NATIONAL CANCER ADVISORY BOARD

convened on September 11-12, 1998, at the:
National Institutes of Health
Building 31-C, Conference Room 10
Bethesda, Maryland 20892

ATTENDEES

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The National Cancer Advisory Board (NCAB) convened for its 107th regular meeting at 9:00 a.m., September 11, 1998, in Conference Room 10, C Wing, Building 31, National Institutes of Health.

NCAB MEMBERS

Dr. J. Michael Bishop (Chairperson)
Dr. Richard J. Boxer
Dr. Kay Dickersin
Dr. Alfred L. Goldson
Dr. Frederick P. Li
Dr. Sandra Millon-Underwood
Dr. Ivor Royston
Dr. Philip S. Schein
Dr. Phillip A. Sharp
Ms. Ellen L. Stovall
Dr. Vainutis K. Vaitkevicius

President's Cancer Panel

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

Alternate Ex Officio NCAB Members

Dr. Steven K. Akiyama, NIEHS
Col. Louis F. Diehl, DoD
Dr. Michael Hodgson, NIOSH
Ms. Rachel Levinson, OSTP (absent)
Dr. Alison Martin, FDA
Dr. Hugh McKinnon, EPA
Dr. Lakshmi C. Mishra, CPSC (absent)
Dr. T. G. Patel, DVA
Dr. Eugene Schwartz, DOL
Dr. Michael Viola, DOE

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 MEETINGA

Dr. J. Michael Bishop

Dr. Michael Bishop called to order the 107th 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 May 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. Dates have been confirmed through 2000.

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

Dr. Richard Klausner, Director, NCI, presented an update on several initiatives in the National Cancer Program (NCP) that had been the focus of extensive press coverage and NCI communication to the public at the time of the May NCAB meeting. In response to the findings in the Breast Cancer Prevention Trial (BCPT), the Oncologic Drugs Advisory Committee (ODAC), Food and Drug Administration (FDA), has approved the use of tamoxifen to reduce the risk of breast cancer. Because tamoxifen and risk reduction represent complex issues for which informed decisionmaking is essential, the NCI convened a workshop in July 1998 to develop risk/benefit assessments useful to the public and professionals. Dr. Klausner reported that the RISK computer program has been developed to assist physicians and their patients in understanding the risk factors for breast cancer and in using the risk models used in the BCPT. The program is available to the public. The National Surgical Breast and Bowel Project (NSBAP), the clinical cooperative group that conducted the BCPT, is proceeding with a followup trial, the STAR trial, to compare raloxifene with tamoxifen. The NCI is also in the process of getting approval for a nested case control study to evaluate whether there is evidence in the data from the BCPT that tamoxifen was helpful to women who were carriers of germ line alterations in *BRCA1* or *BRCA2*. Separately, in other breast cancer news, Dr. Klausner noted the recommendation has been made to the FDA to approve the use of the monoclonal antibody Herceptin®, joining the anti-CD20 antibody Rituxan®, as the second approved monoclonal antibody in cancer.

Research Project Grant (RPG) Funding Update. Dr. Klausner reported that, as FY98 draws to a close, the R01 payline continues at the 24th percentile, with a projection that more than 700 competing R01s will be funded. Total funding for R01s is expected to be more than $670M for about 2,465 awards, an increase of 15 percent over FY97. In the program project (P01) grants line, 36 competing awards will be funded automatically—through the priority score of 135—for a 10.6 percent increase in the overall P01 funding level from $202M in FY97 to$224M in FY98.

Dr. Klausner reviewed new mechanisms and approaches being implemented in the NCI grants programs. The Center for Scientific Review (CSR), NIH, will convene a Clinical Oncology Special Emphasis Panel (SEP) for the next grant receipt date, the details of which will be available on the CSR Web site. The process by which the NCI makes funding decisions continues to be expedited and broadened. Through the accelerated executive review (AER) initiative for unamended R01s, the NCI continues to fund at a success rate of between 50 percent and 60 percent. The AER program will be continued in FY99, assuming an adequate budget. Applications considered for AER are those within 10 percentile points of the automatic payline for patient-oriented research and 5 percentage points for all others. In an initiative to be discussed later in the meeting, the

NCI plans to the extend accelerated review processes to P01 applications within a particular range of the payline.

Requests for Applications (RFAs). Dr. Klausner briefly reported on NCI's recent use of RFA set asides that are directed toward priorities identified through NCI's decisionmaking processes, especially the Bypass Budget, and in response to approved and accepted review group recommendations. During the past year, a series of RFAs have been advertised in the areas of adolescent and smoking-prevention behavior to communicate NCI's commitment to behavioral research, from basic science to community applications. Another RFA for cancer control supplements to cancer center support grants (CCSG) resulted in applications from all but two of the centers. Additionally, the Tobacco Research Implementation Group (TRIG) will be presenting recommendations for continuing and strengthening NCI's tobacco research program at the December NCAB meeting. These recommendations also may be implemented through the use of RFAs. Dr. Klausner indicated that plans developed together with the Department of Health and Human Resources (DHHS) are to move NCI's ASSIST program and place it under the purview of the Centers for Disease Control and Prevention (CDC), where it will be extended to all states as a public health application. The NCI will continue to be involved in the analysis and will maintain its commitment to community-based intervention research.

Program Announcements (PAs). Dr. Klausner announced that the process by which the NCI prioritizes and releases PAs has been revised to communicate to the research community that PAs are an important aspect of NCI's funding commitments, even though they are not associated with fixed set asides. The NCI will comply with the NIH sunset clause that now automatically inactivates announcements unless they are renewed and will limit the number of active PAs to approximately two dozen. This figure was based on the fact that the NCI—in its budgeting—sets aside approximately 10 percent of available new and competing grant dollars for exception funding. Dr. Klausner emphasized that the priorities being set in the limited number of advertised PAs will be linked to the use of exceptions by the extramural funding divisions. These changes and new emphases will be communicated through the Board of Scientific Advisors (BSA) "NCI Listens" sessions at professional society meetings, and through NCI's Web site and other communication venues.

Update on NCI Research Awards Programs. Dr. Klausner reported a strong response to NCI's initial release of the new Phased Innovation Award, which called for Innovative Technologies for the Molecular Analysis of Cancer. This award supports the development of new technologies for research through the R21 for the beginning phase with measurable milestones and through the R33 for a credible development plan, with minimal or no gap between the two awards. A parallel fast track was created for Small Business Innovation Research (SBIR) and Small Business Technology Transfer Research (STTR) applications. Approximately 23 applications were received in response to this initial dual release. Dr. Klausner noted that the extension of the phased innovation award for new technology development to the SBIR and STTR mechanisms holds promise for ensuring the optimal use of congressionally mandated set aside funds for small businesses

and for providing valuable linkages in the growing small business environment for cancer research. He reported that the NCI Executive Committee (EC) recently approved a concept to combine the R25 educational award, which supports the development of curricula or educational materials for cancer, and a fast-track SBIR to form a hybrid award that would support the further refinement and dissemination of materials developed under the R25, without a break in funding. Details remain to be resolved, but the NCI has received a commitment from the NIH to facilitate this dual-application process. The NCI will coordinate and conduct the review and awards processes. This fast-track mechanism is expected to facilitate the creation of flexible funding mechanisms in the business community for the discovery and development of therapeutics, from early stages to clinical trials. For example, this new award mechanism and the Rapid Access to Intervention Development (RAID) program will be used as the NCI begins to implement the recommendations of the Developmental Therapeutics Program (DTP) Review Group, which will be presented at the December meeting.

NCI Education and Training Awards. Dr. Klausner announced that the NCI K22 Scholars Program would be reviewed in closed session and that proposals for creating an overarching new set of awards to support the continuum of training phases from mentored to unmentored status for clinical, cancer control, and behavioral scientists would be presented later in open session. NCI's efforts to improve and provide mentoring and training for minorities and the underserved will be the focus of a presentation at the December meeting.

Consumer Participation on NCI Review Panels. Dr. Klausner reported continued progress in the initiative to encourage consumer participation on NCI review panels. This initiative has been overseen by the Director's Consumer Liaison Group (DCLG) and has proceeded under guidelines developed by the DCLG working closely with Dr. Marvin Kalt, Director, Division of Extramural Activities (DEA).

FY99 Budget/FY2000 and FY2001 Bypass Budgets. Dr. Klausner reviewed prospects for the FY99 budget, noting that despite the President's proposed 9.1 percent budget increase for the NCI and encouraging marks proposed by the House and Senate (9.6 % and 15.1 %, respectively), it is not yet known whether the NCI will enter the new fiscal year on a continuing resolution. He announced that *The Nation's Investment in Cancer Research: A Budget Proposal for Fiscal Year 2000*—the Bypass Budget—was being printed and would be ready for general distribution after presentation to the Director, NIH, and Secretary Donna Shalala, DHHS, and transmittal to the President. The NCI is beginning to develop a new set of extraordinary opportunities to be included in the FY2001 Bypass Budget. Letters will be sent to all advisory boards, NCI staff, grantees, cancer center directors, professional society members, and advocacy groups with guidelines for participation in the identification of extraordinary new investment opportunities for this next 3-year cycle. The Bypass Planning Committee will meet in December to evaluate and select, from suggestions received, a limited number that fit the agreed-upon criteria, and the final list will be developed. Major planning for the new cycle also includes rewriting the section entitled *NCI's Challenge*. This will be a major focus of the annual NCI leadership planning retreat in January 1999.

Dr. Klausner emphasized the importance and challenge of ensuring that Congress, the NCAB in its oversight role, the public, and the research community know how the NCI plans, prioritizes, and implements initiatives toward the goal of making progress against the diseases for which it has responsibility, and that these constituencies are aware of the opportunities. He stated that the NCI has been working to ensure that the visions, ethos, and approaches to planning and implementation contained in the Bypass Budgets explain and provide a real and measurable framework for NCI initiatives. He noted the need in the planning process to consider the linkage between the Bypass Budget approach of identifying crosscutting scientific opportunity and the need for disease-based planning as indicated in the reports of the Breast and Prostate Cancer Progress Review Groups. Dr. Klausner then presented highlights of the more than 30 initiatives developed to capitalize on the four extraordinary opportunities included in the current 3-year cycle of Bypass Budgets—Cancer Genetics, Signature of Cancer Cells, Preclinical Models, and Detection/Imaging.

Cancer Genetics. Dr. Klausner highlighted some of the major initiatives in this area of opportunity. The ***Cancer Genetics Network*** was described as a new national resource that provides the infrastructure—linked by state-of-the-art informatics—to conduct a broad range of collaborative research on cancer genetics and translate research findings to change the practice of both preventive and therapeutic oncology, as well as to address the psychosocial, ethical, and legal issues associated with inherited cancer susceptibility. Established by the NCI progressively since 1995, the ***Cooperative Family Registries for Breast and Colorectal Cancer Studies*** (CFRBCCS) provide a comprehensive, collaborative infrastructure to accelerate the genetic and epidemiologic study of heritable cancers. Twelve participating institutions are located in the United States, Canada, and Australia. Dr. Klausner noted that the Cancer Genetics Working Group will be having a targeted discussion on these infrastructures to determine whether they are optimally structured and have the requisite expertise, technology, and access to other researchers to accelerate gene discovery in terms of cancer predisposition. ***Cancer center supplements*** were awarded in FY96 to stimulate a broad national effort in genetic risk factor research and education. Accomplishments to date include the funding of 12 pilot projects involving genetic susceptibility studies in breast, colon, prostate, and bladder cancer; the funding of 12 resources ranging from family collections for linkage studies to clinics for high-risk genetic predisposition; and 19 new training and education programs in genetic counseling and genetic risk factors related to cancer for primary physicians, nurses, counselors, and the lay public.

Dr. Klausner described the ***Genetic Annotation Initiative*** (GAI) as an example of the intellectual resource and infrastructure programs linked to the Cancer Genome Anatomy Project (CGAP) that the NCI has been developing. The GAI is a research program to explore and apply technology for identification and characterization of genetic variation in genes important to cancer. The goals for the next year include the characterization of at least 3,000 gene-based variants. A database for this project, which was created in a collaboration with the National Center for Biotechnology Information (NCBI), will be linked to the CGAP and other related databases. The ***Cancer Chromosome Aberration Project*** (C-cap), another CGAP resource development initiative, is designed to develop technologic tools that will allow for the definition and detailed characterization of the

chromosomal alterations that are associated with malignant transformation. A repository of genetically and physically mapped DNA bacterial artificial clones (BAC) anchored across the human genome will be generated. Dr. Klausner anticipated that chromosome 7 would be completely mapped and available on the NCI Web site in October, and that the C-cap project would be completed in the next 2 to 3 years. Goals for the next fiscal year include identifying funding that will enable NCI cancer centers and grantees to link to the technologies and the growing public database to stimulate technologic advances in cytogenetic and positional cloning areas.

Signature of Cancer Cells. Dr. Klausner briefly reviewed progress in the CGAP, whose overall goal is the comprehensive molecular characterization of normal, precancerous, and malignant cells. Information on new genes is made available immediately in the CGAP Web site. During the past year, CGAP gene discovery has been progressing at a rate of 3.7 percent monthly, adding about 283,000 new CGAP sequences and 10,600 new genes to the public database. Through the NCI internet, a new process—the NCI Tissue Expediter—has been developed to match investigators with appropriate resources. An advisory committee has been established to oversee general issues related to tissue resources.

Preclinical Models. Dr. Klausner reported that an RFA has been advertised for the Mouse Models of Human Cancer Consortium. This mechanism is expected to provide the systematic funding of model development and dissemination and connection of developers of models to the evolving technologies and resources that are needed. The NCI also is providing supplements to investigators to support the added cost of maintaining animal models. Other ongoing projects include the mouse CGAP, mouse genetic mapping, trans-NIH mouse genetics initiatives, and non-mammalian models development.

Detection/Imaging. Dr. Klausner highlighted two imaging networks that are being created. In the ***Diagnostic Imaging Network***, a national infrastructure will be established for multi-institutional clinical trials and the rapid identification and assessment of innovative imaging technologies. The ***Small Animal Imaging Resource Programs*** (SAIRPs) will provide both an imaging resource to oncology researchers and a laboratory for research and development of small animal imaging technologies, in particular, functional imaging. The NCI has issued an RFA entitled *"Development and Application of Imaging in Therapeutic Studies"* to stimulate multidisciplinary research that incorporates novel imaging agents into the assessment of therapeutic agents. Planning is under way on a proposal to establish ***chemistry resource centers*** from which the novel imaging agents could be supplied. Also being planned is a proposal that would create a ***Detection Research Network*** for studies in biomarkers for early detection and risk assessment. Goals would include the development of a quality assurance plan for biomarker testing and evaluation and decision criteria for development to further clinical and application studies. Interaction would be fostered among academic, clinical, and industrial leaders for the development of high throughput, sensitive assays for biomarkers for cancer detection, risk assessment, and prevention. Another diagnostic/imaging project will be undertaken as part of NCI's ***Unconventional Innovations Program*** (UIP), which

supports unconventional innovation in technology discovery for cancer research applications and invests in entirely novel technologies or quantum improvements in existing technologies. The scientific goal of this UIP initiative is noninvasive sensing and signaling of specific molecular alterations in patients with capabilities for controlled and monitorable interventions specific for these molecular alterations. The NCI is currently soliciting suggestions from the scientific community about technological opportunities for the UIP and plans to use a Broad Agency Announcement (BAA) contract mechanism. The BAA will be issued in late 1998 or early 1999. In closing, Dr. Klausner emphasized the message that the NCI has a process in place and a plan to implement the objectives of the Bypass Budget.

Questions and Answers

In response to a question about the availability of the RISK disk, Dr. Barnett Kramer explained that the disk can be ordered through NCI's Web site. A questionnaire will accompany the disks when they are sent out, asking for comments and suggestions that will be used to expand or refine the next version of the disk. The disk also is being advertised in the newsletters of professional societies.

Dr. Phillip Sharp and Dr. Bishop asked if the NCI had any indication of the degree to which the extramural research community has been able to restructure itself to respond to the challenges set forth in this package of initiatives. Dr. Klausner pointed out that many of the initiatives have already been funded, but he acknowledged the need to effectively communicate these new programs beyond the disciplines and institutions usually involved in cancer research. For example, the UIP staff is attempting to build a new network by meeting with personnel in agencies and groups such as the National Aeronautics and Space Administration, the Jet Propulsion Laboratory, and Motorola. Also, advertisements are being placed in the *American Physics Journal and Chemical Engineering*.

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

Dr. Harold Freeman, Chair, President's Cancer Panel, presented a summary of the second of three meetings this year in which the Panel is addressing quality of cancer care and quality of life issues. In April, at the Jonsson Comprehensive Cancer Center, University of California, Los Angeles, the Panel initiated an examination of what quality means in the context of cancer care in the National Cancer Program (NCP). At Yale University on June 2, the Panel explored issues under the topic *Quality of Life and Survivorship* in a meeting attended by more than 200 people, including many survivors. The meeting focused on special health care needs of cancer survivors and the need to enhance research on survivorship as part of the continuum of cancer care and cancer research. Dr. Freeman noted that the growing and diverse community of survivors whose concerns are now being heard indicates the success of the NCP during the past 27 years. At the meeting, Dr. Vincent DeVita, former NCI Director, reminded the Panel that the National Cancer Act mandates that the results of basic research be applied to extending and improving the quality of life for survivors and that the NCP has a responsibility to maintain a balance between research and application of research. Dr. Freeman reported that the recurrent

theme expressed at this meeting was that prolonged survival is not enough. Individuals diagnosed with cancer want to know how the disease will affect their lives and the lives of their families to make the best personal decisions regarding their well being. Existing studies show that quality-of-life issues associated with cancer survivorship fall into three broad areas—physical, psychosocial, and economic—and their effects are complicated by the diversity of cancer survivors. The Panel believes that differences among cancer survivors, which include income, culture, and age, must be considered in the application of research results to cancer care.

The Panel heard that a comprehensive research agenda is needed which includes research on methods for quantifying the risk of secondary cancers, research on the prevalence and nature of psychological problems among cancer survivors, and research on the long-term physical effects of cancer diagnosis and treatment. Other survivorship issues of concern were: (1) the question of where cancer survivors should go for long-term surveillance and followup care—primary care giver, oncologist, or other health care provider; and (2) end-of-life care, recognizing that about one-half of those diagnosed with cancer die of their disease. Particular recommendations made to the President's Cancer Panel during the June meeting were: (1) include long-term followup of cancer survivors in clinical protocols; (2) develop "centers of excellence" in palliative care to provide leadership for research in this area; (3) promote interdisciplinary research and the development of guidelines for long-term care, rehabilitation, and followup; (4) identify opportunities for interventions that can ameliorate negative effects of treatment and improve quality of life; and (5) include palliative care, hospice care, and related medical education and training as research issues associated with cancer survivorship.

In conclusion, Dr. Freeman invited all interested persons to attend the third and final meeting of the Panel on the topic *Quality of Cancer Care/Quality of Life*, to be held at Roswell Park Cancer Institute on October 6. He stated that the Panel expects to formulate a report to the President by the end of the year and will report to the NCAB on progress in addressing these important issues.

Questions and Answers

Dr. Frederick Li referred to the stated need for a comprehensive research agenda suggested that the Panel identify extraordinary opportunities that can be a focus for NCI action. Dr. Klausner noted that the NCI instituted a formal program review process in the area of cancer survivorship about 2 years ago and had received a formal report of a research agenda that has been guiding NCI's program development and funding in this area. He agreed to provide the Panel with a copy of the Office of Cancer Survivorship report. Dr. Philip Schein suggested that, because therapeutic successes have led to longer lives for individuals diagnosed with cancer, specific initiatives may be needed and specific measures or modalities developed to change the mentality of treating oncologists to impact the overall problem of treatment-related toxicities and their long-term consequences. Dr. Sharp asked how much research NCI supports in the area of new agents for or new insights into the control of pain. Dr. Klausner agreed to provide budget figures and programs that are included in the NCI's research portfolio on new agents for

pain control. Ms. Ellen Stovall pointed out that the Panel's initiatives have led to a greater public awareness and the White House recognizes this as a constituency.

NEW BUSINESS I
Dr. J. Michael Bishop

Dr. Bishop called for new items of business to be added to the next day's agenda. He requested that Ms. Stovall provide a brief informational update on The March Coming Together To Conquer Cancer. No other items were offered for consideration.

NCI PROSTATE CANCER PROGRESS REVIEW GROUP
Dr. Richard Klausner, Dr. Donald J. Tindall, and Dr. Peter T. Scardino

Dr. Klausner introduced Co-Chairs Dr. Donald J. Tindall, Professor, Department of Urology, Biochemical and Molecular Biology, Mayo Clinic Foundation, and Dr. Peter T. Scardino, Chief of Urology Service, Memorial Sloan Kettering Cancer Center, to present the report of the Prostate Cancer Progress Review Group (PCPRG) entitled "Defeating Prostate Cancer: Crucial Directions for Research." Dr. Tindall reviewed the extent of the public health problem created by prostate cancer and noted that the growth of scientific knowledge and the developments in technology present unique opportunities to advance research against the disease. He briefly reviewed the membership and process of the PCPRG, which began deliberations with a large-scale roundtable meeting in July 1997 to identify important issues in prostate cancer. Key questions were identified and prioritized, and the NCI research portfolio was analyzed on the basis of these questions as part of the research prior to developing the PCPRG's recommendations and report. Dr. Tindall reported that the portfolio analysis produced an estimate of approximately $87M in support of 490–520 prostate cancer projects in the areas of biology, etiology/prevention, detection/diagnostic prognosis, systemic/local therapy, outcomes research, and resources.

Basic Science. Dr. Tindall discussed the PCPRG's statement of the problem, findings on the status of the fields, available opportunities, and research recommendations in the basic science areas of biology/progression/metastasis, etiology/prevention, and laboratory/clinical models. Recommendations in the areas of ***biology, progression, and metastasis*** included renewed emphasis on understanding the genetics of prostate cancer, including progression and metastasis; and the cell biology of prostate cancer, including cell-cell interaction, hormonal progression, and proliferation, apoptosis, and angiogenesis. In the area of ***etiology and prevention***, the PCPRG recommended that future research focus on (1) understanding and defining the genes that are important in the etiology of this disease; (2) examining dietary supplements that affect prostate cell growth, apoptosis, and angiogenesis; and (3) studying exogenous risk, race/ethnicity, and hormonal factors. PCPRG's recommendations regarding ***laboratory and clinical models*** needed to advance prostate cancer research were the development of (1) additional animal models that recapitulate various aspects of prostate cancer; (2) animal prostate tumors that metastasize to bone; (3) animal models that were both hormone-dependent and -independent; and (4) cell lines for studying gene regulation.

Clinical Science. Dr. Scardino presented a summary of the PCPRG's statement of the problem, findings, research opportunities, and research recommendations in the broad clinical areas of early detection/diagnosis/prognosis, staging and treatment of localized disease, systemic therapy, outcomes research, and resources needed. Recommendations to advance research in the areas of ***early detection, diagnosis, and prognosis*** were to develop and validate (1) additional biological determinants with prognostic utility; (2) surrogate markers for use as endpoints for prevention and new therapeutics trials; (3) molecular assays that can augment or replace tissue-based assays; (4) computer and mathematical modeling techniques; (5) improved body imaging techniques; and (6) more refined computer-assisted imaging. In the area of ***staging and treatment of localized disease***, the PCPRG recommended (1) development of assays to detect cancer cells and methods to characterize the biologic potential of cancer cells; (2) standardization of assays that are developed; (3) inclusion of these assays in the clinical trials conducted by the NCI-supported clinical trials cooperative groups; (4) support of a few well-designed clinical trials to determine efficacy of therapy, in particular, trials that address fundamental questions; (5) testing and refinement of 3-D conformal therapy; and (6) development of novel staging tools and treatment approaches to optimize the assignment of therapeutic options. Dr. Scardino noted that the PCPRG also considered the role of gene and cellular therapy in prostate cancer.

In the area of ***systemic therapy***, the PCPRG recommended research to: (1) understand the mechanisms of resistance to treatment; (2) understand the role of gene and cellular therapy; (3) identify relevant endpoints for clinical trials; (4) characterize targets for novel therapeutic agents; (5) optimize treatment for androgen-independent disease; and (6) optimize the delivery of novel therapeutic agents. PCPRG's recommendations for ***outcomes research*** were to: (1) support development of validated instruments to assess quality of life and other patient-focused outcomes; (2) support interventions that will enhance health-related quality of life for survivors; (3) evaluate provider characteristics with respect to outcomes; (4) develop standardized measures for outcome; (5) include outcomes measures in existing surveillance activities—such as NCI's Surveillance, Epidemiology, and End Results (SEER) program—and in treatment clinical trials; and (6) include aspects of patient-focused outcomes in early detection and screening trials.
Dr. Scardino explained that the PCPRG had compiled the list of necessary resources from the recommendations in all of the scientific areas that could be addressed by the NCI. Resource needs were identified in the broad areas of education and training of prostate cancer investigators; informatics networks of databases and specimen repositories; patient consent issues to promote enhanced collection and utilization of tissue samples and patient/subject information; preclinical models, both animal and cell line; new technology development and dissemination, including regional centers that provide access to the technologies and Web-based programs to inform the scientific community; and clinical trials, to take advantage of the new scientific information as it becomes available. In summary, Dr. Scardino stated that the current biomedical research presents real opportunities for understanding the genetics, biology, and epidemiology of the disease as well as prevention and the use of experimental therapeutics. The PCPRG believes that the national agenda can best move forward by increasing the scientific

expertise in this area, by understanding the fundamental biology and pathology of the disease, by developing widespread bioinformatics networks, by incorporating new technology, and by improving clinical trial design.

Questions and Answers

Dr. Bishop expressed that progress in developing animal models for prostate cancer will require knowing what appropriate genetic lesions to install, based on the human disease, which adds urgency to the CGAP gene search. Dr. Schein suggested that an infusion of new funding is needed in all areas of prostate cancer research as recommended by the PCPRG to advance prostate cancer management to the level already achieved in breast cancer. He asked whether data presented on p27 found in biopsy material from a small recently detected tumor might provide insights for predicting which tumors will be virulent. Dr. Tindall agreed that studies of basic biological processes have important implications for understanding the disease process. He predicted that understanding the fundamental processes and using the new microdissection technologies will provide an answer to the question of future virulence.

Dr. Alfred Goldson asked whether the PCPRG had considered disease management practices for men under age 50 and suggestions for the best available therapies for that age group. Dr. Scardino noted that decisionmaking for these men relies on an evaluation of the nature of the host, years of exposure, state of health, and age. The problem has been that Phase III screening trials are needed to provide the necessary long-term information on which to base anything more than an expert, informed opinion on a particular case. Dr. Freeman asked about the status of advice regarding the use of prostate-specific antigen (PSA) screening. Dr. Scardino responded that, from the public health perspective, long-term screening data are not available to advocate PSA screening, and from the patient perspective, informed decisionmaking by the individual is needed. Dr. Tindal reminded members that the PCPRG report indicated initially that prostate cancer has received so little funding in the past that any increase would be beneficial. He stated that PCPRG efforts to prioritize questions gives some emphasis to areas that should receive greater support and that the NCAB in its deliberations would be able to consider those priorities. Dr. Klausner reminded members that the PRGs were convened not as consensus panels but as review groups to describe a set of challenges for a research agenda. The breast and prostate cancer reports will form a basis for the NCI and the research community to formulate responses to the challenges.

NCI BREAST CANCER PROGRESS REVIEW GROUP
Dr. Richard Klausner, Dr. Harold Moses, and Dr. Nancy Davidson

Dr. Klausner introduced Co-Chairs Dr. Harold Moses, Director, Vanderbilt Cancer Center, and Dr. Nancy Davidson, Associate Professor of Oncology, The Johns Hopkins Oncology Center, to present the report of the Breast Cancer Progress Review Group (BCPRG). The BCPRG was one of several PRGs established to help the NCI assess the state of knowledge in its large site-specific research programs and identify scientific opportunity and resource needs. Dr. Moses described the BCPRG review process, which

began in May 1997 and consisted of a breast cancer roundtable meeting, with about 250 participants, meetings of the BCPRG, and the NCI Internal Task Force's research portfolio review. The eight major areas of breast cancer research as defined by the BCPRG were biology, early detection/diagnosis/prognosis, etiology, treatment, genetics, cancer control, prevention, and outcomes.

Biology. Dr. Moses stated that the review of NCI's research portfolio showed that most of the funding was supporting initiation and progression studies, with very little funding for the basic biology of the mammary gland. Key questions were related to the genetic and biologic bases of mammary gland development; the genetic/epigenetic bases of pathologic lesions that occur along the continuum of breast cancer development; and the molecular, genetic and cell biology processes involved in metastasis. Recommendations included: (1) support of studies on the basic biology of mammary gland development, differentiation, and regression; (2) support for animal models; (3) mechanisms to support mouse colonies with appropriate training; (4) human tissue and compound repository that is accessible to academics; (5) support for new technologies; (6) increased support for bioinformatics and training related to gene analytic tools; (7) support for a scholar exchange fellowship mechanism with biotechnology and pharmaceutical companies; (8) support for cross-training of individuals, the engagement of engineers in investigations of treatment barriers; (9) joint conferences to educate the academic community about the capabilities of the biotechnology industry; and (10) more effective use of Web sites for technology transfer.

Genetics. Key questions and opportunities were to identify and clone the remaining major predisposing genes, identify somatic mutations and epigenetic alterations due to exogenous factors or chance, identify the rate-limiting genetic changes and their pathways during disease development, characterize genetic and expression profiles for normal breast epithelium and for breast abnormalities, and generate mice with human genes. Recommendations were to: (1) work with private industry to make new technologies available; (2) create a resource for human tissue at different stages of both normal and pathologic development; and (3) support a transgenic mouse resource to maintain and breed mice.

Etiology. Key questions were to identify the types of intermediate markers that would be useful to the advance understanding of mechanisms involved in breast cancer carcinogenesis; the best approaches to understanding gene-environment interactions; factors that influence disease progression; and a useful approach to expand knowledge regarding etiology. The PCPRG recommendations included: (1) better animal model systems to develop serum or tissue biomarkers; (2) networks of clinical investigators with appropriate technical support for biomarker developmental research; (3) interdisciplinary workshops to study gene-environment relationships; (4) projects that develop genotype-phenotype relationships for candidate polymorphisms; (5) a funded initiative to determine the basis for breast cancer protection by early pregnancy; (6) funding of high-risk "idea" grants without the need for substantial preliminary data; and (7) statistical research to analyze large datasets.

Prevention. Key questions and opportunities were to identify the need for: (1) better precancerous models, including animal, xenograft, cell lines, and in vivo human models; (2) delineation of the key surrogate endpoint biomarkers (SEB) for breast cancer development; (3) determination of the degree to which preclinical prevention trials are indicative of outcomes in humans; and (4) an increase in the number of Phase II trials with SEB endpoints to increase new agent development. Recommendations were to: (1) initiate RFAs or other targeted funding for xenograft/transgenic models with application to chemoprevention; (2) address the problem of proprietary rights for the use of transgenic models; (3) establish national laboratories as clearing houses for transgenic mouse models; (4) target funding for prospective biomarker studies; (5) establish a National Prevention Research Working Group; (6) target funding to address the comparability of preclinical models and human prevention outcomes; (7) target funding for methodology transfer and standardization of techniques for tissue sampling and SEB assays; and (8) encourage a legislative ban on insurance discrimination based on disease risk or participation in prevention trials.

Detection/Diagnosis/Prognosis. Key questions related to improving the interpretation of conventional mammograms; identifying imaging characteristics of specific types of benign and malignant breast lesions detected by newer imaging technologies; determining whether tumor-specific biomarkers can be identified and used as contrasting agents; searching for biomarkers that predict the clinical outcome/response of precancerous/cancerous lesions; and understanding how panels of abnormal biomarkers could be used and interpreted. BCPRG recommendations were to: (1) increase support in the field of biomarker development; (2) target funding to the most novel imaging technologies; (3) provide a mechanism for academic institutions to purchase the most advanced technology; (4) fund more translational studies that address the area of biomarkers in premalignant and early breast cancer; (5) create and maintain banks of normal and premalignant breast tissues; (6) consider a SEER-like registry of patients with premalignancy; (7) develop miniaturized high-throughput technology for protein expression in small tissue samples; and (8) establish national guidelines for human tissue banking, which promote scientific progress while protecting patients' rights.

Treatment. Key questions focused on how to develop innovative and biological approaches to treatment in the laboratory and then in pilot clinical trials; how to facilitate large clinical trials with a focus on disease-free survival and ease of delivery to the entire population; how to develop the expertise for modern clinical investigation; and how information about breast cancer biology can be used to predict clinical course and response to therapy. Recommendations were to: (1) encourage legislation to protect corporate interests while fostering cooperative drug development; (2) increase funding for better integration of basic and clinical sciences; (3) establish a study section for clinical investigation; (4) develop trial designs for biologic agents that require new efficacy endpoints; (5) facilitate coordination among cooperative groups, cancer centers, and SPOREs; (6) streamline Office of Protection from Research Risks (OPRR) regulations; (7) support training for a new career track—translational investigator; (8) develop large databases of biological plus appropriate clinical information; and (9) reinstate the Breast Cancer Task Force to steer and fund "small idea grants."

Cancer Control. Key questions were related to finding the mechanisms responsible for basic behavioral change; determining whether psychosocial factors influence traditional disease outcomes; finding ways to facilitate better decisionmaking, especially that based on risks and benefits; and ascertaining whether the delivery of breast cancer care can be improved to maximize desirable outcomes and minimize cost. Recommendations were to: (1) target research funding for the study of basic behavioral mechanisms; (2) create a unit focused on basic behavioral and social research within the Division of Cancer Control and Population Sciences (DCCPS); (3) sponsor a consensus conference on the current state of knowledge about the impact of psychosocial factors on disease initiation and progression; (4) partner with health care organizations having information systems that can integrate and analyze clinical, biological, and psychosocial data; (5) initiate new programs in basic research on decisionmaking under conditions of uncertainty in cancer care; and (6) support the creation of information systems that would encourage health care organizations to participate in cancer control research.

Outcomes. Major questions included: (1) determining the short- and long-term effects of multimodal treatment for breast cancer; (2) discovering how patient-focused outcomes can be studied across the continuum of age; (3) ascertaining what the patient-focused outcomes are for women with *in situ* breast cancer; (4) using the clinical cooperative groups to foster outcomes research beyond the current scope; (5) upgrading existing cancer registries to capture patient-focused outcomes; and (6) convening a working group to identify and make recommendations for systematic inclusion in trials of the key patient-focused variables.

Dr. Davidson summarized what the BCPRG considered to be the overarching issues in the advancement of breast cancer research. These issues included: (1) enhanced understanding of normal breast biology and genetics; (2) better model systems for premalignant and malignant breast disease; (3) fuller understanding of molecular changes through the continuum of breast cancer progression; (4) identification of biomarkers and surrogate endpoints for epidemiologic, prevention, and therapy trials; (5) investigator access to necessary technology; (6) enhanced infrastructure at academic health centers; (7) modifications of existing mechanisms to promote translational, prevention, and therapy trials; (8) improved communications efforts that incorporate patient-focused outcomes; (9) research in basic behavioral change, decisionmaking, and communication; (10) recruitment, training, and retention of translational investigators; (11) enhanced communications among investigators in various disciplines; (12) reassessment of funding strategies to target innovation and accommodate longitudinal studies; and (13) streamlined consent process for clinical research.

Questions and Answers

Dr. Kay Dickersin asked if the BCPRG considered recommending research on mechanisms for training doctors to practice evidence-based treatment for patients. Dr. Davidson replied that such education would fall under the broader rubric of communication and education and would include both the physician and health

practitioner. Dr. Bishop asked Col. Louis Diehl if the BCPRG report resonates with the breast cancer initiatives being funded by the Department of Defense (DoD). Col. Diehl answered that much of the DoD funding for research might be equated with the Bypass Budget. Dr. Moses expressed that the DoD breast cancer program has been working successfully to complement, not duplicate, the work of the NCI, based on his observations as a member of the original DoD integration panel and on major input to the NCI review from Col. Irene Rich, DoD, who was a member of the BCPRG.
Dr. Sharp noted that neither PRG report specifically addressed access to breast cancer therapies through health maintenance organization (HMO) prepaid health plans, which control much of the access to health care. Dr. Klausner indicated that the BCPRG recommendation for new informatics systems would deal with health care delivery systems for outcomes, prevention, and behavioral research. Dr. Robert Hiatt, Deputy Director, DCCPS, provided information on three initiatives that are addressing outcomes issues: (1) an Outcomes Research Branch has been established in the DCCPS; (2) a network of approximately eight HMOs is being funded to address outcomes questions among others; and (3) the Surveillance Implementation Group (SIG) is investigating ways to capture performance measures—process, structural, and outcomes—in surveillance research activities.

Dr. Li asked about the process for coordinating the use of NIH and DoD funding for breast and prostate cancer research. Dr. Klausner explained that one barrier to avoiding duplication of effort has been the need for a mechanism to display, analyze, and organize the projects being funded. A coding system was subsequently developed that organizes all funding mechanisms—intramural, extramural, contracts, grants—according to these scientific questions. Dr. Klausner noted that the Scientific Information System used to code NCI projects will be made available on the Web and the software and informatics will be shared with the DoD and other funding agencies.

NCI Response to PRG Reports. Dr. Klausner stated that the reports of the PCPRG and BCPRG would be useful instruments for the NCI and other agencies funding research in these areas. He briefly outlined how the NCI would respond to the recommendations. He reminded the Board that the BCPRG and PCPRG were pilot projects for testing a planning process that involved seeking crosscutting scientific and infrastructural issues across diseases, mapping the needs for specific diseases as identified by the research community to resource infrastructures already in place, and identifying elements the NCI needs to establish to answer questions as articulated and prioritized by the PRGs. The next steps for the NCI will be to analyze the recommendations and report the results of this initial analysis to the PRGs. Dr. Klausner suggested that one challenge will be to ensure that the knowledge maps, which were indicated as basic needs by a consensus of these research communities, are completed in the environment of investigator-initiated research filtered through peer review. Dr. Klausner stated that one final issue to address is whether PRGs should be created for other disease sites. He challenged members of the NCAB to be prepared at the next meeting to assist in articulating the intersection between planning based on a general infrastructure for science that cuts across cancer and planning integrated to the needs of specific diseases.

SCIENTISTS AS ADVOCATES
Dr. J. Michael Bishop

Dr. Bishop reminded the Board of his earlier suggestion for short talks by individual members about their interests, scientific or otherwise, for solidifying working relationships among members. Having been drafted to give the first talk, he announced that his talk would focus on his first experience at public advocacy. Dr. Bishop described how in his private capacity, he and his colleagues were instrumental in forming the Joint Steering Committee for Public Policy, a coalition of four basic biomedical research societies. The purpose of the Joint Steering Committee is to assess government policy related to the conduct of research and to ensure that funding is provided in scientifically effective ways. With guidance from a hired lobbyist and former member of Congress, the group crafted four major initiatives: (1) catalyze personal visits of scientists to Capitol Hill and local centers of government; (2) create a rapid response constituency; (3) form a Congressional Caucus on Biomedical Research; and (4) organize extensively in the field. Dr. Bishop recounted this group's success in implementing these basic biomedical research initiatives. Within the first year, 85 scientists had visited members of Congress, and hundreds have since gone to Capitol Hill for information dissemination purposes through the auspices of this group. The rapid response constituency now numbers almost 5,000 scientists, about 30 percent of whom write an original letter on a particular cause. Four members of the House of Representatives were identified who were willing to organize a Congressional Biomedical Research Caucus to respond to this interest. Since its initiation, the Caucus has held 76 luncheon meetings featuring speakers on a variety of diseases and biomedical research issues. Work has begun on the fourth initiative: groups of scientists from Pennsylvania and North Carolina have been organized to visit members of Congress and write letters, and field organization will begin soon in California. Dr. Bishop counseled the Board that this private, personal activity was not meant to imply that any course of action should be taken by the NCAB as an advisory body.

CHERNOBYL UPDATE
Dr. Alan Rabson, Dr. Faye Austin, Dr. Bruce Wachholz, Dr. Gregory R. Howe, and Dr. Richard J. Jackson

Dr. Alan Rabson, Deputy Director, NCI, and Dr. Faye Austin, Director, Division of Cancer Biology (DCB), introduced Dr. Bruce Wachholz, Chief, Radiation Effects Branch, DCB, and Dr. Geoffrey Howe, Professor and Head, Division of Epidemiology, School of Public Health, Columbia University, to present an update of radiation studies being conducted in collaboration with the governments of Belarus and the Ukraine. As an aftermath of the nuclear accident in reactor number 4 at Chernobyl, North Central Ukraine, on April 26, 1986, fallout of I-131 heavily contaminated the area surrounding the accident in Ukraine and a large area of neighboring Belarus, which received about 70 percent of the fallout. Dr. Wachholz briefly outlined the events leading to NCI's involvement in the studies. A formal agreement was signed in 1988 by the United States and then-U.S.S.R. for cooperation in the area of civilian nuclear reactor safety. As signatory for the United States, the Nuclear Regulatory Commission (NRC) undertook a

number of activities, including environmental and health activities. Assistance from the Department of Energy (DOE) was enlisted because of its decades-long involvement in radiation studies, and several areas of possible research were recommended by teams of U.S. scientists established by the DOE to address those issues in the contaminated areas. Subsequently, the NCI was invited by the DOE to develop protocols for long-term followup studies of thyroid cancer in children and a study of leukemia among cleanup workers (the "liquidators") to be funded jointly by the NCI, DOE, and NRC.

Background and Organization. Dr. Wachholz announced that he would address only the thyroid studies, and he reviewed data showing an increased incidence in thyroid cancer diagnosed in exposed children in Belarus and Ukraine who were *in utero* to age 18 at the time of the accident, as well as a comparison of incidence rates in the two countries. Objectives are to measure dose- and time-related morphologic and functional changes in children exposed to radioactive materials released from Chernobyl; provide risk estimates for cancer and nodules as a function of dose in relation both to sex and age at the time of the accident; and compare the relative effectiveness of I-131 with that of x-ray and gamma irradiation with respect to radiation-induced thyroid cancer. The study consists of two cohorts (15,000 in Ukraine and 30,000 in Belarus) comprised of residents who were less than 19 years old at the time of the accident and had measurements of radioactivity in their thyroids within about 2 months of the accident. Dr. Wachholz noted that this situation in which large numbers of children exposed at varying ages and with a wide range of radiation doses to the thyroid presents a tragic opportunity to determine the risk coefficient for thyroid cancer from I-131. He discussed the status of the thyroid studies, noting that with all three countries—Belarus, Ukraine, and the U.S.A.—scientific review of the research protocols is complete, IRB approvals have been obtained, and international (U.S.A. - Belarus and U.S. - Ukraine) protocols have been signed between the U.S. and each country. The infrastructure (e.g., organization, equipment, supplies, personnel) has been established in both Belarus and Ukraine and the projects are operational.

Status of Chernobyl Studies. Dr. Howe announced that he would discuss the role to be played by Columbia University, the status of the studies, and how these studies will fit, numerically and scientifically, into the knowledge base for the radiation, epidemiology, and etiology of thyroid cancer. He noted that Columbia University is providing scientific and some administrative support to the studies. Scientific disciplines provided by Columbia range from data management and epidemiology to endocrinology and dosimetry of various types. Turning to the studies themselves, Dr. Wachholz explained how the screening has been implemented. In Belarus, 15,000 children were originally identified from the 1986 dose file. By linking records of these children to the Chernobyl State Registry and passport and medical records, about one-half that number were identified and traced. More than one-half of those with identified current addresses were identified were invited to participate in the screening, and this group will be screened every 2 years. They will be followed through time as they age, and the incidence of thyroid cancer and other thyroid diseases will be measured. Similarly, the Ukraine cohort is being assembled from the 80,000 Ukrainian children on the 1986 dose file. A random sample of 20,000 has been selected for the first effort, and the process of identifying

current addresses, sending invitations, confirming contacts, and screening is ongoing. Dr. Howe noted that the questionnaire completed at the time of screening is geared towards reconstructing the doses and the epidemiologic variables that might interact or confound the association. A detailed pathological review is planned that will involve U.S., U.K., Belarusian, and Ukrainian pathologists to confirm the validity of the high doses that were reported.

Next, Dr. Howe discussed the role that the Chernobyl studies would play in the knowledge of I-131-induced thyroid cancer. He cited the detailed results available in studies of x-ray and gamma ray exposure based primarily on treatment and diagnostic procedures and the combined analysis of these data. A critical question to be answered is whether RG-131 has the same effect per unit of dose as gamma and external x-rays. One prediction of the possible outcome of the studies was made by Dr. Roy Shaw who estimated that the power of the studies in Belarus and Ukraine to identify a statistically significant increase in risk after 15 years of followup will be substantial if the effect of RG-131 is either the same as gamma or x-rays or as much as a one-third to one-sixth. He concluded that although 15 or 30 years of followup is the real goal, some results can be achieved that will substantially increase the body of knowledge surrounding RG-131-induced thyroid cancer.

NCI/CDC Collaboration on Radiation Studies. Dr. Klausner cited the current public and congressional interest in NCI's responsibilities for studies that relate to accidental public exposure to radiation, in particular the studies associated with the Nevada Test Sites. He stated that the NCI assignment to the Chernobyl studies specified that a method be developed for assessing risk for thyroid cancer associated with exposure to I-131. When news of the Chernobyl studies was released, public concerns became manifest regarding public oversight and communication about radiation studies. An ongoing working relationship with the CDC was formalized through a memo of understanding under which the NCI would share information on all of its human radiation exposure studies and present the information to the CDC oversight board. The agreement also will make it possible to develop new collaborations and interactions. Dr. Klausner introduced Dr. Richard J. Jackson, Director, National Center for Environmental Health, CDC, to present an update on CDC's Health Radiation Program. Dr. Jackson explained that CDC's traditional role has been to work with state health departments and other federal agencies to translate the scientific breakthroughs into applications at the local and community level. With the disclosure of radiation information associated with weapons production sites around the United States, community distrust grew and, in 1990, the Secretary of Energy signed an agreement committing the DHHS to conduct epidemiologic studies and community relations activities in the vicinities of DOE nuclear weapons complexes. The Advisory Committee on Energy Related Epidemiologic Research (ACERER) was established to advise the Secretary, DHHS, regarding the risk, dose reconstruction, and epidemiologic activities that are being implemented with extensive community involvement. Dr. Jackson emphasized the enormity of the community relations effort required to restore the confidence in government and the importance of ensuring that the various federal agencies involved in this task act cohesively and transparently. As a result of the letter of agreement between the NCI and NCEH, a joint working group has been

established. Current collaborations include a joint review to compare current and proposed thyroid studies and a project to update "probability of causation" tables for radiation-induced cancers.

Dr. Jackson concluded by relating another valuable initiative that has begun as a result of the U.S. involvement in the Chernobyl studies. The high incidence of thyroid cancer in the radiation-exposed children suggested an iodine deficiency in addition to the exposure. A binational meeting was organized with help from the World Health Organization and U.S. FDA to discuss strategies for eliminating micronutrient malnutrition. Teams from Belarus and Ukraine have begun to visit U.S. production facilities to learn how processed foods are being enriched.

Questions and Answers

Dr. Schein noted that these presentations raise a question as to whether the government realizes the full extent of the potential environmental risk that exists around the country at these nuclear reactor weapon site storage facilities as well as the daily threat of terrorism. The risks that are being faced include, not only thyroid cancers, but also for leukemias and acute bone marrow and gastrointestinal toxicities.

LESISLATIVE UPDATE
Ms. Dorothy Foellmer

Ms. Dorothy Foellmer, Director, Office of Legislation and Congressional Activities (OCLA), directed NCAB members to the meeting books or the NCI Web site for a complete update of congressional briefings, visits, and hearings, the status reports on pending legislation of interest to the cancer community, and the legislative scorecard. She highlighted a few of the briefings, hearing, and visits to show the range of topics that were addressed. For example, briefings and/or hearings were held on NIH support for Complementary and Alternative Medicine (CAM) cancer therapies; NCI studies on radiation, including the NCI Fallout and Chernobyl Studies; the development of cervical cancer vaccines; and new advances in cancer treatment research. Ms. Foellmer summarized areas of special emphasis for the House and Senate in terms of requests for new initiatives, increased funding, reports, and briefings. She concluded with an overview of the Patients' Bill of Rights Act of 1998, which is a bill of particular interest to the public.

Questions and Answers

Dr. Dickersin alluded to the growing public interest in CAM therapies and the absence of any consideration for this area of research in the breast and prostate cancer reports. She asked about NCI's plans for research in this area. Dr. Rabson responded that the NCI will be involved in clinical trials to evaluate CAM therapies for cancer. He noted that Dr. Jeffrey White has been appointed to work out of the ODDES, NCI, to integrate and oversee NCI's processes and collaboration with the Office of Alternative Medicine (OAM), NIH. Dr. Klausner explained that Congress has provided a dollar amount for

CAM funding to the OAM, but the actual funding is carried out in appropriate Institutes after review of proposals by the OAM Advisory Committee. In extensive negotiations, the NCI Cancer Advisory Panel (CAP) for CAM research was created to interact with the advisory committee. He stated that the NCI will report to the NCAB on NCI plans related to CAM research and to NCI's interactions with the CAM community.

NEW TRAINING INITIATIVES
Dr. Robert Wittes, Dr. Brian Kimes

Dr. Robert Wittes reported that various scientific groups had emphasized the importance of training future scientists, and that they recommended it be a high priority for the NCI, in terms of reevaluating the current training effort and making it both more flexible and more suitable to the present scientific and biomedical environments. In response to these recommendations, the NCI has developed a strategic plan for training. Dr. Wittes introduced Dr. Brian Kimes, Associate Director, Cancer Centers, Training and Resources Program (CCTRP) ODDES, to present this strategic plan for the Board members' comments and consideration.

Dr. Kimes described the NCI's Strategic Plan for Research Training and Career Development, which was approved by the Board of Scientific Advisors (BSA) on June 22, 1998. Major goals and objectives of the strategic plan include: (1) constructive responses to recommendations of the NCI review groups and the needs of NCI extramural divisions—NCI's division leaders reviewed these recommendations and developed a total plan for the NCI; (2) the stabilization of endangered disciplines (M.D.s and population scientists); (3) addressing future needs for more multidisciplinary, team science, and translational research approaches; (4) providing flexibility needed to attract new scientific disciplines into cancer research; and (5) engaging underserved populations more effectively—the movement of the Comprehensive Minority Biomedical Program (CMBP) into the CCTRP has been an important step toward realizing this goal.
Dr. Kimes next reviewed five operating principles that are critical to the strategic plan: (1) utilize competitive, investigator-initiated awards that use PAs instead of RFA-driven awards, which will provide more flexibility than the current RFA award system—in terms of dollars, application cycles, and provisions for revised applications; (2) ensure equal opportunity of different disciplines through effective management of the peer-review process; (3) phase-in new activities based on priorities and the availability of adequate resources to sustain them; (4) provide an uninterrupted continuum of training, career development, and career stabilization opportunities where needed by providing a spectrum of career awards; and (5) improve communication of training opportunities to scientists.

Dr. Kimes then described the strategic plan's career tracks, which refer to the progression of scientists from a mentored state (where they are still being developed and trained) to junior faculty state (where they are developing their independent research programs) to an established scientist state (where they are clearly R01-supported scientists).

- Basic science research track—primarily for the Ph.D. scientist. Funded through the National Research Service Awards (NRSA), the basic sciences track provides more flexibility for the scientist by extending the 3-year postdoctoral limit to 5 years. After that, the Howard Temin Award (K01) is a "bridging" award that begins in the mentored state and provides salary stability for the scientist from the postdoctoral level and "protected time" during the first few years as junior faculty to develop a successful research program. A 25 percent budget increase is being projected for FY99.

- Basic science research track for M.D.s. This track includes a planned mentored postdoctoral career development award with the addition of a specific transition award (K08), which allows individuals the opportunity to apply for a 3-year award while they are at the postdoctoral level. This will provide salary stability for the M.D. scientists while they are developing their basic science research programs. The K08 will not be in place until the year 2000.

- Clinical science research track for M.D.s. This track is a high priority for the NCI. The institutional clinical oncology mentored career development award (K12) and the individual mentored clinical scientists award (K23) provide an initial career opportunity for the clinical scientist, to be followed by a 3-year transition award (K22), which will ensure salary stability for the clinical scientist who is developing an independent research program. The established investigator award (K24) provides protected time for the clinician who is conducting research-related activities. The clinical infrastructure award (K30) is a trans-NIH core support program that offers the clinician more stability in terms of protected time and salary to devote to training activities.

- Prevention/control/behavioral population science track. This career track, which is similar to the clinical sciences track, is based on a mechanism that was established 10 years ago by Dr. Peter Greenwald. The cancer education and training award (R25) is flexible and offers a salary structure that will provide career stability to the population scientist. In addition, an individual career award (K07) and the established investigator award (K05) are being developed.

- The underserved minority research track. The Continuing Umbrella of Research Experience for Underserved Minorities (CURE) Program is a new plan that focuses on the underserved/minority populations from the high school and undergraduate school levels to the established scientist. Supplements to three awards—cancer center support grants (P30), clinical oncology institutional career development programs (K12), and population sciences grants (R25)—along with individual bridging and transition awards (K01) will help to increase the number of underserved scientists in the basic, clinical, and population science fields.

Dr. Kimes stated that, if this plan can be implemented fully, for FY99 through FY03, an estimated budget increase of $120M will be needed for all areas of training and career development—career awards would increase by 400 percent during this 5-year period

because they are fundamental to the strategic plan. The proposed $120M increase is one potential barrier to the immediate implementation of the strategic plan. Another barrier is the fundamental policy changes that must be approved by the NIH, including: (1) establishment of new transition awards; (2) applications without institutional affiliations; and (3) elimination of the salary penalty when a career award recipient also seeks salary support from an R01.
Dr. Kimes concluded his presentation by emphasizing the importance of training. He stated that training is research; one cannot be separated from the other. Trainees are in fact doing most of the research. Training opportunities must be linked to research opportunities. Trainees must have a research environment in which to receive training.

Questions and Answers

Dr. Vainutis Vaitkevicius commended Dr. Kimes and commented that this was the most exciting report he has heard in many years. Dr. Sandra Millon-Underwood cautioned against developing marketing strategies solely around a Web site because many of the minority students may not have access to it. She asked whether the training opportunities would be linked only to comprehensive cancer centers. Dr. Kimes replied there are no current plans to work with other centers until the program appears to be working. Dr. Ivor Royston applauded the NCI's efforts regarding the training issues and stated that a potential barrier to the program might be the 8 percent indirect cost recovery limit on K series awards. Dr. Kimes responded that the issue of indirect costs is a trans-NIH policy.

CANCER INFORMATION SERVICE RESPONSE TO OFFICE OF THE INSPECTOR GENERAL REPORT

Ms. Susan Hubbard, Dr. Robert Wittes

Ms. Susan Hubbard, Director, Office of Cancer Information, Communication and Education, (OCICE), NCI, reported on the Cancer Information Service (CIS) implementation plan that was drafted as a result of the recommendations made by the Office of the Inspector General (OIG) after conducting a study on the CIS in response to concerns about the frequency of busy signals on the 800 number.

- The CIS telephone technology will be upgraded in the next several months and will: improve a caller's access to the 800 number; enable the CIS to expedite more calls; provide the caller with access to voice mail and automated standard responses for questions about general topics; strengthen networking among CIS branch offices; and improve management reporting. In addition, a CIS Web page will be available on the Internet and will provide general information.

- Minimum technical requirements and performance standards for the CIS, in terms of busy rates and abandonment calls, were established. In May 1998, CIS busy rates were 30 percent; through active intervention, the number decreased to 6 percent in August 1998. This is a significant drop that is close to the NCI's goal of a 5 percent or less busy rate.

- Implementation teams are redesigning the Physician's Data Query (PDQ) system to increase its functionality and navigability, integrate all NCI information, and tailor information to meet diverse user needs.

- Data collection and reference materials will be computerized. The CIS is streamlining all current documentation procedures to reduce the time required by the telephone specialist after the completion of the call. NCI resource materials can be accessed through the CIS Web site, which became available in July 1998. In addition, a CIS Intranet is being constructed where all training materials can be accessed.

- The collection and dissemination of community service information was discontinued. A new and more effective system will partner the CIS with other organizations to develop and maintain high-quality information materials that will be available on both the CIS and the NCI Web sites.

- The regional structure will be reconfigured to reduce the number of regions. The proposed regions will be reviewed by the NCI, and public comment will be solicited before the recompetition begins.

- Career development will be supported, and core CIS training will be enhanced by the introduction of Web-based instructional training programs that can be accessed on the CIS Intranet.

Questions and Answers

Dr. Klausner commented that he has been working with Ms. Hubbard and Ms. Chris Thomsen to implement these recommendations. He emphasized that the central component is providing satisfactory service to a caller. It is crucial to respond to callers in a timely manner and to provide valuable and helpful information. Dr. Sharp asked about the quality aspects of the available information and the satisfaction level of the callers. In addition, he questioned the need for obtaining demographic data from callers. Ms. Hubbard responded that quality was not an issue in the OIG report and, in fact, the report noted that the CIS training and quality assurance programs were model programs. The OIG's concern concentrated on the frequency of busy signals and the CIS methods of data collection about community services. In terms of the demographic data, Ms. Hubbard stated that the focus on data gathering in the future will be to provide information for quality control and specific projects. Data collection is important but it will not be conducted at the expense of the service that the CIS provides. Ms. Stovall commended Ms. Hubbard on her efforts and mentioned that CIS staff often are faced with doing casework on the telephone when that is not their job.

SUBCOMMITTEE REPORTS AND NEW BUSINESS: SESSION II
Dr. Philip Sharp, Ms. Ellen Stovall

Subcommittee Reports. Dr. Sharp reported that at the Cancer Centers Subcommittee meeting, held the previous day, most of the recommended changes to the Cancer Center Support Grant (CCSG) guidelines were unanimously agreed on by the committee. The comprehensiveness redefinition issue will be reviewed, and recommendations will be forthcoming. He stated that another issue is how to use core facilities to effect more change in research and for defining more flexibility. There is still work to be done before an ideal set of guidelines is developed.

New Business. Ms. Stovall, Executive Director of the National Coalition for Cancer Survivorship (NCCS), provided information to be the Board on the March, to be held September 25-26, 1998. She stated that it is a public education campaign that primarily will leverage attention to the need for more funding for all biomedical research—specifically cancer research—and for access to quality cancer care for all Americans. It is the first massive demonstration about cancer that will involve groups inside and outside of the cancer community. Almost every national cancer organization and more than 500 national organizations unrelated to the cancer community have endorsed the March, and nearly every professional society actively will participate in it. The March officially begins on Friday, September 25, 1998, when the Senate Cancer Coalition will hold hearings on the March Research Task Force reports and its recommendations. The March will continue with candlelight vigils on the Mall in Washington, DC, and in all 50 states—the NCCS will continue to hold candlelight vigils every year until there is a cure for cancer. On Saturday, there will be health and educational displays on the Mall, a public forum to be presented by the American Association for Cancer Research (AACR), and a rally featuring national speakers and celebrities. Ms. Stovall reemphasized that the focus of the March is to bring greater public attention to the issue of cancer and to make it a research health care priority in the United States.

INFORMED CONSENT REVISION INITIATIVE
Dr. Robert Wittes

Dr. Wittes stated that one barrier to more rapid national clinical research is the fractionated nature of the informed consent process. He introduced Ms. Mary McCabe, Director, Office of Clinical Research Promotion, ODDES, who presented an overview of the informed consent initiative. Ms. McCabe stated that the initiative was initiated as a result of concerns of NCI staff and extramural investigators that informed consent documents were becoming too lengthy, very complex, and difficult to understand by the prospective cancer clinical trial participant. The NCI formed a working group to review these documents and make recommendations that would assist clinical investigators when developing the consent documents and help the Institutional Review Board (IRB) members when reviewing them. The working group was divided into two subgroups: the Recommendations Subgroup, which was formed to develop both recommendations and a template that could be used by investigators as an outline when developing their own consent documents; and the Model Document Subgroup, which used the recommendations and the template to rewrite sample consent documents.

Using slides, Ms. McCabe listed the major recommendations that were made by the working group for consent documents: (1) inform the patients which medical tests will be part of standard care rather than a part of the clinical trial; (2) describe the potential benefits of the clinical trial and distinguish between potential benefits for the individual and for future patients; (3) present risks for the entire research regimen rather than listing them by drug or by procedure; (4) categorize and describe risks to help patients determine the importance of the side effects; (5) only include information required by the *Federal Guidelines for Essential Elements*; (6) include certain information in supplemental material rather than in the consent document; and (7) information about legal protection for the investigators conducting the research should not be included. In addition, other recommendations included readability, the need for cultural sensitivity, notification of new information, and communication techniques.

Ms. McCabe stated that the recommendations and the template were presented to various focus groups for their feedback and suggestions; the focus groups overwhelmingly concluded that the recommendations and the template presented an understandable informed consent document. At this time, an implementation process is being developed that will disseminate the information. The template will be available on the NCI cancer trials Web site at http://cancertrials.nci.nih.gov for investigators who are developing informed consent forms. Following the implementation process, an evaluation process will be developed to determine if these recommendations and template are being used and, if so, if they have positively affected the prospective patient.

Questions and Answers

Dr. Bishop noted that assuring compliance is a critical issue. Dr. Richard Boxer asked if the new informed consent document will help to acquire more prospective patients for clinical trials. Ms. McCabe responded that the primary purpose of the initiative is to increase the patients' understanding of the clinical trial and not to increase accrual; however, if the patients understand what is involved in the research, more might be willing to participate.

STREAMLINED REVIEW OF AMENDED P01s
Dr. Marvin Kalt

Dr. Marvin Kalt, Director, Division of Extramural Activities (DEA), stated that the program project review needs to be a less labor-intensive effort for applicants, reviewers, and staff—while still maintaining quality assurance—and the amended application process is one element of the program that would be appropriate for a streamlined effort. The payline for FY98 is 135, meaning that some very competitive program projects scoring in the outstanding range cannot be funded. Dr. Kalt proposed that when an application is considered outstanding by peer review and it is within the 15-20 point range—but it is not within the payline—the applicant will be given the option of submitting an amended application that responds to the criticisms contained in the

original statement; this response would constitute a full amendment. An accelerated peer re-review (APR) would be conducted by the same initial review group that reviewed the original application, and this submission would be considered as one of two amendments allowed by the NIH. The amendment would receive a new priority score, and the applicant would be apprised of the result within 4 months of submission, instead of the 8 month normal cycle. Currently, there are about 110 to 120 P01 applications per year; of the total number of applications, about 15 (5 per cycle) would fall into this range of eligibility.

Dr. Kalt asked for and received the Board members' approval to implement this process by publishing a notice in *The NIH Guide*.

Questions and Answers

Dr. Royston asked if exception funding for the 15-20 point range beyond the payline will be eliminated. Dr. Kalt responded that it would not. Some applications clearly have approached the best score that they can receive and can only be funded as exceptions, but other applications with some minor changes would easily improve in priority score. There is no guarantee, however, that any amended application will receive a higher priority score in peer review, so exceptions always will constitute an option in the decisionmaking process.

FUTURE AGENDA ITEMS AND ADJOURNMENT
Dr. J. Michael Bishop

No immediate items of new business for consideration at the NCAB meeting to be held in December 1998 were suggested by the Board. The 107th meeting of the National Cancer Advisory Board was adjourned at 11:38 a.m. on Friday, September 11, 1998.