



FUNDING OPPORTUNITIES

ADVISORY HOME

NATIONAL CANCER ADVISORY BOARD

convened on December 3-4, 1997, at the:
National Institutes of Health
9000 Rockville Pike
Conference Room 10, C Wing, Building 31
Bethesda, Maryland 20892

ATTENDEES

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Dr. J. Michael Bishop

The National Cancer Advisory Board (NCAB) convened for its 104th regular meeting at 8:30 a.m., December 3-4, 1997, in Building 31, C Wing, 6th Floor, Conference Room 10, National Institutes of Health.

NCAB MEMBERS

Dr. J. Michael Bishop (Chairperson)
Dr. Richard J. Boxer
Mrs. Zora K. Brown (absent)
Dr. Pelayo Correa
Dr. Robert W. Day
Dr. Kay Dickersin
Mrs. Barbara P. Gimbel (absent)
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

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

Members, Executive Committee, National Cancer Institute, NIH

Dr. Richard Klausner, Director, National Cancer Institute
Dr. Alan Rabson, Deputy Director, National Cancer Institute
Mr. Philip D. Amoruso, Associate Director for Extramural Administrative Management
Ms. MaryAnn Guerra, Associate Director for Intramural Administrative Management
Dr. Faye Austin, Director, Division of Cancer Biology; Chairperson, Extramural Advisory Board
Dr. Joseph Fraumeni, Director, Division of Cancer Epidemiology and Genetics
Dr. Peter Greenwald, Acting Director, Division of Cancer Prevention
Dr. Marvin Kalt, Director, Division of Extramural Activities
Dr. Edison Liu, Director, Division of Clinical Sciences
Dr. Robert Wittes, Director, Division of Cancer Treatment and Diagnosis

Dr. Barbara Rimer, Director, Division of Cancer Control and Population 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

Ms. Kerrie Wilson, American Cancer Society
Dr. Stanley Zinberg, American College of Obstetricians and Gynecologists
Dr. Bernard Levin, American Gastroenterological Association
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
Dr. Edwin Mirand, Association of American Cancer Institutes
Dr. Robert Frelick, Association of Community Cancer Centers
Ms. Laura Lieberman, Candlelighters Childhood Cancer Foundation
Dr. Lovell Jones, Intercultural Cancer Council
Ms. Jean Ard, Leukemia Society of America
Ms. Dorothy Lamont, National Cancer Institute of Canada
Dr. Margaret Foti, National Coalition for Cancer Research
Dr. Tracey Walton, National Medical Association
Dr. Eve Barak, National Science Foundation
Ms. Pamela Haylock, Oncology Nursing Society

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

Dr. J. Michael Bishop



Dr. Michael Bishop called to order the 104th meeting of the National Cancer Advisory Board (NCAB) and introduced guests representing cancer education and research associations as well as 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 September 1997 meeting. They were approved by the Board unanimously. Dr. Bishop reminded members that this fourth meeting of the year focuses primarily on the NCI program review.

FUTURE BOARD MEETING DATES

Dr. J. Michael Bishop



Dr. Bishop called Board members' attention to the meeting dates listed in the agenda. They have been confirmed through 1999.

REPORT OF THE DIRECTOR, NATIONAL CANCER INSTITUTE

Dr. Richard Klausner



Dr. Richard Klausner welcomed Dr. Bishop as interim Chair of the NCAB. He noted that the presentations included in the NCI program review were directed at eliciting NCAB comments and discussion of issues of importance for the NCI and National Cancer Program. As background and to give an idea of the productivity of the research enterprise in cancer supported by the NCI and many other many agencies, Dr. Klausner briefly discussed discoveries in basic, clinical, and population science as published in recent journals and suggested their possible significance for cancer research.

Dr. Klausner next reported on the FY98 NIH and NCI budgets and progress in formulating the NCI distribution plan. The NIH budget increased by 7.1 percent in FY98, and NCI received a 6.97 percent increase, which translates to about \$160M in new dollars. Although the NCI distribution plan is still in progress, some early figures are available. About \$86M of the \$160M in new funding is targeted for the research project grant (RPG) pool to maintain NCI commitments to pay the majority of approved Request for Application (RFA) responses that are expected, and to fund exceptions and grants receiving accelerated executive review (AER). The R01 payline will be the 24th percentile, and the AER paylines will be the 34th and 29th percentiles for patient oriented and non-patient-oriented research, respectively. An increase of about 4 percent to the intramural program will provide needed funds for recruitment and a number of new initiatives. However, the intramural budget decreases as a percentage of the total NCI budget for the third consecutive year. About \$9M of the new dollars will be allocated to commitments prescribed by Congress or the Department of Health and Human Services (DHHS) such as NIH program evaluation. The remaining portion of the new dollars, estimated at between \$80M and \$100M, plus dollars redirected from other programs is being distributed to the extramural divisions through the as-yet incomplete distribution plan. In the first draft of the distribution plan, a Director's reserve of about \$20M is set aside to address uncertainties encountered in predicting exact budget needs. These are based on the numbers of grant applications that will be received, the average costs of those grants, peer-review- recommended levels, and funding plans recommended through peer review for programs such as clinical trials and the cancer centers. More precise allocations will be reported at later meetings. Dollars are

distributed to the divisions according to division directors' prioritization of new initiatives, which evolves from multiple processes involving the NCI advisory boards, working groups, and Executive Committee (EC).

Review of the *Ad Hoc* Working Group of the NCAB on the Intramural Research Program of the NCI (the Bishop-Calabresi Report). Dr. Klausner reminded members that a final NCAB review of the NCI response to recommendations is still pending and is planned for the February meeting. He directed members to a review of the documentation included in the meeting notebook listing the recommendations of the *Ad Hoc* Working Group and activities already completed by the NCI in implementing this review process. Dr. Klausner noted that the NCI, in this material, has responded to recommendations about strategic planning, oversight, obtaining advice from the extra- and intramural communities, scientific structural changes, budget accountability, and creating a clear and functioning review process. He asked the Board also to attempt to discern changes in ethos within the intramural program, over and above the tangible actions, as a measure of the successful implementation of the report.

Priorities of the NCI Extramural Research Program. Dr. Klausner listed priorities of the extramural divisions that will be addressed in the NCI budget distribution plan. The Division of Cancer Prevention (DCP) published an RFA in October 1997 to develop an approach to intermediate-sized clinical trials to complement the Phase I/II and larger Phase III trials already in operation. Other DCP priority areas are: (1) assuring adequate minority and ethnic representation on the large prostate, lung, colon, and ovarian cancer (PLCO) trial and (2) evaluating the use of the new and developing generations of selective estrogen receptor modulators as chemopreventive agents. For DCP and the Division of Cancer Control and Population Science (DCCPS), a new set of priorities involves the development and expansion of survivorship initiatives. Four areas of emphasis in the DCCPS, which will require new funding, include establishing a basic behavioral research program, establishing a Cancer Genetics Network and informatics base, expanding efforts in cancer control in children, and expanding cancer surveillance activities. Priorities for the Division of Cancer Treatment and Diagnosis (DCTD) include funding for cancer drug development, new chemistry biology centers, the new Rapid Access to Interventional Development (RAID) program, clinical trials reconfiguration, and cooperative, multiinstitutional trials in diagnostic imaging related to cancer. For the Division of Cancer Biology (DCB), funding will be available to explore ways to enhance collaborative research approaches such as support of workshops specifically focused on developing research collaborations and limited focus administrative supplements. Another DCB priority is the expansion of developmental diagnostics approaches and the Cancer Genome Anatomy Project (CGAP), specifically, to generate a resource of arrayed bacterial artificial chromosomes (BAC) for fluorescent *in situ* hybridization (FISH) mapping of human genes. Funding vehicles to support this extramural research vary according to the project but will include RFAs, investigator- initiated R01s and P01s, supplements for cooperative groups or registries and contracts. For some of the initiatives, more than one type of mechanism will be used. In addition, some initiatives that are linked to the working groups associated with the Bypass Budget continue to be funded out of the Office of the Director (OD). A summary of the new initiatives and their funding mechanisms will be provided to NCAB members.

CGAP Update. Dr. Klausner reported that the CGAP Web site is up and already receiving about 5,000 hits a day. Of the 840,000 human express sequence tags (ESTs) in the database, about 100,000 were from CGAP as of November 1, 1997, and that number increases by 10,000 per week. The largest number of human EST libraries currently in the public database were discovered by Merck through the Washington University Genome Center. But that 5-year commitment has ended, and the majority of new gene libraries were discovered through the CGAP project. Participation in CGAP by other Institutes that have found the infrastructure attractive holds the promise for even more rapid discovery. Dr. Klausner demonstrated use of the library browser page and explained how CGAP data can be used for research purposes. He

described a recent study by Dr. Ira Pastan that proved the database to be informative about particular tissues and changes in those tissues. A new feature of the Web site is the digital differential display (DDD) capability that enables an investigator to amass a large amount of information about the libraries.

REPORT OF THE DIRECTOR, NATIONAL CANCER INSTITUTE

Questions and Answers



In response to a query about the percentage of extraordinary opportunities from the Bypass Budget that it will be possible to fund, Dr. Klausner acknowledged that the number of available dollars falls short of the amount projected for full funding for the opportunities; however, each will be implemented at a certain level. He indicated an intention to provide a report comparing the recommended full-funding levels for all of the opportunities and the actual amounts in the distribution plan for FY98.

Dr. Bishop asked if cooperative funding could be arranged with the National Center for Human Genome Research Institute (NHGRI) to further expedite CGAP gene discovery. Dr. Klausner explained that NHGRI has assisted in the planning and oversight of the CGAP, but its funds are tied up in the effort to complete the mapping and sequencing of the genome. However, the Department of Energy (DoE), National Library of Medicine (NLM), and four pharmaceutical and biotechnology companies are providing funding. Dr. Phillip Sharp asked about plans for integrating functional genomics with the public database. Dr. Klausner noted that the NCI helped sponsor a workshop at Cold Spring Harbor on global databases for functional genomics, and a pilot project has already been initiated intramurally through CGAP. Gene discovery in several cancer sites is being coupled with data on arrays, put into a useable database, and linked to anonymous clinical information, including stage, characteristics of the tumor, treatment, and outcome. This pilot project is slated for eventual use in building a functional genomics prototype that will be linked to an understanding of gene pathways based on the global literature.

The Preclinical Models Working Group is considering recommending development of a useable database linking an understanding of cancer in other organisms to human cancer. Building these multidimensional databases that link genomic and molecular characterization of cells or tumors to clinical and functional information continues to be a learning experience for the responsible individuals. Dr. Sharp advised that input related to this new and rapidly changing technology should be sought from a variety of sources. In response, Dr. Robert Strasberg, Chief, NCI Office of Strategic Technologies (OST), noted that the Developmental Diagnostics Working Group is addressing this issue and the area will be aggressively pursued. The OST also has developed a database for new technologies with links through the World Wide Web (WWW or Web) to connect investigators with technology entrepreneurs and developers.

Dr. Klausner asked NCAB members to be prepared to comment at the February meeting on the Bypass Budget (*The Nation's Investment in Cancer Research: A Budget Proposal for Fiscal Year 1999*). An agenda item is planned to discuss dissemination and education plans for the document, as well as how it is currently being used.

LEGISLATIVE UPDATE

Ms. Dorothy Tisevich



Ms. Dorothy Tisevich, Director, Office of Legislation and Congressional Activities, directed attention to the full text of the NIH appropriation bill report for FY98 and to the legislative scorecard included in the update package in the meeting notebooks. Using slides, she highlighted areas of interest in the language by the House and Senate that accompanied the appropriation bill. Areas mentioned by the Senate overlap in many cases with those of the

House. Differences include reference to adolescent tobacco use, diethylstilbestrol, brain tumors, translational research, and digital mammography. Both Houses of Congress referred to the need for coordination on cancer issues within the NIH and with other federal agencies. New legislation introduced since the November NCAB meeting were the Clinical Research Enhancement Act, Prostate Cancer Research Stamp Act, Health Effects Study of Nuclear Weapons Tests, and several tobacco bills, many of which relate to the tobacco settlement. An example of the latter is the NIH Trust Fund Act of 1997 that would disallow a federal tax deduction for any payments related to the tobacco settlement or litigation and place these funds in a trust fund for research at the NIH, without any offset to regular appropriations.

LEGISLATIVE UPDATE **Questions and Answers**



In response to a question, Ms. Tisevich noted that the FDA Reform Bill passed in 1997. The one-stop shopping bill, introduced previously as stand-alone legislation, was folded into the FDA bill and now requires that the NIH put mechanisms in place that are more comprehensive in providing information about ongoing clinical trials across the NIH and health information in general. Dr. Klausner added that the NCI has been assigned to lead the project to coordinate access to information about clinical trials. As part of the reexamination and redesign of the Physicians' Data Query database (PDQ), a template providing for a simplified and accessible user-friendly approach to clinical trials information will be developed that will be exportable across the Institutes. A February meeting is planned to review examples of clinical trials information systems and develop specifications for the new design. The objectives are to incorporate new information technologies and address a larger number of audiences than are reached by the current PDQ. This design process will be essential to the task of developing uniform entry for information about all clinical trials associated with the NIH.

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



Dr. Harold Freeman reported on the final two of four meetings of the President's Cancer Panel in 1997 directed toward concerns with special populations. In September, a meeting on the Real Impact of the Reduction in Cancer Mortality was held in Bethesda. Dr. Klausner and many other speakers were invited to consider the significance of the slow but real decline in the overall rate of cancer mortality in the United States since 1990. A consistent theme heard by the Panel was that the benefits of this reduction in cancer mortality have not been shared equally by all segments of the population and have not been uniformly distributed across all types of cancer. Other speakers noted that national data do not always reflect the true burden of cancer within a particular community of the population. They suggested that reports of reduced cancer mortality could lead to a false sense of security among members of special populations who may not be experiencing reductions of the same magnitude. Moreover, there is scientific value in studying the disease patterns in local populations, which may differ from the reported national experience. Dr. Freeman noted that although inconsistencies in mortality rates among various populations have been studied, more and better data are needed, together with better methods of obtaining these data. A special committee has been appointed within the NCI to address this need.

The Panel heard that cancer incidence continues to rise for the entire population, even as cancer mortality is declining. Participants at this conference recommended that the National Cancer Program should place greater emphasis on cancer prevention and control efforts at the community level where risk behaviors may be ultimately controlled. Healthy People 2000 goals are some distance from being met in most states. Moreover, these goals do not set targets for all of the special populations in the United States. Representatives of several NCI initiatives that focus on special populations and from the Native American peoples testified before the Panel,

including the National Black Leadership Initiative, National Hispanic Leadership Initiative, and Appalachian Leadership Initiative. These speakers stressed the importance of involving community leaders in the communication of cancer-related information to ensure that such information is perceived by special populations as trustworthy. Also, it was noted that programs that start and stop sporadically tend to erode confidence and trust in these communities. These programs require a long-term commitment to be effective. Participation in clinical trials was emphasized as being essential for maintaining the downward trend in cancer mortality, particularly in these special communities. Suggestions for increasing participation included: (1) raising community physician awareness of clinical trials; (2) educating consumers about the benefits of participation; (3) involving the leadership of minority organizations in recruitment efforts; (4) removing structural barriers to participation; and (5) establishing a better body of evidence on the benefits of participation in clinical trials.

In November, the Panel met at the H. Lee Moffitt Cancer Center in Tampa, Florida, to explore the topic entitled Responsiveness of the Health Care System for the Needs of Special Populations. This topic related to the Panel's 1996 hearings on managed care. Participants were asked to identify areas in which the current health care system addresses health care concerns of special populations and where improvements are needed. Participants uniformly voiced the need for increased funding for cancer research, along with the development of research studies that take the needs of special populations into account, for any real hope of conquering cancer. The first of two broad issues discussed at the meeting was the problem of defining special populations. Suggestions to the Panel were to consider expanding the traditional list of special populations to include subgroups of special populations like Native Americans and groups with special health care needs but which are not recognized by current census definitions (e.g., migrant workers and children). The Panel listened to a continuing debate on the scientific merits of grouping individuals according to self-reported racial status in an increasingly multiracial society. The Panel heard suggestions that a better approach to research on special populations may be to design smaller studies targeted toward concentrated groups which may be particularly at risk, to answer specific scientific questions related to identifying and addressing the needs of those specific groups.

The second broad area of discussion was the ability of the current health care system to address the needs of special populations. Most of the testimony was centered on managed care and continued to be negative in its assessment of the current status. Patient advocates testified to difficulties in gaining access to services caused by delays in referrals, denial of payment for participation in clinical trials, incomplete workups due to cost cutting, use of preferred sites that may be inconvenient for patients, and difficulties in navigating preauthorization and reimbursement systems. Services offered in the fee-for-service setting were regarded as providing an underlying sense of security that treatment prescribed by the physician would tend to be implemented. It was noted, however, that many of the same exclusions for experimental treatment are present in fee-for-service settings and enforcement of narrow criteria for health care reimbursement appears to be limiting the latitude formerly granted physicians in authorizing treatment. Consistent with a previous Panel recommendation, participants strongly recommended that legislation be enacted to require managed care organizations to contribute to the costs of clinical care.

In conclusion, Dr. Freeman stated that the Panel believes access to health care, cost containment, and quality of care continue to be competing priorities in the current health care system and that only by achieving a balance among these priorities can access to appropriate treatment and care be ensured for underserved populations. The Panel believes that issues related to managed care and the concerns of special populations will be central to the future of cancer research and, more importantly, for the health and well being of society as a whole. However, the Panel in formulating recommendations to the President faces the problem that accepted patterns of data collection are being questioned and yet they form the basis for

scientific investigation and most health care policy. Fundamental questions to be addressed are: (1) how to collect meaningful data and scientific data that will ultimately lead to accurate conclusions about the causes of cancer, and how cancer burdens can be alleviated; and (2) how to apply that knowledge to improving the health of the total society.

REPORT OF THE PRESIDENT'S CANCER PANEL

Questions and Answers



In discussion, Dr. Richard Boxer commended the Panel for the excellent series of programs and pointed out that special populations involve more than one-half the total U.S. population. Dr. Kay Dickersin asked if the Panel could mount a formal literature review of this topic to supplement the information gained from the testimonies. Dr. Freeman responded that the Panel is planning a series of three meetings on quality care issues in cancer and will be conducting a study to collect hard data on the issue.

DIVISION OF CLINICAL SCIENCE UPDATE

Dr. Edison Liu



Dr. Edison Liu, Director, Division of Clinical Science (DCS), stated that the DCS program review presentations would focus this year on clinical questions that pose a challenge to the Division. The unique mission of the DCS within the NCI is to work at the interface between science and patients to find cures for cancers. In addition to the standard medical hospital branches for Medicine, Surgery, Pathology, Radiation Oncology, and Pediatric Oncology, the DCS has branches for Urologic Oncology, Metabolism, Dermatology, HIV and AIDS Malignancy, Radiation Biology, and Cancer Prevention Studies. Components of the clinical infrastructure are the physical plant, clinical research initiatives to devise clinical protocols structures, training, recruitment, communication, collaborative programs, and the new Clinical Center slated to open in 2001. Under development as part of the physical infrastructure are a Key West facility that has a technology focus and is in collaboration with the Division of Cancer Epidemiology and Genetics (DCEG) and the NHGRI, a bone marrow transplant unit, and the conversion of 3B South in the present Clinical Center for recruitments.

CLINICAL TRIALS INTRAMURAL PROGRAM

Dr. Gregory Curt



To examine the clinical research infrastructure, the Clinical Trials and Clinical Pathology Advisory Committees were organized, chaired by Drs. Elizabeth Eisenhauer and Robert Reddick, respectively, members of the intramural program's Board of Scientific Counselors (BSC). Dr. Gregory Curt, Deputy Director for Clinical Affairs, presented the report of the Clinical Trials Advisory Committee. As background, he reviewed intramural management initiatives since 1990 that have added to the central infrastructure including: (1) a prototype for tracking the costs of clinical trials as a management tool for the branches, which was later adopted by the Clinical Center as whole; (2) central data registration and eligibility checks; (3) a clinical data registry and standard operating procedures for randomization and regulatory reporting; (4) a standard database for the branches, with a fourth-dimension platform; (5) an off-site, fireproof data vault; (6) internal audits of patient eligibility, informed consent, and clinical trial conformance; (7) a data management training series; and (8) standardized terminology to facilitate implementation of a standard database. In addition, new positions were added to further centralize DCS operations in areas such as computer architecture, patient outreach and recruitment, and regulatory affairs. Dr. Curt briefly reviewed the specific findings of the Clinical Trials Advisory Committee in 10 areas, pointing out where implementation has already begun. He noted that the Eisenhauer report was presented to the branch chiefs, senior clinical leadership, and the BSC, and all uniformly endorsed these recommendations. For the formal response, DCS has organized three groups to look at specific questions related to

Protocol Planning, Implementation, and Monitoring, and has invited the Clinical Trials Advisory Committee to return in 1 year to review DCS steps in conformance with these recommendations.

TRAINING OF FELLOWS **Dr. Carmen Allegra, Dr. Lee Helman**



Dr. Carmen Allegra, Chief, Medicine Branch, and Dr. Lee Helman, Chief, Pediatric Branch, described four new training initiatives that were designed to enhance training opportunities for clinical investigators, an important priority of the DCS. The **Clinical Scholars Program**, a Medicine Branch initiative, is a 2-year program for Clinical Associates desiring to receive in-depth training in the science and art of clinical investigation. Trainees will have both clinical and laboratory mentorship, and training will involve didactic course work, on-the-job experience in designing and implementing a clinical trial with their mentors, and attendance at clinical meetings. The **Medicine Branch Best Clinical Teacher Award** was created to recognize senior staff of the Intramural Research Program (IRP) who excel in the ability to teach trainees the art and science of medical oncology and clinical investigation. Dr. Wyndham Wilson, a resident expert in the therapy of lymphomas, was chosen as recipient for the 1997 award. The **Senior Fellowship Training Award** is for fellows who have come through either the Medicine Branch or Pediatric Branch. It provides up to 3 years of additional support for promising trainees in a mentored environment to help them progress to the level of independent investigator. Support includes salary, travel, supplies, and services. The application process is competitive, with review by a committee appointed by the DCS. An **Advanced Studies Program in Pediatric Oncology** has been proposed as a resource for the pediatric oncology community. This program would provide up to 3 years of post-fellowship support to promising, newly trained pediatric hematology and oncology fellows to develop into independent clinical investigators. Candidates would be solicited from training communities nationwide and would be returned to their respective institutions as fully trained investigators. The program for the first 2 years would include the development and execution of a hypothesis-driven clinical research question, with close supervision by a chosen mentor, and a third year may be added to pursue an M.P.H. degree. Review of applications would be conducted by a committee of extramural and intramural scientists with a specific interest in clinical investigation.

TRAINING OF FELLOWS **Questions and Answers**



In response to a reservation expressed by Dr. Dickersin about the requirement in the Clinical Scholars Program for the completion of a clinical trial, Dr. Allegra explained that the design of the clinical trial is undertaken with the two mentors assigned to the trainee. It is their responsibility to adequately design a trial, but the design will ultimately be reviewed at multiple levels for its adequacy. Dr. Charles Wilson asked whether the Surgery Branch would be involved in the training initiatives. Dr. Liu explained that the Pediatric and Medicine Branch training initiatives are planned as the first step in building a training infrastructure for the DCS. If they are successful, other branches in the DCS will follow suit.

TRANS-INSTITUTE AND TRANS-DIVISIONAL INTERACTIONS **Dr. Edison Liu**



Dr. Liu expressed strong support of trans-Institute and trans-divisional interactions in the restructured DCS, and he reviewed several DCS projects already begun or being planned: (1) the Molecular Epidemiology Groups in collaboration with DCEG and DBS; (2) meetings with the National Institute of Dental Research (NIDR) and the National Institute of Deafness and Communication Disorders (NIDCD) to plan a head and neck cancer program centered on treatment as well as genetics and prevention; (3) a new program in neuro-oncology that takes

into account pediatrics, medicine, and neurologic diseases with the National Institute of Neurological Disorders and Stroke (NINDS); and 4) a smoking cessation and nicotine addiction initiative with several Institutes and the new DCCPS.

PLANS FOR THE CLINICAL CENTER

Dr. Edison Liu



Dr. Liu reviewed plans for the new clinical center slated to open in the year 2001. The infrastructure of the current Clinical Center located in Building 10 will be completely revamped and relocated in the new facility. The number of beds has already decreased from the original 600 to about 370 and will eventually decrease to 250, the optimal number projected for a research institute within the NIH. The new center also will service all Institutes but with a completely restructured governance. Previously, each Institute had a geographic localization and autonomy of command of that localized structure. Under the new approach, Institutes will work together in a disease or modality orientation. The governing body will be the Clinical Center Advisory Council, a small working group of major users empowered to speak for the Institutes, which will provide institute-based advice to the Deputy Director for Clinical Research and Institute governance of the new Clinical Center. One of the first accomplishments of the new planning process was to convene Partner's meetings beginning in August to develop a working plan for the configuration of the new facility. The completed design was presented to and approved by the ICD Directors in early October, and the new Partner's structure is being used to initiate long-term governance decisions for the Clinical Center. Using a slide, Dr. Liu briefly described the internal architecture of the seven-story hospital and showed a template for the third floor, which will be dedicated almost entirely to the cancer question.

BONE MARROW TRANSPLANTATION PROGRAM

Dr. Ronald Gress



Dr. Ronald Gress, Acting Chair, Department of Experimental Transplantation and Immunology, described the new structure for bone marrow transplantation (BMT) studies in the Transplantation Therapy Section of the Medicine Branch, DCS. Because of its unique derivation from the Transplantation Immunology Section of the Division of Basic Science, this structure will forge a close association between the clinical effort and a large basic science effort in immunology. Scientific and clinical goals of the section are to generate new understandings in transplantation biology by focusing on control of T cell responses for therapeutic benefit, and then to translate this knowledge into unique clinical studies. The research agenda of the section is based on the biology T cell generation and function, with efforts in T cell generation and regeneration by different pathways, regulation of mature T cells, and antigen-presenting biology. Dr. Gress presented a more in-depth discussion of two of those efforts and their implications for the program. The clinical BMT program emerges as a highly collaborative, inter-divisional effort, bringing to bear the expertise of a sizeable community of basic immunologists on issues related to clinical issues. It was established also as a focal point for inter- Institute collaborations, currently with the National Heart, Lung, and Blood Institute (NHLBI) and the National Institute for Allergy and Infectious Diseases (NIAID). Intra- and extramural collaborations will be fostered. Prototypes for these are the formal arrangements with the University of California, San Francisco, in T cell regeneration and population dynamics and with the University of Washington in cytokine regulation of T cells and the relationship to new BMT strategies. A physical unit for the BMT program will begin construction by February, and a staff recruitment effort is underway.

BONE MARROW TRANSPLANTATION PROGRAM

Questions and Answers



Dr. Philip Schein commented that the Clinical Center in past years set the standard for other

programs and with the excellent leadership and unique resources that currently exist can be restored as the best and most attractive training and research environment. He expressed concern that overreaction to indictments by the Eisenhower Committee as they relate to structure could lead to rigidity and paralysis. He advised that the program needs a spirit of innovation, efficiency, and speed in bringing discoveries rapidly to further validation and translation outside the Institute. He further advised the use of the total resources that exist in the surrounding cancer centers and medical schools to cooperate on training and in completion of key protocols, with adequate provision for receiving credit for the cooperation they are providing to the IRP. Dr. Liu gave assurance that the Division is sensitive to the issue of bureaucratization in every change.

OVERVIEW OF THE NCI BOARD OF SCIENTIFIC ADVISORS ACTIVITIES

Dr. David Livingston



Dr. David Livingston, Chair, NCI Board of Scientific Advisors (BSA) and Professor of Medicine, Dana-Farber Cancer Institute, reviewed the organizational and operating characteristics of the BSA, the 30-member Board whose primary responsibility is for oversight of NCI's Extramural Research Program (ERP). In addition to the three regular meetings per year, small groups of experts are instituted to study and propose solutions to specific problems, most recently issues related to the logistics of NCI-monitored clinical trials, NIH review of R01s in clinical cancer research, and SP0RE program review. The BSA has developed a process that has the potential to provide NCI leadership with information on major issues affecting the extramural community and new opportunities for NCI investment. Beginning in December 1996, dedicated open sessions called "The BSA Listens" have been and will continue to be held at national cancer meetings to give speakers an opportunity to air their views. A process has been developed for transmitting issues to the NCI leadership and Institute responses to the societies. During the year, the BSA at its regular meetings tracked paylines for investigator-initiated grants; analyzed and commented on Program Review Group reports on the cancer centers, cancer prevention, clinical trials, and cancer control and behavior; reviewed and commented on the work in progress in the Developmental Therapeutics, Preclinical Models, and Cancer Genetics Working Groups; reviewed the NCI AIDS research program; initiated an effort aimed at creating a dedicated cancer clinical/translational research study section within the Center for Scientific Review; initiated an effort to expedite transmission of results of clinical trials to principal investigators before their formal closure; and reviewed and made decisions regarding the disposition of numerous RFA and new contract concepts.

OVERVIEW OF THE NCI BOARD OF SCIENTIFIC ADVISORS ACTIVITIES

Questions and Answers



In response to a question from Dr. Dickersin, Dr. Livingston explained that the BSA has not addressed the optimal mix between RFAs and investigator-initiated grant proposals as a dedicated subject, but attends to this question in the context of every RFA concept review. Dr. Sharp asked about the relationship between the BSA and BSC. Dr. Livingston explained that none exists except for informational purposes. Dr. Klausner pointed out that this configuration represents the response to a recommendation in the Bishop-Calabresi report that the traditional NCI Boards of Scientific Counselors for each Division be reorganized around a Board for the IRP and one for the ERP. An additional set of functions for the BSA will be quadrennial review of each ERP program analogous to that of the IRP. Dr. Livingston gave assurance that the BSA has agreed to carry out the reviews of the ERP divisions, their leaders, and the Office of the Director in keeping with the spirit of the Bishop-Calabresi report.

Dr. Ellen Sigal asked about a mechanism to receive informational copies of BSA comment on the reports of the Program Review Groups. Dr. Marvin Kalt, Director, Division of Extramural Activities, and Dr. Livingston explained that the BSA meetings are open and formal minutes are

available to the public after they are approved at the next regular meeting. However, draft minutes could be provided to the NCAB. Schedules of future BSA meetings are published on the NCI Web site under Advisory Boards.

NEW BUSINESS I
Dr. J. Michael Bishop



Dr. Bishop listed four items that have already been received for discussion at the New Business II session: (1) structure of subcommittees; (2) how to come to closure with the NCI response to the *Ad Hoc* Working Group on the NCI Intramural Program (the Bishop-Calabresi Report); (3) the NCI role in advocacy and public relations and how the NCAB can contribute; and (4) information items from the DEA.

**INTRAMURAL EPIDEMIOLOGIC AND GENETIC TRANSLATIONAL
INITIATIVES**

Dr. Joseph Fraumeni



DCEG OVERVIEW AND UPDATE

Dr. Joseph Fraumeni



Dr. Joseph Fraumeni, Director, Division of Cancer Epidemiology and Genetics (DCEG), presented an overview of the objectives, operating goals, organization, and staff of the DCEG as background. The DCEG was created to strengthen and expand NCI programs in cancer epidemiology, genetics, and statistics and to ensure that recent discoveries in molecular biology and genetics are accelerated and broadened through a population-based etiologic study. The Division places major emphasis on an interdisciplinary approach to causes of cancer and has a special mandate to augment research activities related to the genetic determinants of cancer, consistent with the extraordinary opportunity in that area included in the 1999 Bypass Budget. To implement this mandate, the DCEG is organized by focus areas: (1) the Epidemiology and Biostatistics Program with a Biostatistics Branch and branches for Occupational, Nutritional, Environmental, Radiation, and Viral Epidemiology; and (2) the Human Genetics Program with Genetic Epidemiology and Clinical Genetics Branches and a Laboratory of Population Genetics. The extramural Epidemiology and Genetics Program was transferred as of October 1 to the new DCCPS, but close coordination will continue on a large number of initiatives developed prior to the transfer. An important priority of the DCEG has been to enhance communications, which is being done through regular meetings of the senior advisory group; a committee of scientists; a number of working groups dealing with specific exposures, tumors, and approaches; a genetics group; an Internet site; and *Linkage*, the quarterly newsletter.

Dr. Fraumeni summarized the scientific highlights of recent studies: (1) a study of BRCA1/2 mutations in volunteers from the Metropolitan DC Jewish community indicated that family history, as well as mutation status, are important considerations in genetic counseling; (2) a study of mechanisms associated with the increased risk for oral cancer with the intake of alcohol; (3) a cohort study of children with retinoblastoma gave evidence that environmental interactions may affect risk even for highly penetrant genes associated with hereditary cancers; (4) an ongoing study of families prone to melanoma led to the discovery of two susceptibility genes for melanoma and to the finding that dysplastic nevi represent the key risk factors for nonfamilial melanoma as well; (5) a strategy for mapping cancer mortality at the county level to monitor changes in demographic patterns and special efforts to identify variations in cancer incidence by subsite and cell type using data from the SEER program, have generated geographic clues to cancer etiology; (6) a population-based, case-controlled study of esophageal adenocarcinoma in three U.S. areas found a significantly elevated risk among cigarette smokers that persisted among ex-smokers and increased even more for obese individuals; the sharp upward trend appears to be related to smoking trends in past decades and the increases in

prevalence of adiposity in the general population; (7) a study of more than 20,000 BMT recipients showed an increased risk for solid tumors with increasing dose of total body irradiation and time since transplant, indicating the need for long-term surveillance; (8) a Children's Cancer Group (CCG) study of children with leukemia and controls residing in nine states found that the risk of leukemia was not significantly associated with quantitative time-weighted measures of residential electromagnetic fields nor with exposures estimated by the wire coating of homes; (9) a meta-analysis of summary data from eight case-control studies of lung cancer revealed an excess risk associated with exposure to indoor radon at a level that was previously predicted by extrapolation of data from underground mines; further studies are planned among a cave-dweller population in China; and (10) a cohort study of benzene workers to address relationships between exposures and level of risk found elevated risk for hematologic neoplasms at average levels of benzene exposure and even greater risk for non-Hodgkin's lymphoma among workers with at least 10 years of exposure.

DCEG program initiatives being planned or under way include conferences and workshops in the area of cancer genetics, familial cancer registries and consortia, the Molecular Epidemiology Coordinating Group, core biospecimen repositories, core genotyping and sequencing facility, and research and mentoring awards supported by the DCEG. The Cancer Epidemiology and Biostatistics Training Program includes a Cancer Genetics Training Program featuring didactic course work, rotations, and research experience.

GEOGRAPHIC CLUES TO CANCER ETIOLOGY

Dr. Robert Hoover



Dr. Robert Hoover, Director, Epidemiology and Biostatistics Program, presented highlights of past accomplishments in the Branch's 20-year study of geographic patterns in cancer mortality, status of current projects, and future directions. Although valuable in the study of infectious diseases and their outbreaks, the process of mapping diseases was not useful in the study of chronic diseases until the late 1960s when the advent of modern computer technology made it possible to experiment with a variety of unit sizes for mapping cancer incidence or mortality. The county was determined to be the optimal administrative unit based on NCI experimentation with National Center for Health Statistics data on cancer mortality from 1950 to 1969. The NCI strategy resulting from these early methodologic experiments was to map cancer mortality at the county level, correlate cancer mortality with county geography and environmental data to develop a hypothesis, and conduct field studies in high-risk areas to test the hypothesis. This activity led to the publication of the first *Atlas for Cancer Mortality for U.S. Counties* in 1975, which was subsequently expanded to include data on non-whites and time trends.

Dr. Hoover then described three etiologic studies that illustrated how the DCEG used various strategies to investigate multiple cancer types in many areas of the country and indicated a number of different exposures. In the first, prominent patterns of excessive rates for lung cancer in the Atlantic and Gulf Coast areas of Southeastern United States were found to result from relatively brief exposure (less than 3 years) to asbestos in the many shipyards that operated in that area during the middle 1940s. A multiplicative effect was found between working in the shipyards and smoking. Moreover, the asbestos was air borne, so an asbestos-related job was not necessary for this occupational type of exposure. In another study, the observation was made that both relatively rural and relatively urban counties with smelter industries had high rates of lung cancer among both men and women. A case-control study of a locale in Pennsylvania with a zinc smelter revealed that lung cancer excesses were due to general environmental exposure from the arsenic (a by-product of the smelting process) emitted from the smokestacks about 30 years prior to the development of the cancers. In a third study, an excess of oral cancer in middle-aged and older females in relatively rural areas of the South was traced to snuff dipping, a lifestyle exposure that was socially more acceptable than smoking.

Future plans for the DCEG include a Biostatistics Branch initiative to publish a new set of maps comparing the old and new data accumulated between 1950 and 1994 and detailing race specifics since 1970; exposure-based correlational studies at the state or county economic area levels (e.g., cancer in relation to I-131 exposure due to A-bomb testing); and investigations of high-risk areas, characterizing them with respect to exposure patterns as possible targets for field studies. Dr. Hoover noted that the Division will continue to evaluate exposure- or disease-based reasons for clusters of disease but expand the focus from fairly localized clusters with common demographics to large-scale clusters needed to look at regional differences in diseases such as colon and breast cancers. He described a new study design that permits assessment of urban and rural high versus low rate risks and regional variation. Dr. Hoover concluded that the mapping of cancer mortality is useful if appropriate administrative units are identified; systematic followup at least with patterns of correlational studies and field studies has been successful in identifying responsible exposures; pursuit of reasons for more general regional excess is likely to be more difficult than for targeted localized patterns; and more discussion is needed on the advantages and cost benefit issues for the development of national incidence data comparisons for mortality.

GEOGRAPHIC CLUES TO CANCER ETIOLOGY **Questions and Answers**



In discussion, Dr. Calabresi asked for an explanation of the high incidence for all cancers for men in rural, north central Maine. Dr. Hoover noted that although that particular study does not specifically answer that question, some of the patterns follow demographics quite closely and indicate the effect of low socioeconomic status on the various rates. Dr. Freeman asked if any study was able to separate the fact of economic status from a particular carcinogenic discovered in a given environment. Dr. Hoover noted that the esophageal cancer excess among blacks in the District of Columbia appear to be a nutritional phenomenon not socioeconomic. In some cases, breast cancer follows a socioeconomic pattern, but other social class excesses are not yet known. Other discussion focused on: (1) reasons for the histological trends from squamous cell to adenocarcinoma and the possible relation to a manipulation in tobacco; (2) the strong association of adenocarcinoma with obesity that also may apply to the increase in adenocarcinomas; and (3) the recent American Cancer Society study that suggests deeper inhalation with low-tar and low-nicotine cigarettes sends nicotine to the periphery of the lungs. In response to a question, Dr. Hoover explained that a field study of excessive rates of colon cancer in five southeastern Nebraska counties localized the risk in a pocket of Moravian migrants from Czechoslovakia. A correlation with the high-fat, ethnic diet of this subgroup may be possible but has not been proven. In closing, Dr. Bishop commented that these quick-turnaround studies in response to a national challenge provide justification for the existence of an intramural program.

GENETIC AND ENVIRONMENTAL DETERMINANTS OF MELANOMA **Dr. Margaret Tucker**



Dr. Margaret Tucker, Chief, Genetic Epidemiology Branch, presented an update on DCEG research into the etiology of melanoma. She presented data from the SEER registry to show that melanoma is one of the most rapidly increasing cancers in the United States and in most predominantly white populations for reasons that are not clear. In the late 1970s, Dr. Mark Greene, then of the NCI, and colleagues examined several families with multiple members who had melanoma. This multidisciplinary study has evolved over the years, and more than 1,000 individuals in the group of about 30 kindreds have been followed prospectively for up to 20 years. One important finding was that family members with melanoma had distinctive nevi, currently known as dysplastic nevi (DN). The 20-year study of these families led to an understanding of the natural history of DN: (1) the first sign in childhood is an increased number of ordinary appearing nevi; (2) the scalp may be the first site of atypical nevi; (3) nevi

increase in number at puberty and DN may become apparent for the first time; (4) DN are most frequent on the back and in sun-exposed areas; (5) DN activity increases during pregnancy; and (6) with increasing age and protection from the sun, nevi may disappear. Clinical findings in melanoma-prone families in the study are: (1) all have DN, which appear to be cutaneous markers for high risk of melanoma; (2) the average age at first diagnosis is 33 compared with 54 in the general population; (3) 9 percent of family members who develop melanoma do so before age 20; (4) 42 percent subsequently develop multiple primary melanomas; (5) age of onset of first melanoma decreases from 48 in the older generation to 28 in the next, giving evidence of genetic anticipation; and (6) the average number of melanomas increases from one to two in the next generation. Results from genetic analyses of these families is that germ line mutations in p16 are the most frequently reported genetic alteration; additional families show evidence of linkage to 9p21 without p16 mutations. Only three families in the world have been found with germ line mutations in CDK4, two of them in the NCI study. Linkage analyses also have indicated a number of candidate regions on a number of chromosomes. Because no one group studying this disease has sufficient families, the NCI is participating in a newly formed melanoma consortium along with investigators from six other countries. A genome-wide scan by NHERI program staff is to be conducted to localize additional genes. The clinical characteristics of 10 families with functional germ line p16 mutations were compared with 9 families without these mutations and were found to be similar. However, the risk of pancreatic cancer was increased within a subset of the families with p16 mutations, but there was no relationship between specific mutations and pancreatic cancer risk. In a large case-control study designed to evaluate the risk of melanoma outside of high-risk families, dysplastic nevi were found to be a central risk factor for melanoma, centering over a 10-fold risk with multiple dysplastic nevi. In contrast, an increased number of small nevi were associated with a two-fold risk, and an increasing number of small and large nevi were associated with a high risk. In the 1980s, program staff in collaboration with the Late Effects Study Group reported an increased risk of melanoma after retinoblastoma, and, where material could be obtained, DN were found in those who developed melanoma. Subsequent groups have confirmed this initial observation, including a DCEG study in collaboration with Dana-Farber Cancer Institute, Cornell Medical Center, and Massachusetts Eye and Ear Hospital. The excess of melanoma was a sevenfold increase, and all melanomas occurred within hereditary RB patients. The intent is to obtain blood samples for genetic analysis and examine patients' skin for DN to attempt to evaluate the role of DN as a precursor in these individuals.

Dr. Tucker noted that these observations and the understanding of mechanisms could have profound implications for melanoma treatment in the future. From the results of the family studies and the case control study, DCEG staff can begin to estimate risks of melanoma in specific subgroups and begin to establish important parameters for designing efficient screening and prevention programs. Questions remaining to be addressed are: (1) other genes that are involved; (2) percentage of familial melanoma associated with DN; (3) whether DN is a genetic trait; (4) the role of recent sun exposure; (5) immune perturbations that predict risk. (6) the role of hormonal changes; (7) how to educate the public about sun exposure; (8) how to minimize childhood exposure; and (9) how to educate health care providers and the public to recognize early melanoma. One area to be pursued is whether the earliest changes in dysplastic melanocytes can be characterized using novel methods of microdissection.

MOLECULAR EPIDEMIOLOGY COORDINATING GROUP

Dr. Joseph Fraumeni



Dr. Fraumeni reported that the Molecular Epidemiology Coordinating Group (MECG) was formed by Dr. Klausner in June to take full advantage of the breadth and depth of the intramural divisions in fostering the development of an interdisciplinary approach to cancer etiology and prevention, often referred to as molecular epidemiology. Goals of the MECG were to identify special opportunities for interdisciplinary research into the causes and prevention of cancer and

barriers to such research; suggest corrective actions; enhance the planning of projects across divisions; and develop the resources and infrastructure needed to sustain this work. Expert epidemiologists from throughout the Institute are members of the committee to identify new ways of conducting and applying research that transcend divisional boundaries. Pilot projects are still being considered by the MECG, but initial interest has centered on a study of lung cancer. The Lung Cancer Subcommittee was formed to develop a protocol to investigate susceptibility mechanisms in lung cancer, including behavioral and genetic determinants of smoking and smoking cessation. NCI's clinical resources will be used.

To address key issues concerning informed consent for genetic testing and public concerns about the privacy and confidentiality of genetic information, the Informed Consent Subcommittee was formed and charged with the task of examining the impact of current procedures for informed consent on the conduct of MECG studies. Critical issues in genetic testing are the definition of genetic testing, IRB review consistency, consent for testing multiple genes, restrictions to the use of archival specimens, risk notification to study participants, and privacy protection. The Committee is currently developing best- case studies and practical recommendations for solutions to the difficult issues of informed consent and access to archival material.

Because molecular assays are being integrated into population studies, a Biospecimen Repository Committee was formed to develop plans for cost-effective and high quality laboratory support for biospecimen processing and storage. The committee is currently looking into prospects for a core facility located at the Frederick Cancer Research and Development Center (FCRDC).

WORKING GROUP ON SINGLE NUCLEOTIDE POLYMORPHISMS (SNPs)
Dr. Kenneth Buetow



Dr. Kenneth Buetow, Member, Fox Chase Cancer Center, and organizer of the DCEG Laboratory of Population Genetics, presented information on the Genetic Annotation Initiative, a new project that is associated with the Cancer Genome Anatomy Project (CGAP). He noted that the use of genetic study designs represents an extremely powerful tool to make novel observations in the areas of biology and human biomedical science as a means to understand disease causation, response, and outcome. Two variables needed for genetic studies are the ability to study hereditary transmission of traits and the ability to catalogue genetic variation. The ability to annotate genetic variation or to have detailed descriptions of genetic variations is a tool that can be used as a critical complement in studies that depend on population definition such as the geographic studies presented earlier. Genetic analysis also will be valuable in conducting pathway dissection and genome-wide association studies. Next, Dr. Buetow assessed the current capacities for conducting such studies.

To provide the necessary tools for genetic analysis, the Genetic Annotation Consortium was formed, which consists of the NCI Laboratories of Genomic Diversity and Population Genetics, the NCI Office of Science Policy (OSP), the National Center for Biotechnology Information (NCBI), extramural collaborators, and corporate partners. The Consortium decided to use the information being accumulated by the CGAP on genes and the differential patterns of expression of genes in cancer cells as a platform for pilot studies. The studies would focus on performing genetic annotation to complement the CGAP information on gene sequences by adding polymorphic tags to the 3' untranslated end and eventually to look for variation in their coding regions. The genes could then be integrated into larger genetic analysis or expression profiles that would be useful in the types of case-control and family studies described earlier.

A key objective of the Genetic Annotation Consortium is to establish a human genetic variation database of well-characterized points that will be publicly available. Another is to attempt to

identify the most cost- and time-efficient strategy for accomplishing genetic annotation. To that end, a variety of new technologies will be brought in, through collaborations with industrial partners and extramural colleagues, to explore different approaches to the identification and large-scale characterization of SNPs. Dr. Buetow summarized the deliverables as follows: (1) genetically annotated genes that are important in cancer phenotypes; (2) a database of human variation; (3) inexpensive variation-discovery protocols; and 4) cost-efficient, high-throughput genotyping.

WORKING GROUP ON SINGLE NUCLEOTIDE POLYMORPHISMS (SNPs)

Questions and Answers



In discussion, Dr. Freeman asked how ethnicity would be defined and whether the Consortium theorized that there would be genetic differences according to ethnic groups. Dr. Buetow explained that the goal would be to include members of the different populations as defined by the U.S. census. He added that dramatic differences are known to exist in the genetic constitution of different subpopulations of humans and, as variations are found, it will be important to build those indexes as well. Dr. Freeman asked if the assumption was made that through race and ethnicity, different groups would be determined according to genetic variation. Dr. Buetow responded that in all studies conducted to date, ethnic group was found to be a poor definition of the boundaries of genetic variation and the dramatic differences are distributed throughout most of the world's populations. Dr. Michael Dean, DBS, added race is not assumed to be genetically definable, but genetic markers do exist that have large frequency differences between groups and those markers can be important research tools in certain populations. In response to a question from Dr. Sharp, Dr. Buetow explained that the genetic annotation database and the highly polymorphic map that already exists will be complementary resources. In response to a question about the private sector's contribution and the NCI's efforts to anticipate that contribution and avoid duplication of effort, Dr. Buetow stated that the issue is complex and initiatives planned in the private sector are not known, but partnerships will be formed contingent on keeping the information in the public domain.

TRENDS IN CHILDHOOD CANCER

Dr. Martha Linet



Dr. Martha Linet, Epidemiologist, Radiation Epidemiology Branch, prefaced her presentation by showing the New York Times article reporting that a recent Environmental Protection Agency (EPA) conference concluded that cancer in U.S. children has been increasing steadily for 25 years and a national research program was needed to focus on preventable causes of childhood cancer. She then described current efforts within the NCI to comprehensively and critically evaluate the U.S. childhood cancer rate patterns. For this effort, the NCI Working Group to Evaluate Childhood Cancer Trends was formed with membership from DCEG, DCCPS, and DCTD. The primary source of data for the evaluation was the population-based registries of the NCI SEER program. Using a series of graphs, Dr. Linet presented data on childhood cancer incidence and mortality trends that resulted from the evaluation. She made the following points to consider in analyzing the data: (1) the most recent internationally recognized classification system includes 12 major categories of childhood cancers and many have additional cancer subtypes; (2) many complex aspects related to subtypes of the major cancers and subgroup variations in morphology, cytogenetic abnormalities, cell surface markers, biologic behavior, clinical characteristics, prognosis, and etiologic factors must be considered when interpreting the pattern for total childhood cancers; (3) in 1997, about 8,800 new cases of childhood cancers will be diagnosed in the United States—from a total of 1.38M cancers among persons of all ages. Dr. Linet highlighted the findings from the Working Group's analysis of the SEER data and noted, as an example, that some of the increases in lymphocytic leukemias and nonlymphocytic or myeloid leukemias were due to improvements in diagnostic specificity that paralleled the need for subtype specification to guide treatment decisions.

Dr. Linet then gave an overview of recent and ongoing etiologic investigations and long-term follow-up studies of cancer survivors supported by the NCI. She referred NCAB members to the meeting notebooks for a list of the many NCI-funded intramural and extramural, U.S. and collaborative international studies, as well as selected publications resulting from the studies in recent years. She noted that although the size and scope of the studies cannot be conveyed in a short presentation, it should be appreciated that several recent studies include four to ten times more subjects and much more detailed exposure assessments per subject compared with earlier efforts. The assessments include biologic and exposure measurements. Dr. Linet concluded her presentation by describing key exposures and other factors that are being evaluated in one or more of the studies, including residential environmental exposures, sociodemographic factors, parental occupational exposures, lifestyle and diet related exposures, medically related exposures, and host factors such as infectious disease history, reproductive factors, and familial and genetic disorders.

TRENDS IN CHILDHOOD CANCER

Questions and Answers



In discussion, Dr. Bishop asked for an explanation of the diametrically opposed conclusions from two federal agencies. Dr. Klausner explained that the NCI leadership was not contacted before the conference but had attempted to reach the EPA administrator afterward. As part of the NCI's mandate to coordinate the National Cancer Program, a SEER Monologue on childhood cancer trends is being published, and information compiled by the NCI Working Group will be distributed widely to other federal agencies, the public, Congress, NCAB, and the EPA. Dr. Klausner emphasized the importance of conducting a careful analysis of the data with the extensive resources of the Institute and dealing with public confidence about a very important set of diseases that cause much concern. He also noted the need to maintain widespread communication about the information, expertise, and analytic capacity available within the NCI for use by the public, in particular for issues that relate to the monitoring of the cancer burden. One major initiative is the evaluation and enhancement of the NCI surveillance system and how findings are communicated. The NCAB will receive periodic reports in this regard. Dr. Wilson asked if it was known whether there was a consistency in the diagnosis of childhood brain and central nervous system tumors internationally similar to that for glioblastoma. Dr. Linet answered that there has been global agreement that some increases in brain tumors in the elderly over the past two decades represent a combination of events, including improvements in diagnosis and improvements in health of the elderly.

EXTRAMURAL CLINICAL AND TRANSLATIONAL UPDATE

Dr. Robert Wittes



Dr. Robert Wittes introduced the Extramural Research Program review by noting that the initiatives to be presented are attempting to capitalize on a series of opportunities across a broad scientific and technical front. Some initiatives originated within the NCI and some from the extramural community, but all represent collaborations between the Institute and its investigator constituencies around the country.

ANGIOGENESIS OPPORTUNITIES

Dr. Judah Folkman



Dr. Judah Folkman, Professor, Harvard Medical School Children's Hospital, prefaced his presentation on new findings in angiogenesis research with a review of the biology of tumor cells. Virtually all tumors and their metastases contain two major cell types—tumor cells and microvascular endothelial cells—in addition to other cells. Each of these two types drives the other with specific growth and survival factors. The endothelial cells generate capillary blood vessels around which the tumor cells grow as small microcylinders. Blood flowing in the

capillaries supplies oxygen, removes carbon dioxide, supplies nutrients, and removes catabolites. But, endothelial cells also have been found to release into the tumor on the back side of the vessel an increasing series of growth factors, mitogens, and survival factors. During its early life, the primary tumor lacks the ability to recruit blood vessels, but after a few years in humans, the tumor switches quite suddenly to the angiogenic state. Because the stimulus from the tumor for new blood vessel growth is so powerful, there is a progression of angiogenesis activity that is not possible to control. About 12 years ago, molecules were discovered that could partially inhibit angiogenesis. This first generation of angiogenesis inhibitors could slow tumor growth in animals but not mediate tumor regression. Over the years, new inhibitors were discovered with increasing power, and 4 years ago it became possible to turn off angiogenesis completely due to the discovery of endogenous proteins (internal fragments) within other proteins. The increase in power in these second generation inhibitors has changed cancer treatment development. One new finding from these discoveries is that the problem of drug resistance can be bypassed experimentally.

Dr. Folkman noted that he and colleagues are beginning to regard antiangiogenic therapy as a first-line therapy, rather than adjunctive to chemotherapy or for use after chemotherapy to maintain dormancy and prevent recurrence. They believe that tumors have two important compartments that drive each other and, while up to now one compartment has been treated with chemotherapy, it might be advantageous to treat both compartments, especially the endothelial compartment to avoid toxicity and drug resistance. The fact that endothelial cells do not develop drug resistance when specific therapy is used that only affects growing endothelial cells is changing the research focus. Implications for cancer treatment is that therapy can be resumed.

Dr. Folkman stated that it can be concluded that various phenotypes of cancer, including tumor growth, invasion, metastasis, progression, and dormancy, are not completely autonomous but are under the tight control of the microvascular endothelial cell. This leads to the unifying concept that suppression of metastases by a primary tumor can be explained on an angiogenic basis. Related to that are the hypotheses that ovarian cancer never leaves the abdomen, the indolent growth of prostate cancer is an angiogenic phenomenon, antiangiogenic therapy may be a good strategy to bypass drug resistance, and antiangiogenic therapy for leukemia either before or after chemotherapy may be imminent. Dr. Folkman suggested that these data argue that, although the best way to understand cancer is to study the cancer cell, the best way to treat cancer may be to ignore the cancer cell temporarily until a molecular cure of the common cancers becomes a reality. In the meantime, antiangiogenic therapy could provide relief from the disease by its potential for reducing toxicity and drug resistance, adding to radiotherapy, and eventually becoming a platform for immunotherapy or vaccine or gene therapy. Dr. Folkman cited as a precedent for this line of thinking the fact that the best way to understand peptic ulceration of the stomach or duodenum is to study acid regulation, but the best way to treat ulcers is to kill the bacteria *Helicobacter pylori*. In conclusion, Dr. Folkman thanked the NCI for 30 years of support for this research.

ANGIOGENESIS OPPORTUNITIES

Questions and Answers



In discussion, Dr. Folkman presented additional data in answer to questions related to: (1) the role of endostatin in radiation treatment of prostate cancer, (2) whether systemic injection of FGF will reactivate dormant tumors, (3) whether ovarian cancer is a target for angiogenesis therapy, (4) how chemotherapy reaches tumors that have been reduced by endostatin therapy, (5) whether the dependence on vascularization seen in an animal setting will be replicated in human solid tumors, (6) whether antiangiogenic therapy can be used prophylactically for tumors *in situ*, and (7) whether endothelial cells in older patients differ in the production of angiogenic agents.

As an epilogue to this presentation, Dr. Wittes explained NCI's role in disseminating Dr. Folkman's findings to the investigator community so results can be replicated, expanded, and generalized. NCI program staff have been working to set up a collaboration with Dr. Folkman's laboratory and the licensee to endostatin, whereby the resources of the NCI can be brought to bear on the synthesis and dissemination of the mouse endostatin as a research reagent now, and the human endostatin in the future. Dr. Wittes noted that the NCI convened a meeting of investigators in the angiogenesis field to discuss opportunities and barriers in the field from the perspective of intervention development. Recommended areas of opportunity were: (1) collaborations that might not occur without some stimulus; (2) development of the science related to pinpointing the mechanisms underlying angiogenesis; (3) development of in vivo and in *vitro* preclinical models that are predictive of the clinical situation; (4) development of resources that can be made available to the community; (5) development of cell-line resources; (6) standardization of reagents; and (7) investigator training. Program staff are actively considering ways to establish consortia of investigators to respond to these opportunities.

CLINICAL INFORMATICS INITIATIVE

Dr. John Silva



Dr. John Silva, Program Manager, Defense Advanced Research Projects Agency (DARPA) and part-time NCI communications expert, presented an update of progress in developing the Clinical Informatics Program, an initiative recommended in the report of the Clinical Trials Program Review Group. Problems that are to be solved related to clinical trials included how to expedite recruitment, facilitate data management, facilitate translation of laboratory findings into routine clinical care, and exploit new technologies to improve clinical trials processes. Dr. Silva noted that most steps in the life cycle of clinical trials are still paper-based, which adds time and much physical transmission of documents to the process. He reviewed the advantages of integrating the Web, Internet, and intranet technology into the conduct of clinical trials. The problem of exploiting this technology has been solved by the Clinical Research Organizations, which use a process called Remote Data Entry. Dr. Silva reported that the Clinical Informatics Program is collaborating with many components within the NCI and with the cooperative groups and cancer centers to create an enterprise for clinical trials, including developing usable standards that help in simplification. A longer range goal is the capability to provide secure information on a need-to-know basis. Underlying principles for the Clinical Trials Enterprise are that it will be user focused, simple, private, standardized, and of value to the prospective users. Existing infrastructures will be used whenever possible. A public-private partnership is envisioned to develop the national-scale blueprint. Information planning tools will include advanced information technology, developed by DARPA and commercially available products. These will be used in the development of models and architecture standards. The use of common definitions for all components of the clinical trials enterprise will permit the electronic generation of data standards and building blocks that can be used by institutions, cooperative groups, and information system vendors. Plans for 1998 are to build data models and process models for breast and prostate cancer trials, encompassing eligibility information, results, safety, common toxicity criteria, and treatment regimens. In addition, a generic protocol template representing clinical trials will be generated and process models developed to elucidate the flow of information. Pilot sites will be chosen to test the models in the actual clinical trials setting. Dr. Silva reviewed the schedule of products to be completed in 1998-1999, which includes the breast and prostate data models, and electronic building blocks for authoring clinical trial protocols. In addition, a summary record system will be installed in the breast centers at Bethesda Naval Hospital and the NIH Clinical Center and linked to the redesigned PDQ. Dr. Silva concluded with a summary of the initial results from the analysis of 20 adjuvant and advanced breast cancer protocols. More than 500 unique entries were generated by analyzing 20 breast cancer trials in the matrix of eligibility criteria by trial as well as 11 general categories of information and 100 data elements. Current efforts focus on harmonizing those elements and reducing the number.

CTEP INFORMATION MANAGEMENT INITIATIVES

Dr. Michaele Christian



Dr. Michaele Christian, Associate Director, Cancer Therapy Evaluation Program (CTEP), explained that this initiative was driven by the need to develop efficient electronic information systems to manage vast quantities of clinical trials data. Further impetus was provided at the spring meeting of the Cancer Center directors when the need for uniform standards and definitions and compatible systems was articulated. CTEP supports and coordinates clinical trials to evaluate anticancer therapies. This function involves responsibility for disease-oriented treatment development, clinical development of new anticancer treatments, drug distribution, responding to multiple regulatory requirements, and quality assurance. These responsibilities generate much data related to the greater than 200 active Investigational New Drugs (INDs) for new agents, greater than 20,000 patients accrued to NCI-sponsored clinical trials, 50 collaborative research and development agreements (CRADAs) and clinical trials agreements, and greater than 40,000 new drug shipments to 9,000 registered investigators. With this data-intensive program, CTEP reports various types of data such as outcome, summary, demographic, and accrual data from clinical trials. This information is used in drug development and approval, long-range planning, accountability, and many other tasks. CTEP interacts with collaborators, investigators in cooperative groups and cancer centers, grantees, industry, and numerous federal agencies as well as providing information and data to other NCI programs, and the NIH and Congress. Dr. Christian described the inefficiencies of the previous paper-based reporting systems, the problems with incompatible databases within CTEP, across the Institute, and with collaborators, and the need to balance the administrative burden of these medical and scientific objectives.

In 1995, a needs assessment and system analysis was conducted, and working groups were organized to develop implementation approaches to respond to the recommendations. Over the past year, several specific informatics programs were developed, which will simplify reporting, speed up information dissemination, and protect privacy. Data collection efforts have been integrated within the the Institute and with the DHHS and FDA. The process also has included extensive interaction with industry, cancer centers, cooperative groups, and even international participants. All systems developed to date have been translated and coded into the international medical terminology (IMT), which was developed by the International Committee for Harmonization (ICH). Dr. Christian noted that the Clinical Data Update System—an electronic system currently in beta testing—collects outcome and accrual data on Phase II and Phase III trials, conforms to international standards, and provides information for monitoring the progress of clinical trials for annual reports to the FDA. The Adverse Event Reporting System—which also is in beta testing—was developed in collaboration with the FDA, conforms to E2B standards for electronic data submission developed by the ICH, and will be used to meet all required electronic regulatory filing standards. CTEP plans to add a long-range planning committee for informatics initiatives overall. Security measures include a separation of the CTEP Enterprise server from the Internet, secure socket layer encryption, user authentication and validation, forced password changes, and full auditing and logging of transactions. Dr. Christian called attention to the printed schematic of the CTEP Information Management Initiatives listing all projects, approximate times for completion, and project tasks so that people can appreciate where there may be opportunities for interaction. A breast cancer project is in early stages of development with Howard University and direct patient communication models are being considered in that context. In the Clinical Trials Enterprise project, CTEP working with Dr. Silva's office to model the way clinical research is conducted in a cancer center (Georgetown University) and in a cooperative group (Eastern Clinical Oncology Group). The initial model will then be refined through similar iterative processes in other cancer center and groups. These models will be integrated with CTEP and NCI enterprise models as appropriate in a manner which results in more efficient and productive interactions. Another initiative aims

to develop a common minimal dataset for collection in clinical trials by reducing the multiple different data elements now used by different groups working with FDA to a single representation for each element. The plan is to identify those that are important for regulatory purposes and stop collecting those that are not. Dr. Christian's presentation concluded with an online demonstration of the Web-based Clinical Data Update System.

RECENT BREAKTHROUGHS IN IMMUNOLOGY

Dr. James Allison



Dr. James Allison, Director, Cancer Research Laboratory, and Professor of Immunology, University of California at Berkeley, presented a review of progress in basic immunologic research in the last several years and application of new techniques, beginning with a brief history of tumor immunotherapy research. Over the past several years, researchers found that tumor antigens can be detected by T cells in human patients, but the problem has been to promote those T cells to treat tumors. Subsequent research demonstrated that the T cell are not activated when its antigen receptor gets a specific signal from a peptide alone—but a second costimulatory signal is also needed for the T cell to make IL-2 or proliferate. Thus, the research focus has been to identify the elements that provide those costimulatory signals. Dr. Allison and those colleagues found that the molecule CD28 is the main source on the T-cell surface of the receptor for costimulatory signals. The CD28 receptor gets its signal from members of the B7 family, which are found only on the professional antigen-presenting cells (APC), namely dendritic cells, activated macrophages, and activated B and T cells. Dr. Allison described the inefficient process by which the host APC initiates an antitumor response, as T cells are not activated until the tumor cell gets big enough to cause an inflammatory response that is recognized by the professional APCs. The focus of tumor immunology in the last several years has been to accomplish the necessary cross-priming by using gene-modified tumor cells that express B7 itself or GM-CSF, a factor that recruits host APCs and helps them differentiate. Dr. Allison and colleagues showed that if a naive CD8-positive cell gets a costimulatory signal along with an antigen receptor signal it does not need help from a helper T cell to differentiate and become a killer cell. Dr. Allison presented data on several experiments conducted to test the hypothesis that CTLA-4 is a negative regulator of T-cell responses, and that a blockade of CTLA-4 can greatly enhance T cell responses. He presented data that demonstrating that CTLA-4 blockade can lead to the rejection of many types of experimental tumors in mice. In conclusion, Dr. Allison presented data on current studies that are indicating that CTLA-4 blockade appears to be a new approach to tumor immunotherapy by augmenting other immunomodulatory approaches or in combination with conventional surgery and chemotherapy. Dr. Allison noted that his laboratory is poised to begin clinical testing of this approach. He concluded by thanking the NCI for 15 years of support for this basic research.

RECENT BREAKTHROUGHS IN IMMUNOLOGY

Questions and Answers



In discussion, Dr. Allison answered Dr. Sharp's question about the comparison between the stimulatory activity of CTLA-4 and IL-2 by presenting data from other studies. In response to Dr. Bishop's query about potential barriers to initiating clinical testing, Dr. Allison described his laboratory's experience, which was complicated at first by patent issues. After resolution of that problem, other barriers have been financial backing to produce the antibody and forming a consortium of individuals to conduct the trials.

RAPID ACCESS TO INTERVENTIONAL DEVELOPMENT PROGRAM (RAID)

Dr. Robert Wittes



Dr. Wittes referred to Dr. Allison's difficulties in arranging for clinical testing of anti-CTLA-4 as the type of problem the RAID Program seeks to address. The plan is to allocate a substantial

portion of NCI's development resources to the service of academic laboratories doing first-rate basic research but lacking a clear path to the clinic. Dr. Wittes noted that the NCI has been engaged in this activity for some time but this fact has not been widely advertised to the community and is not known to basic biologists. Moreover, the decision-making process in place in the NCI is viewed as hard to use by single investigators seeking assistance, although NCI's track record in supporting such people in selected cases is good. The NCI perceived a need for a higher visibility program intended for the discovery laboratories to take as direct a path to the clinic as the developmental circumstances will permit. Dr. Wittes described the developmental pathway as involving scale-up synthesis according to Good Manufacturing Practices—necessary pharmacology and toxicology studies under quality-assured circumstances and production of clinical grade product for proof-of-principle testing in the clinic. The RAID Program as envisioned will be competitive. Although details have not been worked out, the NCI would probably announce a competition twice a year for exciting discoveries ready to be taken to the clinic; applications would be reviewed for merit by a panel of experts. Dr. Wittes explained that the program is seen as complementary to industry's efforts in this regard by adding value to a product. He cited the taxol experience and the subsequent Cooperative Research and Development Agreements (CRADA) as an example. Based on the availability of funds, the NCI would establish a rank order and substances judged meritorious would enter a development queue wherever appropriate, based on the level of development already achieved by the originating laboratory. The program is intended to be flexible so it can be tailored to the needs of the individual laboratories or clinical groups submitting the products. The NCI sees this experiment as reducing a significant potential barrier, the extent of which will be indicated by the number and quality of applications received.

RAPID ACCESS TO INTERVENTIONAL DEVELOPMENT PROGRAM (RAID) **Questions and Answers**



In discussion, Dr. Li asked Drs. Allison and Folkman what NCI could do to help the process. Dr. Folkman commended the RAID project as very helpful and he concurred that proof-of-principle testing would ease the transition of a product to industry sponsorship. Dr. Allison noted from experience that companies seemed unwilling to get involved because the path to ownership was not clear, but if a product were validated by proof-of-principle testing they would probably take the chance. Dr. Sigal asked about the scope of the program and the available resources. Dr. Wittes replied that the program as described would be scalable. Discussions with SPORE principal investigators evoked enthusiasm for the idea and the advice to advertise the competition and find out what the response will be. To Dr. Sharp's question, Dr. Wittes explained that product development and test management could be done inhouse, through contracts already in place, or through new contracts. Arrangements with companies that involve the transfer of intellectual property would be between the originating laboratory and the companies. Dr. Schein commended the program as one that is needed to translate the large numbers of new discoveries.

DIAGNOSTIC IMAGING INITIATIVES **Dr. Daniel Sullivan**



Dr. Daniel Sullivan, Associate Director, Diagnostic Imaging Program, reported on the Diagnostic Imaging Program, which was formally created within the DCTD in 1996. Organizational components are the Office of Technology and the Imaging Diagnosis, Functional Imaging, and Image-Guided Diagnosis and Therapy Branches. Two recent initiatives of the Program were an RFA for Cooperative Trials in Diagnostic Imaging and the suggested topics, and a Program Announcement for Exploratory or Developmental Grants (R29s) for Diagnostic Cancer Imaging. Because diagnostic imaging is one area of extraordinary opportunity included in the Bypass Budget, the Diagnostic Imaging Working Group was formed to help the Program develop research priorities. Seven task forces will advise on screening and early detection, *in*

vivo molecular imaging development, emerging technologies, longer range technology development, image-guided treatment, training, and the evaluation/approval process. Dr. Sullivan reported that the Diagnostic Imaging Program is working with Drs. Silva and Christian to incorporate Web-based informatics into diagnostic imaging clinical trials. A 14-institution program funded by the NCI to study magnetic resonance imaging (MRI) for breast cancer will begin accruing patients in early 1998 entirely without the use of the telephone system or paper forms. Thus, the two German institutions will be able to enter patients without having to account for time and language differences.

To illustrate the current state of the technology, Dr. Sullivan showed a high-resolution MRI from a breast cancer patient in which very small blood vessels, although not at the capillary level, of the tumor were discernible. He noted that resolution that allows one to find such small structures calls into question the biologic significance of those structures, a possible role for functional imaging. Two technologies that have the potential to provide such information are magnetic resonance spectroscopy (MRS) and positron emission tomography (PET) scanning. Using slides, Dr. Sullivan showed how superimposing an MRI structure image over an MRS scan of prostate cancer could produce information of biologic and clinical significance. Similar information can be obtained by superimposing a PET scan of lung cancer on a computed tomography (CT) scan. Using a videotape featuring MR microscopy images from a guinea pig cochlea, Dr. Sullivan demonstrated image segmentation, the technique of isolating a very tiny structure from multiple images. This technique is used in treatment planning for image-guided surgery. Similar information can be obtained from ultrasound with a decrease in costs. In conclusion, Dr. Sullivan presented a video of the image-guided surgery, which showed the configuration of the operating room of the future and surgical techniques in which radiologists and surgeons work together. MRS information is superimposed on the lesion to guide the surgery. He noted that this surgery, with its keyhole access, has revolutionized brain surgery and could have a similar impact on head and neck and sarcoma surgery in the limbs, as well as on cancers in other sites. Although this type of surgery is expensive, the past history of these technologies has been to miniaturize, integrate, and decrease costs, and this will be one focus of the Diagnostic Imaging Program and Working Group over the next few years.

DIAGNOSTIC IMAGING INITIATIVES

Questions and Answers



In discussion, Dr. Wilson commented that the radiologist of the 21st century will be required to understand basic science and informatics. Dr. Sullivan replied that one task will be to address training and education issues in the area of functional imaging. Dr. Dickersin encouraged future working groups to try to recruit women as leaders.

NEW BUSINESS II

Dr. J. Michael Bishop



CHANGES IN NIH GRANT PROCEDURES

Dr. Marvin Kalt



Dr. Kalt reported that the NIH has decided to end the R29 award and replace it with the standard R01 specially tagged for study sections and the Institutes, so that funding decisions can be based on whether the investigator is a first-time applicant and adjusted accordingly. This change takes effect with the June 1, 1998 receipt date. The existing R29 awards will be allowed to follow their natural course. The NCI intends to use both the AER process and the regular exceptions process to ensure that a pool of new investigators continues to move forward over time. Dr. Kalt called attention to the announcement in the *NIH Guide* of changes to the previously separate rebuttal and appeals process. In the new process, the second level of oversight has been abolished and the one-level process will be called the appeals process. In the

closed sessions, NCAB members will continue to be provided with information on each of the appeals as they are received, complete with the action proposed by staff or recommended for the Board to consider. However, a formal process will be followed where Board members who are assigned a specific area of science to look at also will be provided the rebuttal information as it is received and considered by program staff. Each appeal will be transmitted in the closed session, and materials related to that appeal will have been reviewed by two Board members. The Institute or the Center for Scientific Review will be provided with the outcome, depending on where the grant was reviewed.

REPORT OF THE SUBCOMMITTEE ON CLINICAL INVESTIGATIONS

Dr. Philip Schein



Dr. Schein summarized the contents of the written report of the Subcommittee meeting for full Board consideration. The agenda consisted of three major themes the Subcommittee has been tracking over the past year. The quality and productivity of NCI-sponsored clinical trials was the first item, and the Subcommittee heard a followup presentation from Dr. James Armitage, Chair, CCPRG, on the clinical trials report and a presentation from Dr. Wittes describing the newly constituted implementation committee. The impact of managed care on clinical cancer investigations was the second item, and that discussion focused on the negotiations between an NIH team chaired by Dr. Wittes and Ms. Mary McCabe with the American Association of Health Plans (AAHP) to explore opportunities to work with the NIH and others to participate in clinical research. Discussion of the third item—the plight of the clinical investigator—focused on the NCI proposal to the Committee for Scientific Review to create a new review body with responsibility for the full spectrum of proposals that constitute clinical cancer review. These areas continue to be followed by the Subcommittee.

REPORT OF THE SUBCOMMITTEE ON CLINICAL INVESTIGATIONS

Questions and Answers



In discussion, Dr. Wilson expressed concern that, in reviewing the success rate of clinically related grants, sufficient weight will not be given to the disincentive to apply due to the perception that such grants have little likelihood of being funded. Dr. Kalt pointed out that the NCI appears to have achieved equity among basic and clinical science grants, and with the exceptions weighting program, including AER, the odds are slightly better for patient-oriented research. The success rate increased when the payline was raised to the 20th–30th percentile and maintained, and the success rate for other kinds of mechanisms that clinicians use is considerably higher on average. Dr. Kalt agreed, however, that impression is as important as reality and should be monitored. He pointed out that clinical R01 applications increased in 1997. In response to Dr. Schein's question about specific communication about the exceptions initiatives, Dr. Kalt pointed out that NCI leadership and the BSA attended all major scientific meetings that involve clinicians to communicate these issues and to hear the expressed concerns of the constituency. Dr. Dickersin suggested that this general issue should be pursued in the future to determine whether there are other reasons and that efforts to attract clinical research should be launched on multiple fronts. Dr. Frederick Li raised the issue of the disappearance of protected time for clinicians as academic institutions struggle financially to survive. The report of the President's Cancer Panel on managed care and an article in *JAMA* were cited as further evidence for this. Dr. Klausner agreed with the need to address all facets of the problem.

Motion: There was a motion to approve the minutes of the Subcommittee on Clinical Investigations. The motion was seconded and approved.

REPORT OF THE *AD HOC* WORKING GROUP ON THE INTRAMURAL PROGRAM

Dr. J. Michael Bishop



Dr. Bishop asked that the Board begin to work toward formal closure on whether the Institute's response to the various recommendations has been satisfactory. This will be an agenda item at the February meeting at which time members will be asked to comment on this issue and additional areas needing to be addressed. Because the NCI response to the recommendations related to the Frederick Cancer Research and Development Center is to be presented in May, full closure will be postponed until then.

CRITERIA FOR STANDING COMMITTEES OF THE NCAB
NCAB Members



Dr. Bishop asked for Board discussion to clarify the issue of subcommittee structure. As background, he read the criteria for standing and *ad hoc* subcommittees under which the Board has been operating since 1996. The current standing subcommittees are Special Actions, Planning and Budget (a committee of the whole as appropriate to the issue), Cancer Centers, and Clinical Investigation. He asked for Board suggestions for additional standing committees or any initiatives that would require *ad hoc* subcommittee considerations. In response to a request for clarification of the committee list in the meeting notebooks, Dr. Kalt explained that the list reflects what is included in the operating charter for the NCAB, which is revised in concert with the nomination/appointment cycle. At the next cycle, the NCI will amend the charter to conform to the guidelines developed in 1996 and the current list of committees. Dr. Sigal suggested as issues for discussion: (1) the need for more time at subcommittee meetings, and (2) what should be the purview of these committees. Dr. Wilson asked if a mechanism could be provided for regular reports to the whole Board on progress being made in areas that were in the purview of the Subcommittee on Special Priorities but which do not require regular meetings of a standing subcommittee. Dr. Kalt replied that upcoming agenda items will address this issue as the Board has asked for and will be receiving informative presentations that will give the Board a report card on the aggregate approaches the Institute is taking in those areas. At Dr. Bishop's request, Dr. Wilson agreed to compile a list of areas, based on the experience of the Subcommittee on Special Priorities, where the Board would like to have a regular report.

ADJOURNMENT
Dr. J. Michael Bishop



There being no further business, the 104th meeting of the National Cancer Advisory Board was adjourned at 12:35 p.m. on Wednesday, December 3.

Advisory Home
Funding Opportunities

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