives together in a way that will be helpful to the American public.

### Questions and Answers

Dr. Frederick Li commended the Panel's overall statement but called attention to the description of quality of life as a "continuum, from the time of diagnosis until death." He commented that quality of cancer control and preventive care is a lifelong process that antedates the date of diagnosis. Dr. Freeman agreed and called attention to another statement that the Panel believes that quality considerations should begin with prevention of cancer and carried through to end of life. He added, however, that the NCPB appears to be considering the spectrum only from screening and diagnosis to the end of life. Dr. Li suggested the need to recognize that providers of prevention differ from providers of

therapy. Dr. Richard Boxer commented that the continuum should be expanded to include family survivors who also live with the cancer experience.

### NEW BUSINESS I

**Dr. J. Michael Bishop**

Dr. Bishop announced the following committee and liaison assignments to replace NCAB members whose terms were expiring: Ms. Ellen Stovall, Dr. Li, and Dr. Phillip Sharp will chair the Subcommittee on Budget, Subcommittee on Special Actions, and the Subcommittee on Cancer Centers, respectively; Drs. Ivor Royston and Philip Schein have been appointed as liaisons to the Board of Scientific Counselors (BSC) and Board of Scientific Advisors (BSA), respectively.

Dr. Bishop called for and received no further additions to the agenda. As a preview for the next day's briefing from Dr. Kalt on the NCI's use of consumer advocates in peer review, a video was shown of DCLG member Ms. Susan Lowell Butler speaking at the White House ceremony that announced the 21st Century Cancer Research Initiative.

### NCI CANCER SURVEILLANCE RESEARCH PROGRAM (CSR/P)

**Dr. Barbara Rimer, Dr. Brenda Edwards, Dr. Eric Feuer**

Dr. Barbara Rimer, Director, DCCPS, prefaced the presentation on cancer surveillance research with a brief review of current activities and changes in the organization and staff of the DCCPS over the previous 4 months. She recalled for Board members the definition of cancer control developed by the CCPRG and emphasized that the DCCPS is focusing on the entire spectrum of objectives mentioned there—reduction of cancer risk, incidence, morbidity, and mortality. She announced that Dr. Robert Hiatt has been appointed Deputy Director, DCCPS, and recruitment has begun for a new Director in the Office of Cancer Survivorship to replace Dr. Anna Meadows, who is returning to the University of Pennsylvania, but will continue to work with the NCI over the next few years. Dr. Robert Croyle was appointed Associate Director, Behavioral Research Program, beginning in July. The DCCPS currently consists of the Epidemiology and Genetics, Cancer Surveillance Research, and Behavioral Research Programs. Dr. Rimer noted that the DCCPS planning process involves input from many different groups, which is used to synthesize recommendations and set priorities toward the goal of making cancer control more evidence based. Dr. Rimer highlighted current activities in the DCCPS program areas, including (1) launching the Cancer Genetics Network; (2) initiating efforts to look at interactions of metabolic factors with lifestyle, social behavioral factors, diet and nutrition, hormones, and medications; (3) looking at genetic factors related to addiction and how to use this information to develop interventions; (4) developing the Tobacco Research Intervention Plan (TRIP) to formulate recommendations to guide NCI's investment in tobacco research; (5) focusing on tobacco use in the very young; (6) developing more effective interventions for heavy smokers; (7) balancing the behavioral research portfolio to span basic biobehavioral research; and (8) developing innovative approaches to overcome behavioral disparities in population groups' access to cancer prevention and control.

Next, Dr. Rimer presented an update of DCCPS accomplishments in implementing working group and program review group recommendations. A unit has been created to

focus on basic behavioral and social research. The biometry program will focus on quantitative research methods for cancer control research and population science. A branch is being redesigned to focus research efforts on the underserved. The Surveillance Implementation Group has been formed to develop future research plans and priorities to expand cancer surveillance; included is a report card to measure progress in cancer control. The DCCPS, in collaboration with the Center for the Advancement of Health, is holding a series of meetings with behavioral scientists nationwide to develop research priorities. The DCCPS worked with the Cancer Centers Branch, ODDES, to release a request for cancer control supplements to P30 grants for innovative pilot research projects.

Dr. Rimer introduced the presentation on NCI's Cancer Surveillance Research Program (CSRP) by defining surveillance research in the 1990s. It is a program activity that monitors the national cancer burden on the population through the measurement of cancer risk factors, health status, incidence, morbidity, mortality, and survival; and the assessment of individual, societal and health services factors that mediate these cancer measures both directly and indirectly. She introduced Dr. Brenda Edwards, Associate Director, CSRP, to describe the work of the program and Dr. Eric Feuer, Statistician, Applied Research Branch (ARB), to demonstrate, using prostate cancer data, questions asked about cancer statistics and methodologic approaches used to interpret surveillance data.

**Cancer Surveillance Research Program.** Using a graphic illustration, Dr. Edwards showed that databases are at the core of cancer surveillance, but that surveillance activity extends beyond the databases to encompass methods research to define the data and assess their quality. Information from these program activities is made available through research tools such as public-use databases, peer-reviewed publications, monographs, reports, web sites, graphs, and programming software. Dr. Edwards stated that, in addition to the SEER Program, the CSRP uses national health data systems that have appropriate data, modifies and adapts other national systems to improve their cancer surveillance capacity, and develops new data systems where they are needed. Using a diagrammatic presentation, Dr. Edwards demonstrated the relationship between cancer control, which addresses the continuum from primary prevention to the end of life, and the many national data sources that are used to augment SEER data, develop preliminary pilot studies to look at the feasibility of expanding data systems, and identify new areas for data collection. Dr. Edwards noted that special studies funded by the NCI SEER Program in this decade have focused on patterns of care, quality of life, health behavior, survivorship, screening, risk factors, and methodologic research in data linkage. Dr. Edwards then reported on recent SEER incidence and national death data, which form the basis for estimates that more than one million new cancer patients will be diagnosed in 1998 and estimates that more than a half million persons will die of cancer. She pointed out that four cancer sites—prostate, female breast, lung and bronchus, and colon and rectum—represent more than 50 percent of both expected cases and deaths. SEER data are gathered in 10 regions of the nation from about 14 percent of the total U.S. populations, and coverage of minority populations has been enhanced. She pointed out that characteristics of populations in the SEER catchment regions are comparable to those

in the total United States, including factors like socioeconomic status (SES), except that SEER areas are more urbanized. Dr. Edwards reviewed other data published in the March issue of *Cancer*, showing that incidence and mortality rates have declined during the period from 1990 to 1995 compared with an increase during the years 1973 to 1990. She stated that this publication featured comparison data on four race and ethnic groups in the major cancer sites.

Dr. Edwards called attention to CSRP's ongoing studies on the role of early detection in breast cancer that are addressing a range of questions related to the delivery of screening mammography and the linkage with diagnostic followup, pathology outcomes, and cancer rates. She noted that NCI software has been developed to analyze and report cancer statistics and stated that the cancer surveillance web site has been accessed almost 100,000 times in its 2.5-year existence. Another recent activity of the CSRP is a collaboration with the *Journal of the National Cancer Institute (JNCI)* in which SEER data and other surveillance information are being made available to the Oxford University Press for a prototype electronic communication project. Users will be able to click on various publications, including the *JNCI*, and access a summary of data that relates to a particular cancer site. In conclusion, Dr. Edwards emphasized that collecting quality data includes a research component when it is necessary to move beyond analyzing existing data to interpreting data, as Dr. Feuer's presentation would demonstrate.

**Prostate Cancer Data.** Dr. Feuer stated that prostate cancer data would be the basis for his presentation partly because of dramatic changes associated with the introduction of prostate specific antigen (PSA) as a screening test in 1988, and partly because the prostate cancer analysis illustrates how the CSRP integrates various data resources and modeling into trend analysis. The prostate cancer analysis is still in progress and is a collaboration involving the Applied Research and Cancer Statistics Branches of the CSRP, the Fred Hutchinson Cancer Center, and Dr. Barnett Kramer, Deputy Director, Division of Cancer Prevention (DCP).

Dr. Feuer demonstrated prostate cancer trends using age-adjusted incidence rates by race from the early 1970s to 1995. Although blacks have a higher incidence rate than whites, trends have been similar, with a modestly increasing rate until 1984 when rates began to increase sharply; rates peaked in 1992 for whites and 1993 for blacks, followed by a steep decline. The decline occurred among all stages, but most importantly among patients with distant-stage disease. Because distant-stage disease plays a large role in mortality, this finding suggests a potential for reduced mortality. Dr. Feuer then presented PSA usage data from 1988 to 1994 for a cohort of men 65 years and older selected from Medicare data from SEER areas. Data showed that the proportion of men getting a PSA test in the past year rose through 1994 and that the proportion getting a first PSA in the past year peaked in 1992 and was correlated with incidence. Dr. Feuer discussed how the data on PSA usage patterns were used to model the potential impact of the introduction of PSA screening on mortality. Also used were estimates from the literature on the proportion of PSA tests that lead to a diagnosis of prostate cancer, lead time as derived from the banked serum for clinically diagnosed cases, survival improvements at the end of lead time taken

from a hypothesized benefit used in designing the PLCO trial, and mortality data taken from U.S. Lifetables.

He noted, in summary, that the decline in distant-stage disease is a positive early indicator of an eventual mortality decline, with the caveat that a stage shift does not always lead to a mortality decline. Moreover, in complex population data, it is difficult to attribute relatively small changes in mortality to any one cause. Randomized screening trials and longer term mortality declines are needed for more definitive answers. If PSA screening is effective, the observed mortality decline could plausibly be attributed to screening, especially if the lead time is short. Dr. Feuer noted that more detailed simulation modeling is underway to model the underlying natural history of the disease in greater detail and the potential of PSA screening to alter that progression.

Dr. Rimer discussed the progress in organizing a Surveillance Implementation Group and briefly reviewed the major questions and issues to be addressed. A multidisciplinary group of 40 individuals from the NCI, the extramural scientific community, other federal agencies, and academia has been assembled to develop plans to enhance the NCI Cancer Surveillance Program and establish priorities and set future directions.

### Questions and Answers

Dr. Freeman noted that groups continue to be defined on the basis of the census and asked if the DCCPS would try to refine methodology to identify more accurately the variables that are causing disparities in incidence and mortality. Dr. Rimer responded that studies planned in the Applied Demographics Branch will use anthropological sciences and ethnographic techniques to determine who are the underusers of services and underserved. Dr. Sandra Millon-Underwood asked about plans for interfacing the activities of the Applied Demographics Branch with those of the Office of Special Populations. Dr. Rimer noted that the two groups have been working together and have pooled resources on one RFA. Dr. Li noted that the SEER registry is a national resource and should be readily available to extramural investigators at sites other than SEER sites. Dr. Rimer agreed and noted that certain tools have been developed over the past few years—such as SEER Stat—that will make access easier. Dr. Charles Wilson asked whether the surveillance data being amassed on the role of socioeconomic status in cancer and health in general would produce information powerful enough to influence public policy. Dr. Rimer responded that data on the impact of cancer on the population is collected not only to understand the impact but also to develop interventions to reduce disparities. Dr. Schein called for an even greater sense of urgency in the DCCPS and the NCI to translate new data into new research programs or policy statements that are brought to the general public and physician community-at-large for either prevention or early diagnosis of cancer, or earlier intervention and a higher probability of obtaining survival. Dr. Pelayo Correa asked about the DCCPS' plans to deal with the problem of tobacco consumption by young people. Dr. Rimer noted that an RFA addressing youth at-risk behaviors will be presented to the BSA at its next meeting and that the goal of the Tobacco Implementation Group is to identify other priorities, some of which will be translated into RFAs and into communications for the extramural community, exhorting researchers to develop grant applications for initiatives in these areas. She emphasized the need for a partnership between the NCI and the extramural community in this effort.

## PRECLINICAL ANIMAL MODELS

Dr. Tyler Jacks, Dr. Douglas Hanahan, Dr. Cheryl Marks

Dr. Klausner reminded Board members that the NCI Working Groups had been created to guide in the implementation of the extraordinary opportunities identified in the Bypass Budget, and the Preclinical Models Working Group (PMWG) was charged with helping to develop and validate preclinical models for cancer. Studies, such as those described earlier by Dr. Gottesman, have demonstrated the high degree of evolutionary conservation of biology, pathways, and molecules across evolutionary distances; the ability to model across these distances in different organisms is imminent, based upon the conservation of gene function. Dr. Klausner introduced Dr. Tyler Jacks, Associate Professor, Massachusetts Institute of Technology; Dr. Douglas Hanahan, Professor of Biochemistry, University of California, San Francisco; and Dr. Cheryl Marks, Division of Cancer Biology, DCP, NCI, to present an update of the work of the Mouse Models for Human Cancers Subcommittee of the PMWG and to comment on the NCI's plans for implementing the recommendations that emanate from this working group.

Dr. Jacks presented a summary of the science ongoing in his laboratory and the work being carried out in the mouse cancer model community—whose interest is in understanding the genetic events that contribute to the development of cancer. This work builds on the knowledge that three classes of mutations arise in normal cells during progression to cancer—mutations in oncogenes, tumor suppressor genes, and genes responsible for DNA repair and overall genomic stability. Dr. Jacks described studies in the tumor suppressor gene class, which are assumed to encode negative regulators of cell growth (whose inactivation cause loss-of-function mutations) or act in other ways to inhibit the tumorigenic process. Mutations of these genes can occur sporadically in the general population or can be inherited. Dr. Jacks briefly summarized Dr. Alfred Knudson's 2-hit hypothesis to explain why individuals who inherit from one parent a defective allele of a particular suppressor gene are cancer prone. This hypothesis figures prominently in the development of mouse model technologies. Because similar genes have been shown to exist in the mouse carrying out similar functions, Dr. Jacks' approach to the study of suppressor genes has been to inactivate the murine homologs of these genes in mice using gene-targeting technology. Reasons for constructing mouse strains with mutations in tumor suppressor genes are to be able to: (1) model the familial cancer syndromes for diagnostic, therapeutic, and basic biology studies; (2) determine developmental requirements for gene function; and (3) provide a resource for obtaining primary cells and cell lines with which to study gene function *in vitro*.

Dr. Jacks then summarized his laboratory's progress in analyzing mouse models made with four tumor suppressor gene mutations—RB, p53, neurofibromatosis (NF) type 1, and NF2. He presented three observations gained from comparing tumor suppressor gene mutant phenotypes in humans and mice: (1) RB, p53, NF1, and NF2 act as tumor suppressor genes in mice as they do in humans; (2) mice that are heterozygous for loss-of-function mutations in these four tumor suppressor genes develop tumors that often differ from the cognate tumor in the relevant familial cancer syndrome in humans; and (3) homozygous mutations for all of these tumor suppressor genes produce embryonic phenotypes in mice. Dr. Jacks described attempts to construct models that could explain why mice that are heterozygous for mutation in the RB gene do not develop



retinoblastoma. Dr. Jacks noted that by probing further, scientists will be able to dissect the relevant differences between humans and mice and ultimately build a better model. Dr. Jacks then discussed a model for NF1, which is being studied in his laboratory. This study involved a patient with multiple cutaneous neurofibromas, who had inherited a defective allele of the NF1 tumor suppressor. Evidence indicated that the cell that initiated the growth of these lesions had acquired a mutation in the intact copy of NF1. A mouse model was constructed with a mutation in the NF1 gene, which encodes a regulator of the ras mitogenic signaling pathway. As in the RB gene studies, the finding was that animals that are heterozygous for mutation in the NF1 gene did not develop the relevant pathology. The methodology to develop an NF1 double-knockout chimera was the same as for the RB gene. Dr. Jacks noted that the resulting model was a reasonably accurate model of NF1, providing an opportunity to study various aspects of disease development or develop therapeutic interventions. He noted that evidence provided through these types of models should also create interest within the pharmaceutical industry in producing NF1 interventions, particularly in light of the prevalence of this type of cancer.

In closing, Dr. Jacks described future directions of research in the animal model field. He noted that, although these models are useful in their present state, they will be improved further by more sophisticated gene targeting to allow the inactivation of a gene in any particular cell type of the mouse or at any particular time in the development of the mouse. In recognition of the significant contribution of genetics to the consequences of inherited mutations, the strategy used in identifying the MOM-1 modifier gene will be used to identify other modifier genes for tumor suppressor genes in an effort to understand the overall genetic contribution to the development of cancer.

Dr. Hanahan continued the presentation with a discussion of mouse model construction and utilization, directions of current research, and future opportunities. New models for pancreatic islet carcinoma, dermal fibrosarcoma, and squamous cell cancer of the cervix and skin have been developed using strategies targeting the expression of dominant oncogenes to particular tissues. These are being studied to understand more about pathways to cancer, the cellular parameters of the cancer machine, and the genetic controls of these pathways, as well as to find better ways to treat and prevent cancer. A series of models has been constructed to illustrate histological pathways, including the prototype model RIP-tag transgenic mice (in which the SV40 T antigen knocks out the RB and p53 tumor suppressors) and the human papilloma virus (HPV)-16 transgenic mice (in which the HPV16 oncogene does the same). Dr. Hanahan also noted that one characteristic identified in all four new models is that, in the tumor development pathway, angiogenesis is switched on well before the appearance of end-stage tumors. A joint NCI grant to support the study of tumorigenesis in transgenic mice has enabled Dr. Hanahan's and Dr. Judah Folkman's laboratories to carry forward the characterization in all of these models of tumor development.

Dr. Hanahan noted that Dr. Jacks had introduced the common denominator of all cancers, namely, firing the cell cycle engine. Dr. Hanahan then described studies relating to acquired resistance to apoptosis and induction of angiogenesis, two other critical components of the cancer machine. The investigation of apoptosis or programmed cell

death—believed to be a protective mechanism to remove aberrant cells from the body—initiated with the discovery that insulin-like growth factor II (IGF-II), which has been shown to be associated with a number of cancers, was activated in tumors in the islet carcinoma model. Dr. Hanahan noted that studies of these types of models have shown that the tumor uses multiple mechanisms to develop acquired resistance to apoptosis, including IGF-II, the T antigen that eliminates p53, bcl-x long when it is upregulated, and angiogenesis. These studies also have produced evidence for genetic changes that may be contributing to an acquired resistance to apoptosis.

Dr. Hanahan explained that human cancer genetics is another important parameter in understanding the construction of a tumor cell—in addition to cell cycle regulation, apoptosis, and angiogenesis—and he discussed lessons of human cancer genetics. In particular, human cancer genetics has shown that the chromosomal loci reproducibly altering cancer cell genomes are, in general, instructive about key components of the cancer machine. Dr. Hanahan described studies to look for genetic changes in transgenic mouse models using the technologies called loss of heterozygosity (LOH) and comparative genomic hybridization, which permit the visualization of alterations in tumor cell genomes. Dr. Hanahan stated that another major application of models is to find better ways to prevent and treat cancers, for example, by targeting critical parameters such as angiogenesis with more selective drugs and by expediting combinatorial testing of distinctive agents. He pointed out the need to extend the rapid and efficient screening methods now used in transplanted tumors into endogenous tumors to test the efficacy of different drugs and drug combinations. He added that the next preclinical trials will move from the pancreatic islet carcinoma model into other good representatives of major human tumors to treat both early- and late-stage lesions and test combinations of angiogenesis inhibitors and other chemotherapies.

Dr. Hanahan concluded with a summary of mouse model studies to determine why the immune system does not eradicate tumors. He described one study to test the hypothesis that the tumor microenvironment can suppress or exclude activated antitumor lymphocytes. These studies would be carried into the cervical cancer model to test whether cervical tumors and premalignant lesions can be treated immunologically with the vaccines being developed against HPV 16 oncogenes, using immune hyperactivators and in combination with modifiers of the tumor microenvironment. Validated strategies developed in the mouse models could then be considered in humans.

Dr. Marks briefly reviewed the organization and meeting history of the PCMWG and its subgroups for Mouse Genomics and Genetics, Mouse Models for Human Cancer, and Non-Mammalian Models for Human Cancer Research. The Mouse Models subgroup, in its meetings over the past year, discussed the need for models that accurately and reproducibly reflect the genesis and progression of human malignancies, as well as their potentially significant impact on the pace of discovery. A fundamental impediment to realizing this goal was the lack of support for model development in its earliest stages. The subgroup recommended that the NCI provide a mechanism to circumvent the problems of support for mouse model development and full characterization. In implementation of this recommendation, an RFA for Mouse Models for Human Cancer

Consortium has been approved by the BSA and will be issued in coming months to attract both cooperative agreement (U01) and NIH Intramural project applications from teams of collaborators with the appropriate scientific and technical expertise. The consortium, when it is assembled in the following year, will enable the individual U01 or NIH Intramural project teams to pursue their most innovative ideas for model development and implement new technologies, and will stimulate interactions among the teams, with the NCI, and with the cancer research community. The consortium members will actively work together to share information and technology, set their own broad priorities, and devise new experimental strategies as needed. They also will establish and maintain linkages to key research communities needed to implement this consortium, and design and conduct workshops to explore new research opportunities and disseminate information. Models validated by the consortium will be distributed to the community to support more discovery through the R01, P01, and other mechanisms.

Dr. Marks noted that a trans-divisional task force within the NCI has been implementing the various recommendations of the working group. Ultimately, the scientific management of the consortium will include all relevant NCI programs to ensure that resources vital to the success of the program are available. In implementing other recommendations, the task force is working to provide the means to distribute to the research community the validated and tested models from the consortium and to develop a concept for an interactive database of mouse cancer models. Also imminent is another initiative to provide administrative supplements to funded investigators for mouse model research to compensate for study section cuts or unanticipated increases in cost. In addition, several program announcements (PAs) will be published to encourage more widespread use of non-mammalian models in cancer research as recommended by the Non-Mammalian Models subgroup.

### Questions and Answers

In response to a question from Dr. Bishop about the planned administrative supplements, Dr. Marks replied that the NCI has not considered a major competitive initiative to supplement mouse costs on a center, geographic, or institutional basis, although the issue has been raised by the working group. Dr. Klausner added that the National Center for Research Resources (NCRR) will attempt to develop better standards and more information about variable costs across institutions for mouse care, and will consider revisiting some regulatory policies and rules that increase those costs. Dr. Klausner added that one objective of the new consortium will be to create an infrastructure that would allow the comparison of different models, generation of multiple layers of data, and eventual validation of the models. Dr. Schein emphasized the importance of knowing whether the parameters defined for the islet cell carcinoma model would apply to other animal models, and if these individual mechanisms are not tumor- or model-specific and might be applied to humans with some relevance.

### UPDATE: TAMOXIFEN STUDY

**Dr. Barnett Kramer, Dr. Norman Wolmark, Dr. Joseph Costantine, Dr. Leslie Ford, Dr. Mitchell Gail**

Dr. Klausner referred to the recently released results of the Breast Cancer Prevention Trial (BCPT) and noted that the update would describe the role of the National Surgical

Breast and Bowel Project (NSABP) in communicating the results of the tamoxifen study and planning for followup research. He introduced Dr. Kramer, who is heading the NCI's response team, to coordinate the presentation. Dr. Kramer introduced speakers as follows: Dr. Norman Wolmark, Chair, NSABP, to give an overview of the BCPT; Dr. Joseph Costantino, Associate Director, Biostatistics Center, NSABP, to review statistical details of the tamoxifen trial; Dr. Leslie Ford, Associate Director, Early Detection and Community Oncology Program (EDCOP), DCP, to discuss risks and benefits to be considered before taking tamoxifen as preventive therapy; and Dr. Mitchell Gail, Chief, Biostatistics Branch, Division of Cancer Epidemiology and Genetics (DCEG), to discuss risk modeling for breast cancer.

**BCPT Overview.** Dr. Wolmark explained that the justification for this chemoprevention trial came from observations in the NSABP and other treatment trials that tamoxifen was able to reduce the incidence of contralateral breast cancer in individuals being treated for primary breast cancer. Next, he presented a brief history of the BCPT, which began in June 1992 and was terminated in September 1997, after 13,338 women (age 35 or older) at increased risk for breast cancer were randomized in a double blind fashion to receive tamoxifen or placebo. On March 24, 1998, the Data and Safety Monitoring Board (DSMB) for this trial informed the NSABP that the primary endpoint of the study had been met, and it was revealed that there was a significant reduction in invasive breast cancer and fractures to weight-bearing bones. Additionally, the data revealed an increased incidence of endometrial carcinoma and vascular events, predominantly in women over age 50. The decision was made on March 26, in discussions of the data with NCI, to inform the participants that the primary endpoint had been met.

Dr. Wolmark noted that important questions will be answered in subsequent presentations: (1) Was the observed phenomenon chemoprevention, chemoinhibition, or chemosuppression? and (2) Will there be a compensatory increase in the incidence of breast cancer in the tamoxifen-treated group after tamoxifen is stopped? Dr. Wolmark reported that additional analyses of data from the treatment trial, NSABP protocol B-14, showed that the reduction in the number of contralateral breast cancers that occurred at 5 years, was still present at 10 years of followup, suggesting that this is not a transient phenomenon. Insight relative to the duration of tamoxifen administration was determined from a secondary randomization at 5 years in B-14, in which the women who were free of all disease after 5 years of tamoxifen were re-randomized to an additional 5 years of tamoxifen or placebo. The findings were: (1) that 10 years of tamoxifen did not provide an advantage relative to the primary endpoints of disease-free survival and survival from the index cancer; and (2) that 5 additional years of tamoxifen appeared to have no dramatic effect on the incidence of contralateral breast cancer. Dr. Wolmark noted that information to substantiate these findings will be forthcoming from the lifetime followup of the patients in the BCPT trial. He added that the adverse effects continue in the second 5 years of tamoxifen, but the benefit relative to contralateral breast cancer is not apparent.

**Summary of BCPT Data.** Dr. Costantino presented data on the study population of 13,338 women at an average followup time of 4 years. The age distribution of the women was as follows: 40 percent less than 49 years of age, 30 percent in ages 50 to 59, and 30 percent above age 60. In total, 154 cases of invasive breast cancer occurred in the placebo

group compared with 85 in the tamoxifen arm, or a reduction of 45 percent (p 0.0001). Tamoxifen reduced the incidence of invasive breast cancer by statistically significant margins in all age groups and mediated a significant reduction in the number of cases of noninvasive breast cancer. Other potential benefits theorized as the trial was initiated were related to heart disease and fractures. At this point in the followup, there is no indication of any type of heart disease benefit related to the four endpoints looked at. However, a statistically significant difference in the combined number of hip, collis, and spine fractures was seen in the tamoxifen arm. The risk of vascular events became evident from the trial; overall, the difference in vascular events between the tamoxifen (97 events) and placebo (68 events) arms was statistically significant. However, a differential pattern of risks was seen in women age 35 to 49 compared with those over age 50. No apparent increased risk of side effects was seen in the younger group, but women over age 50 appear to have increased risk for vascular events and endometrial cancer.

**Implications of the BCPT Data for Risk/Benefit Assessment by Individuals.** Dr. Ford noted that the BCPT had produced real data on the 5-year probability of invasive breast cancer for use by women in deciding whether to initiate preventive therapy with tamoxifen. The BCPT information will be refined further and communicated to the public for use in decisionmaking. Dr. Ford pointed out that a woman age 35-59 was considered eligible for the trial if her risk was that of an average 60-year-old woman, women 60 and above were eligible based on age. She gave examples of risk profiles for women ages 35, 40, and 45 who were considered eligible for accrual to the BCPT. Dr. Ford reported that the new Cancer Trials web site has been enhanced with many pages of other high-risk profiles for use by the public. Current estimates are that this therapy could potentially apply to about 21 percent of the U.S. population of women (about 29M). Dr. Ford concluded that although the results of the BCPT provide women with a proven option to prevent breast cancer, the decision to take tamoxifen is a complex one that must be made by each individual, based on the best information that is available. The NCI and NSABP are developing tools to assist women and their health care providers in making these decisions.

**Projecting Individualized Absolute Risk of Breast Cancer.** Dr. Gail stated that the ability to project individualized absolute risk of developing breast cancer is useful in weighing the potential benefits of chemopreventive therapy as well as in the counseling process. Absolute risk depends on several factors, the most important being age for breast and most other cancers. Dr. Gail described two models for projecting risk that are widely used at this time. One is a model with a genetic basis developed by Dr. Elizabeth Claus and colleagues that includes age and detailed family history; the other is the model developed from data in the Breast Cancer Detection Demonstration Project (BCDDP) by Dr. Gail and colleagues, which was used by statisticians working on the BCPT. The BCDDP model (also known as the Gail model) controls very closely for age and includes family history, reproductive factors, and information from the medical history. Dr. Gail demonstrated, using a computer program called RISK, how the BCDDP model can be used to project an individual's absolute risk. He discussed the use of data from women in the placebo arm of the BCPT, who were followed and screened annually, to validate the

projections made from the BCDDP model. Preliminary data indicate that the ratio of the observed incidences to expected—as predicted by the BCDDP model—were in close agreement (perfect for women in the <50 and 50–59 age groups and slightly underestimated in the >59 age group). Dr. Gail advised that a user of these models should be prepared to take other risk factors into account, noting that the BCDDP model would underpredict to a certain extent if a woman had a previous diagnosis of breast cancer, was known to carry the *BRCA1* or *BRCA2* gene, or was a member of a family carrying a familial syndrome (e.g., Li-Fraumeni, Cowden). He noted that in using this type of model, the counselor should be aware of the clinical epidemiology of the disease and the special features not included in the model.

**BCPT Long-Term Communication Plan.** Dr. Kramer reported that he was heading an NCI response team to develop a long-term communication plan to translate and disseminate the BCPT findings. This would facilitate decisionmaking regarding the use of tamoxifen as a breast cancer preventive. The approach has been to provide the objective information needed about the risks and benefits of tamoxifen so that women, with the help of their physicians, can make this personal decision—looking to the NCI and the NSABP as sources of credible information. Communication strategies have included: (1) loading the newly created Cancer Trials web site with slides from the BCPT press conference; (2) evaluation of the impact of the announcement and solicit requests for additional information; (3) developing easy-to-interpret resources, including further refinement of the Gail model; (4) responding to calls from the media; (5) disseminating and promoting new information resources; (6) promoting the NCI's points of access to information and evaluating them to make mid-course corrections; and (7) organizing a workshop to be held in July to develop risk/benefit assessments useful to the public and professionals. Dr. Kramer demonstrated how the Cancer Trials web site can be accessed and the types of information that are available. An electronic order form for the RISK computer program is available on the web site. Dr. Kramer stated that the OCC sent a survey immediately after the announcement to cancer centers, cooperative groups, community clinical oncology programs, and Cancer Information Service (CIS) sites to find out what additional information was needed. Two hundred responses were received—for an overall response rate of 45 percent—and more than half indicated that the information provided by the NCI met their needs. Dr. Kramer called attention to the summary of feedback on the announcement of the BCPT results included in the meeting books.

### Questions and Answers

Dr. Bishop asked for an estimate of the number of counselors nationwide who would be confident to use the kinds of risk/benefit models described by Dr. Gail. Dr. Kramer agreed that generalists, primary care physicians, and oncologists will be increasingly called on to counsel, and the need for qualified counselors must be addressed. To that end, the NCI is working to make the RISK computer program more user friendly. Dr. Kay Dickersin and Dr. Bishop raised an issue concerning death as a study endpoint and the fact that ending the trial early may have forfeited the prospect of gathering data on mortality. Dr. Costantino stated that 118 total deaths occurred in the study population (65 in the placebo arm and 53 in the tamoxifen arm) and only 8 were breast cancer deaths (5 in the placebo arm and 3 in the tamoxifen arm). He explained that the BCPT was

designed to test the hypothesis that tamoxifen is a preventive agent in the reduction of incidence of invasive breast cancer; therefore, the DSMB role was to monitor the trial only in terms of this hypothesis. The decision was made that the primary question had been answered; the benefits to be gained by improving the estimates of the confidence limits of the side effects did not justify withholding from the placebo patients the knowledge about tamoxifen as an effective preventive. A trial to detect significant differences in mortality would have been much larger and longer.

Dr. Dickersin suggested that the question remains as to when to initiate preventive therapy and when to end it. Dr. Wolmark explained that the BCPT established that 5 years of tamoxifen has an unequivocal benefit and that ancillary information from NSABP adjuvant tamoxifen trials suggests that 10 years of therapy provides no additional benefit. Dr. Kramer added that the current recommendation is for a 5-year period of therapy. Dr. Sharp asked if the NCI would issue more specific guidelines as to who should initiate preventive therapy. Dr. Klausner reiterated that prevention and treatment decisions are to be made by each woman and her physician. The NCI role is to create a simple model that will allow each person to enter her particular information to get a sense of her individualized absolute risk. Ms. Frances Visco asked if the NCI had any plans for followup trials to address the questions about the optimal initiation date and what happens in the long-term. Dr. Kramer pointed out that there is a lifetime followup for all women who have entered NSABP breast and colon trials, and women on placebo during the BCPT now have the option of initiating tamoxifen therapy. Dr. Li asked about plans to ensure equal access—by all types of physicians—to the information on the BCPT results and use of the Gail or Claus model. Dr. Klausner noted the NCI's plans to meet with professional societies and arrange to work with their practice guideline groups. He emphasized the need for the entire community to digest and discuss this new information over time, develop evaluation parameters, and provide feedback to the NCI. Dr. Klausner and Dr. Wittes noted the need to avoid creating an oversimplified approach to what will always be a complex personal medical decision and to avoid taking that decisionmaking process out of the relationship between a woman and her doctor.

### **NEW EXPLORATORY/DEVELOPMENTAL GRANT**

**Dr. Robert Hammond and Dr. Carol Dahl**

Dr. Robert Hammond, Chief, Office of Advisory Activities, DEA, described the new Exploratory/Developmental Grant, which includes a number of innovative features, notably the new R33 grant mechanism. He stated that several NCI working groups had identified a need for a support mechanism for the rapid review and funding of large-scale technology development studies. Existing grant mechanisms did not meet the NIH's need to address rapidly evolving technology opportunities. Therefore, an inter-divisional task force was assembled to consider innovative strategies. The task force recommended the development of the R33 mechanism to provide the second phase of support for developmental research initiated under the R21 mechanism. The first use of the R33 mechanism will be in the Phased Innovation Award. Applications submitted in response to RFAs or PAs can request an initial first R21 phase of up to 2 years support of \$100,000 a year for preliminary exploratory and developmental studies. The second phase, (R33), does not have a budget cap; therefore, it is suitable for support of full-scale

technology development. The overall purpose is to support technology research from evolution of concepts to full-scale development. The major advantage of the proposed process is that there is a single submission and evaluation of both R21 and R33 as one application—without a funding gap between the two.

Dr. Hammond introduced Dr. Carol Dahl, Director, Office of Technology and Industrial Relations (OTIR), OD. Dr. Dahl said that ideas were solicited from NCI program staff, which resulted in a series of suggestions—about 75 percent of which related to molecular analysis. These ideas were compiled into the research scope of the *Innovative Technologies for the Molecular Analysis of Cancer*. In addition, all divisions were included in the planning process to determine program needs which were then integrated into the PA that spans the Institute in terms of interest. Dr. Dahl added that it is looking for technologies that will support basic, clinical, and population research. The announcement also is seeking technology that supports *in vitro* analysis, as well as *in situ* and *in vivo* analysis tools.

The program will be managed through interaction of participating programs. The OTIR will manage interactive scientific matters across the Institute. Dr. Dahl asked NCAB members for help in distributing information about this program to their colleagues.

#### Questions and Answers

Dr. Bishop asked about the amount of funding the NCI is willing to invest in this program. Dr. Dahl responded that the funding derives from two regular pools: the RPG and the SBIR line. The management team is planning to put forward a consolidated plan for funding so that Executive Committee members can evaluate it in terms of the Institute's perspectives and needs. Dr. Dahl estimates that the RPG cost in the first year would be \$3-4M. In terms of individual grants, the total award can be for no more than 4 years. The first phase has a cap of \$100,000 for up to 2 years; the second phase does not have a cap. Dr. Li asked if people proposing innovative technology might have difficulty obtaining critical tissues. Dr. Dahl replied that the Cancer Diagnosis Program has procurement networks, and Dr. Wittes added that there is a tissue expediter who serves as a broker between investigators needing tissue and available resources and repositories. Dr. Wilson asked if these tissue repositories have been identified. Dr. Wittes replied that the Institute funds many of them, including the Clinical Cooperative Groups (CCGs)—which are connected to patients who have been enrolled in their clinical trials. These are national resources that have the necessary policies and procedures to make tissues available to qualified researchers.

#### RESPONSE TO THE BISHOP-CALABRESI REPORT

##### Dr. Richard Klausner

Dr. Klausner discussed the NCI's ongoing response to the Bishop-Calabresi Report. He said that profound and deliberate changes have taken place in the Intramural Program as a result of the report, and these changes represent a commitment to an ongoing long process of further changes. He added that the Intramural Program has enormous strengths and terrific people who have made a tremendous commitment to their work.



**Budget.** Dr. Klausner noted that in 1995 it had in some cases been difficult to determine what was intramural and what was not and, at that time, the IRP represented about 20 percent of the NCI budget. During the past 3 years, the IRP budget allocation was reduced by establishing goal percentage decreases, limiting growth, and initiating Institute-wide cost-management principles, the last of which resulted in a reduction in IRP operating expenses of \$11M in FY97. In FY98, an additional \$6M was recovered. Immediate changes reduced the IRP budget to less than 20 percent of the overall NCI total, and the prediction for FY99 is that the intramural budget will be 16 percent of the total Institute budget. However, there has been an absolute dollar growth of approximately 17 percent between 1992 and 1998 to meet mandatory changes in salary, cost-of-living increases, and assessments for the Intramural Management Fund. As an example of budget reduction and redirection, Dr. Klausner noted that in FY95, 50 percent of the NCI AIDS budget was spent on Intramural Programs; in FY98, it is 28 percent. This has had a significant effect on the extramural RPG pool.

**IPP Scientific Review.** Dr. Klausner stated that the issues of the budget and scientific review are interrelated. He added that there is a need for a rigorous scientific review process that is conducted by high-quality reviewers—with a high-quality process—who would report to the BSC. The most critical aspect of scientific review is the people who participate in the process. To ensure such quality, a new Office of Intramural Review was created to administer the formal evaluation process. A professional staff, drawn from NCI extramural scientific review administrators, reports directly to the Deputy Director for Management.

Dr. Klausner next commented on the relationship between the review and the implementation of the review's recommendations. He used, as an example, the reviews of 73 principal investigators (PIs). The BSC recommended that 8 laboratories be closed, 10 reduced, 36 continued, and 12 expanded. The BSC also recommended a \$3M collective reduction in the total budget. After an appeals process and final judgments about the implementation were determined by the division directors, the final budget adjustment was \$2.7M, or 90 percent of the recommended amount.

Dr. Klausner discussed the ad hoc review selection process, which is presented in the *NCI's Intramural Organization and Principles Manual*. An external site visit team consists of two regular board members—one is the chair of the site visit who, together with the BSC chair, provide a list of recommended reviewers to the Intramural Office's executive secretary. Any changes to the list are determined by the BSC chair and the division director. The formal rebuttal and appeals process arises from the completed site visit report, is circulated among members of the review team, and is finalized based on the team's comments. PIs may respond to recommendations, criticisms, and questions raised in the site visit report. The report, along with the responses, are then submitted to the BSC for consideration. This full consideration is used to make modifications in the site visit recommendations and the PI has an opportunity for rebuttal. If the PI continues to be dissatisfied with the response, he or she can appeal directly to the NCI Director.

**Frederick Cancer Research and Development Center (FCRDC).** In an effort to clarify issues surrounding the FCRDC, Dr. Klausner described the Center and its relationship to the Intramural Program. He noted that much of the science at the FCRDC is presently undergoing an extensive review and he added that its laboratories represent a series of contracts, as well as NCI staff. Dr. Klausner added that it would be necessary to identify all intramural activities at the FCRDC. In 1997, \$35M (29% of the total effort at FCRDC) was assigned to the IRD. All research is done within the structure of one of the three NCI intramural divisions and is reviewed using the same criteria of cost management, continuation, closure, and expansion. In addition, another \$25M (20% of the budget) is spent on contractor investigator-initiated research, which appears indistinguishable from intramural research but is not presently included in the Intramural Program. The majority of that is through the Advance BioSciences Laboratory (ABL) contract; Dr. Klausner added that there have been discussions between the NCI and ABL to evaluate whether their activities could be moved into the NCI's Intramural Program. There are technical problems in doing this, and the goal is to ensure that the program does not suffer in transition.

Dr. Klausner stated the remaining FCRDC budget is devoted to investigator-initiated research programs associated with other Institute programs: drug discovery; structural analysis, and the supercomputer. He added that non-Intramural Program funds total about \$87.8M, with allocations for some of the activities previously discussed as well as the following four areas: (1) indirect costs—the overall management fund—which constitutes about 22.8 percent of the budget and is a complicated revenue source involving the U.S. Army, contractors, and other institutes that use the FCRDC; (2) special programs, including the Developmental Therapeutics Program (DTP), the Supercomputer Program, and new initiatives such as the Cancer Genome Anatomy Project; (3) specialized resources, comprising repository systems and projects such as the PLCO trial; and (4) research support services, which include organic synthesis, mass spectrometry, NMR spectrometry, biopolymer spectrometry, protein isolation, animal bacterial cell production, mycoplasma testing, animal holding, and electromicroscopy. After deducting overhead, the remainder of the budget—about \$60M—is divided among these programs.

Dr. Klausner added that the FCRDC should be strengthened because the flexibility it provides the Institute for initiating programs is outstanding.

### Questions and Answers

Dr. Alfred L. Goldson asked about staff reductions resulting from laboratory reductions or closures. Dr. Klausner noted that the NCI does not dismiss tenured people. In addition, the Institute helps postdoctoral fellows in such laboratories slated for reduction to pursue opportunities in other laboratories. Dr. Bishop asked Dr. Klausner why he does not share the burden of being the "court of last resort" with the entire EC. Dr. Klausner replied that the present process works well and he believes that, ultimately, he should be responsible for personally interacting with the PIs. Dr. Freeman asked about the determining factors for shifting funds within the Intramural Program. Dr. Klausner responded that the NCI's decisions about policy and distribution of funds are guided by a variety of parameters,

including the goals of excellence, productivity, and output. Dr. Klausner added that the issues of excellence, morale, program building, and training are critical—in terms of accountability and fiscal responsibility.

Dr. Paul Calabresi asked if the change in the distribution of the AIDS budget was the dependency on AIDS funding for the NCI rather than the shifting of funds from the IRP to the ERP. Dr. Klausner responded that there are mandates that need to be fulfilled as a result of recommendations made by the Office of AIDS Research (OAR) oversight group and the Levine Report—which specifically called for increasing support of extramural investigator-initiated research with NIH AIDS funding. As a followup question, Dr. Schein expressed concern about the Levine Report and the amount and proportion of funding for the Developmental Therapeutics Program (DTP). He questioned whether the program has been sustained and, if so, if the funding source is sufficient. Dr. Klausner replied that funding for the DTP's AIDS research was more than \$30M in 1995; it will be \$6M next year and \$2M the following year. As part of the DTP's AIDS review, the NCI has initiated an external review of opportunities for the Institute in developmental therapeutics for AIDS and AIDS-associated diseases.

Dr. Dickersin noted that there is contractual funding related to FCRDC, and to intramural clinical trials and trials elsewhere. She added that there is a possibility of staff repositioning at the FCRDC as a result of budget reductions and questioned whether this applies to both laboratory and epidemiology clinical trial contractual funding. Dr. Klausner said that this is a complex issue because contracts are used for a variety of projects and programs. He noted that the IRP's contractual funding is included in the overall NCI budget; Intramural Program funds do not have a separate line for contractual work.

Dr. Calabresi asked if other institutes use these FCRDC resources. Dr. Klausner replied that other Institutes pay for what they use in a fee-for-service arrangement. In closing, Dr. Klausner noted that NCAB members will be reviewing the "Response to Bishop-Calabresi Report" prepared in response to questions raised at the February 3, 1998 NCAB meeting. Further discussion is scheduled for the September NCAB meeting.

### **INTRAMURAL ADVISORY BOARD RESPONSE**

**Dr. Allan Weissman**

Dr. Allan Weissman, NCI, discussed issues of communication and long-term planning in regard to the IAB, specifically the different types of communication that exist on campus and the means by which PIs communicate with administration. He stated that the traditional and most common means of communication is downward—from division director, to branch and laboratory chiefs, to PI. If PIs believe they are unable to address issues with their immediate supervisors, there are two other routes of communication available to them: (1) direct contact with division directors (including the Employment Relations Office and the Equal Employment Opportunity Office), and (2) geographically based ARCs with administrative officers who are supervised by ARC managers and who report to the Deputy Director for Management. He added that the ARCs have been effective and minimize red tape. In terms of communication, the IAB is a sounding board

for policy initiatives and provides a source of direct feedback to the NCI director. Over the last 2 years, numerous policy initiatives important to NCI scientists have passed through the IAB:

- Scientist and Staff Clinical Programs enable the appointments of Ph.D.s and M.D.s with expertise in specific areas for renewable periods of time.
- Employee evaluations have been simplified.
- The Cancer Research Training Award (CRTA) Program has been established. This program simplifies hiring trainees, provides a defined experience-based pay scale, and allows for travel reimbursement for people coming to the NCI.
- The NCI Scholars Program brings young scientists to the Institute to launch their careers. The program should enhance the intramural community.
- Competitive intramural research programs that reward innovative collaborative interactions with additional postdoctoral support have been developed in the Division of Clinical Sciences (DCS) and the DBS.
- Guidelines for site visits have been developed. These guidelines are distributed to reviewers and investigators and, during the visit, a private session occurs between each PI and the site review committee. This personalization of the process allows for resolution of misunderstandings and facilitates confidential assessment of mentoring.

There has been concern that the IAB is not fulfilling its potential as an effective means for involving the general intramural community in reshaping the IRP. Because of this, the IAB has taken steps to increase its visibility with colleagues. For example, IAB members have been assigned to each branch or laboratory, with assignments based on the Administrative Resource Centers. PIs are made aware of assignments and scientists are encouraged to contact IAB members with appropriate issues. In the future, the IAB will monitor the effect that new policies have on the scientific community, and will pursue formulation of concrete initiatives in areas of paramount importance to the IRP. Special focus will be on two major areas.

**Assessment of Core Facilities and New Technology.** Until recently, the Intramural Program had not kept pace with other academic institutes' with regard to making cost effective core services available. Recently, efforts by NCI leadership and individual scientists have resulted in significant headway toward remedying this situation. These efforts have resulted in the following: cost-effective contracts for oligonucleotide synthesis and peptide synthesis; arrangements that make automatic DNA sequencing widely available and affordable; a confocal microscopy facility now coming online; and a core fee-for-service knockout facility.

**Recruitment and Retention of Scientific Talent at All Levels.** The Institute is faced with a human resources deficit at the postdoctoral level and beyond. The difficulty in recruiting capable individuals parallels a significant shortfall in recruiting highly

qualified minority and women candidates. The reasons include: the financial constraints and full time employee (FTE) crunch of the past decade, which resulted in cutbacks in programs that traditionally attracted physicians who came to NIH to begin their careers in medical research; demographic and economic factors that are not unique to NIH; and the perceived quality of NCI research programs.

Specific measures to improve recruitment at the post-doctoral level being considered are largely centered on the creation of a supportive infrastructure in the form of an office. Such a recruiting office may be based on that of the Cancer Prevention Fellowship Program, which has been highly successful in recruiting talented candidates including significant numbers of underrepresented minorities. This office would serve to enhance recruitment to specific programs and individual labs, disseminate information to candidates regarding opportunities, and serve as a place where applicants can obtain information about quality of life and career development issues. Other means of improving recruitment include the use of congressionally mandated loan repayment programs, use of these will require FTE positions.

Dr. Klausner concluded the review of the Intramural Program by emphasizing the amount of recent activity that has taken place within the Program. He noted that this is a time of great challenges and extraordinary opportunities for excellent translational research to be linked with epidemiological research.

#### **Questions and Answers**

Dr. Sharp noted that restricting external travel was a great disservice to the NIH and the NCI. He said that resources should be committed to promoting the exposure of young people at the NCI who are the most likely postdoctoral applicants. Dr. Sigal asked about the issue of compensation in recruitment. Dr. Klausner responded that the training program was reorganized, in part, to make salary scales comparable to and competitive with other institutions—and to devise a single hiring mechanism. He added that salaries are comparable now, including those for senior scientists.

#### **OFFICE OF INSPECTOR GENERAL REPORT: CANCER INFORMATION SERVICE AND NCI RESPONSE**

##### **Ms. Chris Thomsen**

Ms. Chris Thomsen, Chief of Public Inquiries, Office of Cancer Information, Communication, and Education (OCICE), summarized the findings of a study conducted by the Office of the Inspector General (OIG) on the CIS. In 22 years of service, the CIS has handled over 8 million calls. The service provides access to the most recent information from the NCI on cancer, clinical trials, and support services for patients, health professionals, and the general public. The OIG is charged with protecting the integrity of the Department of Health and Human Services (DHHS) programs. It often conducts customer satisfaction surveys, but this was the first time it had studied a telephone service. As the study evolved, it was divided into two parts: access to the 800 number, and how cancer organizations around the country use and value the CIS. The study originated because of the frequency of busy signals on the 800 number and the need for recommendations about ways to reduce it. The OIG focused on interviews and

site visits around the country. Major findings include the following: (1) confirmation of the value of the program and the unique service it provides; (2) commendation of the CIS training program and quality assurance efforts; (3) the need to increase access and operate more efficiently; (4) outdated telephone system and computer support services; (5) criticism of data collection; (6) criticism of the regional program structure (calls are not routed to the first available information specialist because there are 19 regional call centers that serve specific geographic areas); (7) lack of support by parent institutions; and (8) inconsistent promotion of the program and management practices through a decentralized network.

Ms. Thomsen reviewed the OIG recommendations and the CIS's plans to respond. Many of these plans were already underway, and the OIG report reaffirmed the CIS's own findings and supported plans to move forward.

- Upgrading technology and setting performance standards will increase public access and allow more people to call the CIS. Mechanisms for people to reach the CIS will be expanded to include taped messages, more links to web sites, and more efficient operations. Collecting information is costly and time-consuming, and the CIS will establish partnerships with other organizations in an effort to reduce those costs.
- The PDQ System will be modernized.
- Data resources will be computerized, but this will depend on the ability to upgrade the infrastructure. The core components of the program will continue to be telephone service; outreach to minorities and underserved populations; and participation in cancer control research.
- Callers interested in community resources and services will be referred to other organizations. The CIS has partnerships with more than 4,500 national, regional, state, and local organizations. They consider their links with the CIS essential, but they believe that the CIS program needs to be easier to access.
- Regarding the regional structure, contracts are up for renewal, and the CIS will reassess regional configuration to ensure that the program is operating efficiently.
- Staff training and career development will be enhanced.

The next steps are to focus on elements that are critical to the NCI in achieving its mission; to increase access, efficiency, and relevance to the public; to contain costs; to expand access to the telephone service; to enhance the capacity to participate in control research; and to strengthen technical assistance to community partners.

### Questions and Answers

Dr. Klausner asked about the cost of these planned improvements. Ms. Thomsen replied that the CIS is in the process of developing a budget for submission to the Director. Dr. Li cautioned against substantially altering the regional structure and noted that there are cultural, ethnic, and other differences that require a heterogeneous service. Ms. Zora Brown requested additional information on the minority outreach program. Ms. Thomsen

said the outreach program complements the telephone service; there are outreach managers and coordinators throughout the country who network and build coalitions with other organizations that work specifically to reach minority and underserved populations (e.g., the Black Leadership Initiative on Cancer and the CDC Breast and Cervical Programs).

## NEW BUSINESS II

### Dr. J. Michael Bishop

No additional items of new business were identified for discussion.

## PLANNING FOR THE BYPASS BUDGET 2001

### Dr. Richard Klausner

Dr. Klausner indicated that the Institute has distributed more than 14,000 copies of the current FY99 Bypass Budget. The distribution list is extensive and includes: advocacy organizations, the Congress, the White House, other federal agencies, professional organizations, and NCI grantees. He added that the Bypass Budget has become a communication device regarding priorities and initiatives. The NCI also has created a series of supplemental ways to view the budget: a web site, which will have a search engine; a pamphlet entitled *A Summary of the Nation's Investment in Cancer Research*, which describes scientific opportunities for researchers and clinicians; and a planned brochure to help advocacy groups work with and through the Bypass Budget. NCI administrators use the Bypass Budget for organization and planning, and to increase the number of RFAs directly tagged to the budget. The budget for FY2000 is well underway; it contains much of the extensive input the Institute received from advocacy organizations, professional societies, and others. A draft will be sent to the Bypass Budget Planning Committee in early June. That group will solicit comments from 130 cancer organizations. The target release date for the FY2000 budget is September 1, 1998. The FY01 budget will contain new extraordinary opportunities, for which ideas are now being solicited. A new brochure, *Planning the 2001 Bypass Budget*, describes the process and criteria for identifying extraordinary opportunities. The brochure will be distributed to the NCAB, the President's Cancer Panel, the National Policy Board, NCI working groups, and NCI program and section heads, as well as various advocacy groups, organizations, and cancer center directors. Input for the FY01 Bypass Budget will be overseen by the Office of Science Policy (OSP). Extraordinary opportunities will be selected by the end of October 1998 and goals defined by mid-November. In addition, the NCI will assemble internal think tanks, comprising NCI staff and external experts, to identify ideas and goals for selected opportunities. Extraordinary opportunities represent very important parts of the NCI's long-term planning process.

### Questions and Answers

Dr. Sigal commended Dr. Klausner for soliciting input about extraordinary opportunities. She believes these opportunities will be incremental rather than overarching and it is important to review the shifting priorities and distribution of funds within the budget.

## PEER REVIEW POLICY UPDATES

**Dr. Marvin Kalt**

Dr. Kalt announced that he had been working closely with the DCLG to involve consumer advocates in a wide variety of activities at all levels of the NCI. Consumers now participate in the following: the DCLG, NCAB, BSA, BSC, Program Review Working Groups, and Progress Review Groups

Dr. Kalt added that the commitment to include consumers is being expanded at the peer review level. This will be phased in carefully, starting with adding the P30 center grant mechanisms and the U10 Clinical Cooperative Groups. The DCCG will help search for individuals who have been involved in the cancer experience as either survivors or persons otherwise affected by the suffering and consequences of the disease. In addition, a consumer representative must show evidence of a larger involvement—defined as advocacy—as well as the ability to communicate and advocate a position effectively, to think beyond one's personal experience, and to work well in groups.

The DCLG has asked the CCGs, the U.S. Army, the ACS, and other groups to identify such individuals who may be interested in participating in the peer review process. Experience has shown that consumers help reviewers focus on the effect of innovation, on population-based areas, and on basic science as it relates to NCI objectives.

## ADJOURNMENT

**Dr. J. Michael Bishop**

There being no further business, the 106th meeting of the National Cancer Advisory Board was adjourned at 11:50 a.m. on Wednesday, May 13, 1998.