

NATIONAL CANCER ADVISORY BOARD

convened on December 7-8, 1999, at the:
National Institutes of Health
Building 31-C, Conference Room 10
Bethesda, Maryland 20892

ATTENDEES

TABLE OF CONTENTS

- I. Call to Order, Opening Remarks, and Consideration of Minutes of Previous Meeting, Dr. J. Michael Bishop
- II. Future Board Meeting Dates., Dr. J. Michael Bishop
- III. Report of the Director, National Cancer Institute, Dr. Richard Klausner
 1. Questions and Answers
- IV. Legislative Update, Ms. Dorothy Foellmer
 1. Questions and Answers
- V. President's Cancer Panel Report, Dr. Harold Freeman
 1. Questions and Answers
- VI. Office of Management Restructuring, Ms. MaryAnn Guerra, Ms. Christina Bruce
- VII. DHHS Confidentiality of Medical Records Regulations, Ms. Mary McCabe, Dr. Lana Skirbol
 1. Questions and Answers
- VIII. Identification of Molecularly and Clinically Distinct Types of Diffuse Large B-Cell Lymphoma by Gene Expression Profiling, Dr. Louis Staudt
 1. Questions and Answers
- IX. Strategies for Dealing With Large-Scale Gene Expression Data Sets, Dr. Richard Klausner
- X. The New CancerNet, Ms. Susan Hubbard, Ms. Nancy Seybold
- XI. New Ways of Analyzing Specific Clinical Trials Portfolio, Dr. Robert Wittes

- XII. Subcommittee Reports and New Business, Dr. J. Michael Bishop
- XIII. The Geography of Cancer: New Developments
 - 1. Introduction, Dr. Joseph Fraumeni
 - 2. The New Atlas of Cancer Mortality in the United States, Dr. Susan Devesa
 - 3. Interactive Mapping on the World Wide Web, Mr. Dan Grauman
 - 4. Geographic Information Systems, Dr. Linda Pickle
 - 5. Update on the Long Island Breast Cancer Project, Dr. Iris Orams
 - 6. Future Directions, Dr. Barbara Rimer
 - 7. Questions and Answers
- XIV. Policy Updates, Dr. Marvin Kalt
 - 1. DHHS Research Integrity Regulations
 - 2. A110 and FOIA
- XV. Adjournment, Dr. J. Michael Bishop

The National Cancer Advisory Board (NCAB) convened for its 112th regular meeting at 9:00 a.m., December 7, 1999, in Conference Room 6, C Wing, Building 31, National Institutes of Health.

NCAB Members

Dr. J. Michael Bishop (Chairperson)
 Dr. Richard J. Boxer
 Dr. Kay Dickersin
 Dr. Alfred L. Goldson (absent)
 Dr. Elmer E. Huerta
 Dr. Frederick P. Li (absent)
 Dr. Susan M. Love
 The Honorable James E. McGreevey
 Dr. Sandra Millon-Underwood
 Dr. Arthur W. Nienhuis
 Dr. Larry Norton
 Dr. Amelie G. Ramirez
 Dr. Ivor Royston
 Dr. Philip S. Schein
 Dr. Phillip A. Sharp
 Ms. Ellen L. Stovall
 Dr. Vainutis K. Vaitkevicius

President's Cancer Panel

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

Alternate Ex Officio NCAB Members

Dr. Steven K. Akiyama, NIEHS
 Dr. Michael Hodgson, NIOSH (absent)
 Dr. Peter Kirchner, DOE
 Ms. Rachel Levinson, OSTP (absent)
 Dr. Alison Martin
 Dr. Hugh McKinnon, EPA
 Dr. Lakshmi C. Mishra, CPSC (absent)
 Dr. T. G. Patel, DVA (absent)
 Dr. Eugene Schwartz, DOL (absent)
 Dr. B.A. Schwetz, FDA

Members, Executive Committee, National Cancer Institute, NIH

Dr. Richard Klausner, Director, National Cancer Institute
Dr. Alan Rabson, Deputy Director, National Cancer Institute
Ms. MaryAnn Guerra, Deputy Director for Management
Dr. Robert Wittes, Deputy Director for Extramural Science; Director, Division of Cancer Treatment and Diagnosis
Dr. Dinah Singer, Director, Division of Cancer Biology
Dr. Joseph Fraumeni, Director, Division of Cancer Epidemiology and Genetics
Dr. Peter Greenwald, Director, Division of Cancer Prevention
Dr. Marvin Kalt, Director, Division of Extramural Activities
Dr. Edison Liu, Director, Division of Clinical Sciences
Dr. Barbara Rimer, Director, Division of Cancer Control and Population Sciences
Dr. Joseph Harford, Associate Director for Special Projects
Dr. Susan Sieber, Associate Director for Special Projects
Ms. Sandy Koeneman, Executive Secretary, NCI Executive Committee

Liaison Representatives

Dr. John Currie, American Association for Cancer Education, Inc.
Dr. Ronald B. Herberman, Association of American Cancer Institutes
Ms. Barbara Duffy Stewart, Association of American Cancer Institutes
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. Robert W. Frelick, Association of Community Cancer Centers
Ms. Kerrie B. Wilson, American Cancer Society
Dr. John Stevens, American Cancer Society
Dr. Stanley Zinberg, American College of Obstetricians and Gynecologists
Dr. Bernard Levin, American Gastroenterological Association
Dr. Edward P. Gelmann, American Society of Clinical Oncology, Inc.
Dr. Ross Abrams, American Society of Therapeutic Radiology and Oncology
Ms. Nancy Riese Daly, American Society of Therapeutic Radiology and Oncology
Ms. Carolyn Corry, Candlelighters Childhood Cancer Foundation
Dr. Lovell A. Jones, Intercultural Cancer Council
Dr. Armin D. Weinberg, Intercultural Cancer Council
Ms. Katharine R. Boyce, Intercultural Cancer Council
Ms. Martha M. Kendrick, Intercultural Cancer Council
Ms. Jean Ard, Leukemia Society of America
Ms. Carolyn Aldige, National Coalition for Cancer Research
Ms. Dorothy J. Lamont, National Cancer Institute of Canada
Dr. Robert A. Phillips, National Cancer Institute of Canada
Ms. Paula Bowen, NCI Director's Consumer Liaison Group
Dr. Eve I. Barak, National Science Foundation
Ms. Pearl Moore, Oncology Nursing Society
Dr. Marston Linehan, Society of Urologic Oncology

**CALL TO ORDER, OPENING REMARKS, AND CONSIDERATION OF
MINUTES OF PREVIOUS MEETING
DR. J. MICHAEL BISHOP**

Dr. J. Michael Bishop called to order the 112th meeting of the National Cancer Advisory Board (NCAB), and introduced guests representing cancer education and research associations and advocacy organizations. He welcomed members of the public and the press and invited them to submit in writing, within 10 days, any comments regarding items discussed during the meeting. A motion was requested and made to approve the minutes of the September 1999 meeting. They were approved by the Board unanimously.

**FUTURE BOARD MEETING DATES
DR. J. MICHAEL BISHOP**

Dr. Bishop called Board members' attention to the meeting dates listed in the agenda. Dates have been confirmed through 2001.

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

Personnel Changes. Dr. Klausner announced the retirement of Mr. J. Paul Van Nevel from his position as Associate Director, NCI Office of Cancer Communications, to work in the private sector. On behalf of the Board, Dr. Klausner recognized Mr. Van Nevel's skills, hard work, and loyalty to the Institute over several decades, as well as his valuable support in the area of cancer communications. In other changes of import to the NCI, Dr. Klausner reported that the search for a new NIH Director is progressing rapidly, and that Representative John Edward Porter, a strong supporter of the NIH and NCI, has announced that he is stepping down as Chair of the House Appropriations Subcommittee.

NCI Budget Update. Dr. Klausner reported that the FY 2000 appropriations bill for the Departments of Labor, Health and Human Services (DHHS), and Education, which was signed into law the previous week, includes a \$2.3B increase for the NIH. The NCI budget to begin the year is \$3.312B (\$3.332B as appropriated, minus a mandated 0.58% cut to reach a total level of government savings), a 14.42 percent increase providing an additional \$418M in appropriated dollars over FY99 obligations. Dr. Klausner stated that the proposed operating budget includes a payline at the 22nd percentile for investigator-initiated grants funded from the Research Project Grants (RPG) pool. The proposed 2-point decrease from FY99 reflects pressures created by the increase in outyear commitments for Type 5 grants due to the larger number of awards and higher average

cost per grant. Other pressures on the payline include the increase by 19 percent in dollars requested for program project (P01) renewals and the mandated higher pay cap. Dr. Klausner noted, however, that the number of grants funded within the payline will increase with the appropriated dollar increase, and that exceptions funding (through accelerated executive review [AER], supplemental, and bridge funding) will add another 18.4 percent to the RPG pool by year's end. Other provisions in the proposed operating budget were increases in: (1) the new phased innovation awards (R21/R33) to fund technologic development; and (2) RFAs aligned with the Bypass Budget or other major NCI initiatives (from 10 to 12% of RPG dollars for new and competing grants). Total grants expected to be funded in FY99 within the paylines was 1,030, compared with 890 in FY98; total RPG grants active in FY98 was 3,950, compared with the minimum of 4,766 expected in FY99. Dr. Klausner noted that applications have gone up by almost 37 percent since FY98, compared with a 32 percent increase in grant awards over the same period.

Dr. Klausner addressed the issue of how the NCI plans to accommodate the provision for delaying obligation of a portion of appropriated funds until the last day of FY2000, which was included in the Labor, HHS, and Education bill. He reviewed strategies being considered by NCI staff, emphasizing that they will adhere to the principle of not delaying research. Dr. Klausner then reviewed the process by which divisions develop and present their budget requests for new initiatives using a variety of mechanisms, emphasizing that the division process incorporates overall NCI planning processes embodied in the Bypass Budget, which form the basis for prioritization of projects and programs. Divisional allocations in the FY 2000 operating budget as proposed and some of the initiatives linked to extraordinary opportunities or challenge areas of the Bypass Budget are as follows: (1) a 19 percent increase over FY99 obligations for the Division of Cancer Treatment and Diagnosis (DCTD) for clinical trials systems, drug discovery and development, diagnostics, repositories, imaging, and radiation therapy; (2) a 22 percent increase for the Division of Cancer Control and Population Sciences (DCCPS) for initiatives in the areas of behavior, tobacco, health communications, epidemiology, genetics, and surveillance; (3) an 18 percent increase for the Division of Cancer Prevention (DCP) for activities of the Community Clinical Oncology Program (CCOPS) and prevention trials, including early detection, chemoprevention, nutrition, and others; and (4) a 16 percent increase for the Division of Cancer Biology (DCB) to provide competitive and supplemental funding for collaborative research and for supporting the Mouse Models of Human Cancer Consortium and other preclinical models. Dr. Klausner explained that these preliminary figures are subject to an iterative and appeal process, and could change slightly over the year. In addition, the 1.5 percent reserve maintained by the Director is distributed as the year progresses to the RPG pool and various programs.

Dr. Klausner then reviewed projections for specific funding lines: (1) a 12–13 percent increase for Cancer Centers/Special Programs of Research Excellence (SPOREs) reflecting the growth in both the number of centers and size of center budgets, as well as the proposed expansion of the SPOREs; (2) an increase in Training Activities to fund an estimated 1,708 slots under National Research Service Awards (NRSAs), implementation of the 5-year plan for the K series awards (K01 Temin awards, K07 prevention and behavioral sciences awards, K23 patient-oriented mentored career award, K24 mid-career

awards, and K22 patient-oriented prevention research award); and (3) a 6.6 percent increase for the Intramural/RMS/Control Inhouse line, in particular, to support a variety of programs in the Division of Clinical Science (DCS) and to raise funding for the restructured clinical trials program to levels recommended in peer review.

Update on Clinical Trials System Restructuring. Dr. Klausner reminded members that the goal of the restructured clinical trials programs is to create a system that is more open to participation by physicians, patients, and idea generators from the entire research community. He briefly reviewed the components of the new structure and how they will interact. He announced the award of the contract to WESTAT to develop a single administrative component—the Cancer Trials Support Unit (CTSU)—to manage the more integrated and interactive open system, with subcontracts to the Coalition of National Cancer Cooperative Groups and Oracle. Key to the effort of improving and expanding clinical trials is the new open menu for all registered investigators and, eventually, expanded participation of physicians who are not currently part of the NCI system. Also critical to the success of the new clinical trials system are the development of the informatics infrastructure (e.g., the Common Data Elements Program), new cancer communications initiatives (e.g., the newly redesigned CancerNet), development of a simplified informed consent form, and the experiment to institute a centralized institutional review board (IRB).

Dr. Klausner noted that the molecular targets discovery program, a Bypass Budget initiative, ultimately will feed into the clinical trials system. He cited, for example, the drug development and testing system aimed at molecular targets. Discovery components of the system, some of which already are in place or planned for initiation over the next several years, will feed into the Rapid Access for Intervention Program (RAID) for development and early clinical trials for proof-of-principle, then into the clinical trials system for definitive testing of the target-based therapies. To illustrate this molecular targets approach to drug development and testing, Dr. Klausner reviewed data on chronic myelogenous leukemia (CML) research presented by an NCI intramural investigator at a recent meeting of the American Society of Hematology. He presented data supporting the need for new therapeutic approaches to CML, traced the discovery of the chromosomal translocation as the first well-defined chromosomal abnormality in cancer, and presented evidence that the resulting fusion gene product (BCR-ABL) is causative for the development of CML and, therefore, a credentialed molecular target for therapeutic drug development. Dr. Klausner then described research by Dr. Brian Drucker (Oregon) and colleagues that led to the identification of a small molecule—STI571—that is specific for ABL kinase, potent in killing BCR-ABL-expressing cells, orally bioavailable, and associated with good pharmacokinetics in animal studies. A subsequent Phase I clinical trial of this agent confirmed that the drug was well tolerated at increasing doses, and that it mediated significant hematologic responses in patients with CML who were refractory to other therapies. Dr. Klausner reported that meetings have been held with Dr. Drucker and Novartis to develop plans for a multicenter study to test the long-term and survival effects of this promising agent. The study will include types of target assays not included in the Phase I trial. This initiative would be considered for addition to the clinical trials

system restructuring as an accessible model of how to develop and design a human target-based clinical trial.

Special Populations Initiatives. Dr. Klausner reported that the recommendations of the NCAB Subcommittee on Coding will be accepted and implemented by the NCI. The work of the Subcommittee has been presented to the NIH Council of Public Representatives and will be disseminated throughout the NIH. He then gave an update on NCI special populations initiatives designed to address the issues of unequal burden of cancer. To respond to the need for diversity of participation in the cancer research enterprise, total dollars for a variety of training programs will increase by 37 percent: (1) a 38 percent increase for supplements to RPG grants, specifically to support minority researchers and training; (2) a 62 percent increase for minority-directed K01s; (3) expansion of a program entitled, Continuing Umbrella of Research Excellence (CURE), to link high school students to the cancer research enterprise, primarily through supplements to the cancer centers; (4) expansion of the R25 and K12 programs; (5) initiation of a new program entitled, Minority Institution Cancer Center Partnerships (MICCP), to develop strong infrastructural and programmatic training, education, and research linkages between the cancer centers and minority institutions; (6) a 20 percent increase in funding for the Minority Biomedical Research Support (MBRS) program; (7) development of a new program called the Special Populations Networks to create a national infrastructure for cancer control and for linking cancer research and research-based information to minority and underserved communities and to a variety of special populations; and (8) planning for the establishment of a Cancer Control Academy on the NIH campus, which will be associated with the Special Populations Network. Dr. Klausner reported that 30 of the 52 applications received in response to the RFA for the Network have been approved, many with high scores. About eight projects will be funded from the \$30M set aside for this 5-year program, and they will enable the creation of infrastructure in communities not touched before, including Hawaiian, Samoan, Appalachian, Asian-American, Native American, Hispanic, and African-American populations. Because of the excellent response, the dollars have been increased to a more than \$50M commitment, which will fund up to 17 Special Population Network awards.

Dr. Klausner called attention to an editorial entitled "Race and Outcomes: Is this the End of the Beginning for Minority Health Research?" published recently in the *Journal of the National Cancer Institute (JNCI)*. Written by Dr. Otis Brawley, Director, Office of Special Populations Research, NCI, and Dr. Harold Freeman, Chair, President's Cancer Panel, the article is the latest of many articles examining the issue of the outcomes experienced by minorities—when and why they are different. The conclusion of these studies, as articulated in the editorial, was that a body of evidence has already been developed, which suggests that unequal outcomes are the result of unequal treatment, not a consequence of distinct or different diseases. Dr. Klausner announced that, after discussions with Dr. Freeman and presidents of major professional societies, it has been decided that the NCI will convene a "virtual meeting" in January with leadership of the professional societies and providers to jointly design an extensive educational campaign. The campaign will be led and funded by the NCI and will have the goals of promoting awareness of what is already known about unequal treatment and of changing behaviors, even as research continues to specifically address the underlying causes.

Questions and Answers

Dr. Freeman noted the growing body of evidence that shows the existence of real bias on the part of health care professionals that seems to be based on race, however unintentional. He emphasized the need to continue studying the causes, which may go deep into societal influences, and he suggested that the proposed initiative may go a long way toward solving the effect, for example, of the many years of socialization individuals undergo before becoming adults and health care professionals. Dr. Sandra Millon-Underwood emphasized the need to aggressively disseminate information about the training opportunities that will now be available for high school and post-doctoral students in the area of cancer prevention and control. Dr. Richard Boxer noted that the extent of the problem suggests the need for a broader approach, perhaps one involving other Institutes and possibly the American Association of Medical Colleges. Dr. Klausner responded that, because much more data are available on cancer outcomes than some other diseases, it is likely that this initiative will attempt to link the data to NCI's target audiences—providers of cancer care. Information about the initiative will be disseminated to the other Institutes. In response to a comment from Dr. Elmer Huerta, Dr. Klausner acknowledged that the proposed initiative addresses only one aspect of the problem, but noted that the proposed quality care initiative to be conducted within the DHHS has the potential to make an impact across the federal government in addressing the problem of unequal treatment for the un- and underinsured. Dr. Bishop emphasized the importance of reaching practicing physicians, because much of what is taught through medical school curricula (e.g., attitude toward patients) is overridden once the student begins to rely on role models.

LEGISLATIVE UPDATE MS. DOROTHY FOELLMER

Ms. Dorothy Foellmer, Director, Office of Legislation and Congressional Activities (OLCA), reviewed events that occurred during the closing weeks of the first session of the 106th Congress. She presented a summary of the report language accompanying the generous increases included in the FY 2000 appropriations bills in the House and Senate, indicating specific areas of interest of various members and the appropriations subcommittee. She reported that authorizing legislation has been introduced—stand-alone bills, which if enacted would instruct the NIH or NCI on specific areas where additional focus is needed. These areas of congressional interest include: (1) health disparities and the need to elevate the current Office of Minority Health Research to center status; (2) biomedical imaging; (3) the need to create an NIH Center for Social Work Research; and (4) the need to establish an NIH Office of Autoimmune Diseases.

Looking ahead to the second session of the 106th Congress, Ms. Foellmer commented that, in addition to the loss created by the retirement of Mr. Porter from his position as Chair, House Appropriations Subcommittee, the NIH and cancer research will lose another source of strong support with the announcement that Senator Connie Mack will

not seek reelection. Legislative activities for the second session include: (1) the possibility of further legislation to adequately address the issue of confidentiality of medical information perceived as not being met by the proposed DHHS regulations, to follow up on requirements of the Health Insurance Portability and Accountability Act; (2) the introduction of several proposals in the area of managed care reform and patient bills of rights; and (3) the introduction of House and Senate bills in the area of group health plans, one with and one without provisions related to clinical trials access.

In closing, Ms. Foellmer called attention to the State Cancer Legislative Database (SCLD) Update included in the meeting notebooks, and asked Board members to indicate to the OLCA whether they wanted future Legislative Update packets to include a copy of this quarterly publication. The SCLD Update is a product of the SCLD Program, which was recently transferred to the OLCA from the DCCPS; it presents a review of 11 major categories of legislation enacted at the state level.

Questions and Answers

In response to a question about state use of tobacco settlement money, Dr. Robert Croyle, Associate Director for Behavioral Research, DCCPS, noted that the state settlement is being tracked closely by the DHHS Office of the Secretary, Surgeon General's Office, and NIH. Dr. Croyle stated that only 13 states have addressed the issue or taken any action. He described DHHS initiatives being considered to provide information in the areas of cancer prevention and control (particularly, smoking prevention, cessation, treatment, and research) that could be used in state legislative sessions to be held in coming months. Ms. Foellmer added that there are restrictions as to what the federal government can suggest. In response to a question from Mr. James McGreevey, Dr. Fine reported that the NCI re-released an RFA on state and community tobacco control research with the anticipation that \$16M will be allocated per year. The goal of this project is to create a large community intervention tobacco research partnership in which the NCI provides the states linkage to research into best practices and how to evaluate programs for cancer control.

PRESIDENT'S CANCER PANEL REPORT DR. HAROLD FREEMAN

Dr. Harold Freeman, President, North General Hospital, and Chair, President's Cancer Panel, reported that four meetings have been held over the past 6 months as part of the Panel's effort to evaluate the National Cancer Program (NCP). He reminded members that the Panel was created in 1971 by the National Cancer Act with the statutory mission to monitor the development and execution of NCP activities and report annually to the President. The Panel also is mandated to bring to the immediate attention of the President any delays or blockages in the rapid execution of the Program. Dr. Freeman noted that the Panel began to address evaluation of the NCP at the July meeting in Boston, when it focused on the following questions: what was the original concept of the NCP, and how was the program envisioned by its creators? The Panel considered changes in the

environment, health care system, and focus of research over the intervening years as important to the understanding of the status of the program today. Other discussions focused on coordination of the NCP and planning. Two questions framed at the July meeting for further consideration were: (1) how should the scope and purpose of the NCP be framed for the next century, and (2) how and by whom could such a program be implemented? On the basis of findings at the four meetings and the recommendations for improving the NCP's design included in the Subcommittee to Evaluate the National Cancer Program (SENCAP) report, the Panel developed a concept paper. In the draft of the paper, the Panel discusses indicators for change in the national response to the cancer problem, and presents suggestions for revitalizing the national response to cancer as follows: (1) muster the political and public will to address this health care crisis; (2) establish a national mechanism for a concerted national effort; (3) increase public and health professional awareness of the magnitude and components of the problem, and what is already known about prevention, detection, and treatment of cancer; (4) increase the focus on patient outcomes relative to discovery; (5) ensure the stability of the workforce of cancer care givers, researchers, and the academic institutions in which they receive training; and (6) find a means of providing all people with appropriate cancer care (from risk assessment through end-of-life care). The concept paper concluded with a list of overarching and specific questions needing to be addressed to achieve a change of sufficient magnitude to reduce cancer incidence and mortality. Dr. Freeman noted that the final report is being written with the hope that the recommendations contained therein will be productive and will promote a greater understanding of the issue of cancer in America.

Questions and Answers

Ms. Ellen Stovall commented that the distinction between health services research and delivery of care versus health and cancer research should be defined and distilled in communications messages to the public. Dr. Philip Schein noted that the current budget increases will spur much new research and information, but at the same time, resources and infrastructure to translate this information, both in terms of the clinical aspects of the comprehensive NCI program and of delivery into the community, are being diminished (e.g., hospitals being closed, medical schools placed in jeopardy). He noted that Congress needs to recognize translation as part of the continuum and support the entire process.

OFFICE OF MANAGEMENT RESTRUCTURING MS. MARYANN GUERRA, MS. CHRISTINA BRUCE

Ms. MaryAnn Guerra, Deputy Director for Management, NCI, presented an update of the NCI Office of Management (OM) restructuring, undertaken in response to recommendations for administrative reform in the June 1995 Bishop-Calabresi Report. She briefly described the first structure implemented from October 1995 to July 1998, in which the Office of Administrative Management was separated into an Office of Extramural Management and an Office of Intramural Management. Ms. Guerra noted that

the OM was subsequently reorganized to eliminate the disrupted communication between the extra- and intramural programs, redundant functions, confused business processes, and unhealthy competition between administrative units, which were the unanticipated outcomes of the first management experiment. She stated that the realignment was carried out according to principles established to build a management infrastructure that would adapt and respond to change, address customer service requirements, integrate best business practices, reflect functional area responsibilities, and facilitate communication and interaction. In the new OM integrated organization, the Deputy Director for Management position was created to permit application of important business principles across all of the NCI, and the various branches with related functions were aligned to create interactive groups that work together under a unified leadership.

In the Administrative Operations Group, which reports to the Deputy Executive Officer, the Administrative Resource Centers (ARC's) were coupled with the Human Resources Management and Consulting Group to ensure ongoing communication; the novel administrative resource center concept from the previous structure was retained to support divisions, offices, and program staff at the local level; and the position of comprehensive administrator was developed with fully delegated human resource budget and acquisition authority. The Technology Development Commercialization, Grants Administration, Research Contracts, and Frederick Contract Branches were realigned under one leadership as the Business Operations and Development Group. The Information Systems and Computer Services Group was formed to integrate information technology functions under a single leadership.

Ms. Guerra reported that several new offices also were created to respond to specific recommendations in the Bishop-Calabresi Report, including: (1) the Office of Space and Facilities Planning to cope with current space requirements and develop a strategic plan to accommodate future growth as outlined in the Bypass Budget; (2) the Strategic Technical Review and Innovative Initiatives Core (known as the Strike Force) to serve as a resource for NCI staff in identifying and solving administrative problems; and (3) an expanded Office of Management Analysis to include formal evaluation of administrative performance, obtain customer feedback, oversee management controls, and develop NCI policy documents; and (4) the Office of Diversity and Employment Programs (ODEP). Ms. Guerra introduced the newly appointed ODEP Director, Ms. Christina Bruce, to describe the new office.

Ms. Bruce listed the NCI's diversity and employment challenges and noted that the ODEP was created to emphasize commitment to diversity by creating a comprehensive program that brings together and supports innovative recruitment and retention programs, responsive equal employment opportunity (EEO) programs, and quality of work/life (QWL) programs supporting employees at all stages. Ms. Bruce described the organization and staffing of the new ODEP and reviewed the specific programs (both planned and already operational) and accomplishments of the EEO, QWL, and Recruitment components.

Ms. Guerra concluded the update by demonstrating how the thematic threads—partnering, administrative responsiveness, simplification, communication, and evaluation—were woven into the fabric of the NCI community to institutionalize NCI

management principles, activate the organization, and integrate the themes. She described new programs, behaviors, and initiatives that have been implemented in each area and reviewed the management lessons learned from the two experiments in organizational restructuring.

DHHS CONFIDENTIALITY OF MEDICAL RECORDS REGULATIONS MS. MARY MCCABE AND DR. LANA SKIRBOL

Update of NCI Best Practices Models Development. Ms. Mary McCabe, Director, Office of Clinical Research Promotion, presented an update on an NCI initiative that evolved from the NCAB discussion in the spring of the NCI White Paper on confidentiality, data security, and cancer research. Two points in the document that formed the impetus for action were that the research community must make certain that strong state-of-the-art security measures are developed and in place for ensuring the confidentiality of data related to research participants; and (2) that the concerned communities should come together to identify best practices where they exist, identify gaps, and propose new procedures or mechanisms as needed. In the planning for this confidentiality initiative, NCI staff made the decision to include the entire oncology community and address the breadth of cancer clinical research. Working groups were formed to focus on clinical trials, databases and surveillance, epidemiology, genetics, and human specimen resources. A list of elements for best practices models was developed to ensure a comprehensive approach while allowing for debate by the working groups in their specific areas of research. Ms. McCabe briefly reviewed the nine elements that were deemed requirements for uniform and comprehensive practices models. Their development was guided by the principle that although the public benefits from research using identifiable data that are sufficiently important to warrant access by qualified researchers, individuals participating in research have the right to expect that their identifiable data will be kept private and protected from unauthorized use.

Ms. McCabe reported that a preliminary meeting was held in October, during which a small group of researchers, patient advocates, and informatics experts drafted best practices documents to be used in a larger meeting that included representatives of all concerned communities. The second meeting was held the previous week, during which the working groups co-chaired by NCI staff and extramural investigators, about 120 participants in all, reacted to, redefined, added to, and changed the draft best practices documents according to the specific focus areas. Participants at the larger meeting included researchers, patient advocates, informatics experts, ethicists, policy experts, and representatives from professional societies, the pharmaceutical industry, and other federal agencies. Ms. McCabe stated that the final drafts of the best practices models are in process and will be published on the NCI Web Site for comment by participants in the meeting and by NCAB members. On the basis of these comments, a unified document relating to the five specific areas will be developed for delivery to the Institute. Following that, a discussion will take place to develop an implementation plan, NCI's role in such a plan, and resource implications of the models that will have been proposed by the inclusive community. Dr. Klausner added that NCAB members will be provided with updates on the development of best practices models, implementation plans, and

resources needed. In a future meeting, the Board will be asked to consider, for example, whether there are policies that should be adopted for grantees and contractees, whether the models should be informational or regulatory, and whether there are policy implications for the Institute and information that can be shared across the NIH and with other federal agencies.

Ms. McCabe noted that participants in the second meeting had been given the additional task of making comments within their working groups on the DHHS proposed rule "Standards of Privacy for Individually Identifiable Health Information" to capitalize on the opportunity presented by the timing of the meeting. The working groups, with the help of a summary provided by the NIH Office of Science Policy (OSP), were able to consider the draft rule as it relates to research and their comments will be forwarded to the DHHS.

Questions and Answers

In response to a question from Dr. Phillip Sharp, Ms. McCabe noted that the subset of participants at the meetings included representatives only from managed care organizations that collaborate in NCI-sponsored research, because the focus was on research information rather than the entire spectrum of health information. In response to a question from Mr. McGreevey, Dr. Robert Wittes, Deputy Director for Extramural Science, reminded members that the NCI initiative to develop best practices models had nothing directly to do with the timelines for the DHHS rule that were unfolding. He noted, however, that if Congress were interested once again in introducing national privacy legislation, the expertise embodied in the NCI document would likely be taken into consideration. In response to a question from Dr. Sharp, Ms. McCabe stated that the working groups have deliberated on the issue of future use of data and human specimens, and recommendations for a consent process that will allow for future research will be included in the final document.

Update on DHHS Proposed Rule. As background to the update, Dr. Lana Skirboll, Director, OSP, NIH, reminded members that DHHS' authority for developing health privacy regulations was triggered when Congress did not enact comprehensive privacy legislation for health records by August 21, 1999, as mandated in the 1996 Health Insurance Portability and Accountability ACT (HIPAA). The notice of proposed rule making (NPRM) was published in the Federal Register on November 3, with comments due January 3, 2000, and a deadline for promulgation of February 21, 2000. Dr. Skirboll stated that the proposed rule entitled "Standards for Privacy of Individually Identifiable Health Information" was created within the context of HIPAA, which lacked sufficient authority to put a sufficiently protective privacy regulation in place, and that the DHHS believes a comprehensive federal health privacy law is needed. She emphasized the need for the public sector and researchers to engage in discussions with Congress if health privacy legislation is introduced in the future. Dr. Skirboll then reviewed and elaborated on the key points about the proposed rule, key definitions, and frequently asked research-related questions that were included in the background information provided by the

DHHS to inform discussion during the comment period. She briefly reviewed new procedures that will be required of researchers and covered entities (e.g., health care providers, health plans, and health care clearing houses) and changes that would occur if the proposed rule goes into effect as written. In signing the NPRM, the intent was to stimulate the broadest possible discussion across the nation, analyze the impact, and stimulate changes. Dr. Skirboll noted that the DHHS has requested an analysis of the fiscal impact of this regulation on extramural researchers. Dr. Klausner commented on the need to use concrete examples in evaluating the pragmatic implications of the rule. Dr. Skirboll stated that the NIH will develop a composite response to the NPRM, taking into account the planned NCAB discussion and comments received from public entities. She welcomed additional questions for response either by her office or Ms. McCabe's, as well as specific examples of research that would be affected by the proposed rule.

Dr. Schein and Dr. Susan Love were asked to provide initial comment on behalf of the Board. Dr. Sharp commented that the proposed rule appeared to have been provoked more by the perceived threat of a new era (i.e., centralized databases, new informatics programs, electronic communication of data) than an actual problem, raising the question as to whether the proposed rule is an appropriate reaction. The era of genetics and the potential consequences of unwanted disclosure were identified as other issues to be considered. Dr. Schein suggested that the NCI is a stakeholder if there is bad legislation or if there are incidents of disclosure that impact the ability to fulfill its mission; the NCI, therefore, must be engaged in the rule making process and proactive in developing its own best practices. Dr. Love commented on the implications to research of the imminent and potentially widespread use of electronic medical records that can be accessed either by physician or patient. She suggested the need for the NCI to be actively involved in the legislative process, and to work toward combining patient authorization into the informed consent form as a simplification measure. Dr. Peter Kirchner asked for clarification of the IRB's role in classifying information generated during research for release to the patient if patients are given access to their own research information, as proposed in the DHHS rule. Following the discussion, it was decided that NCI's draft response to the NPRM would be distributed to Board members as soon as it is finalized, with a late January deadline for receiving input and comments for incorporation in NCI's official response. The decision as to whether the Board would comment individually or through a subcommittee was postponed until the New Business session on the following day.

**IDENTIFICATION OF MOLECULARLY AND CLINICALLY DISTINCT
TYPES OF
DIFFUSE LARGE B-CELL LYMPHOMA BY GENE EXPRESSION PROFILING
DR. LOUIS STAUDT**

Dr. Louis Staudt, Senior Investigator, Metabolism Branch, DCS, who has been actively involved in the Cancer Genome Anatomy Project (CGAP) and is a recipient of Director's Challenge funding, reviewed research ongoing in his laboratory on new genomic approaches to studying gene expression in cancer cells and the clinical implications of this research. Immediate goals were to look specifically at cancers of the lymphoid system to: (1) address how these cancers relate to normal lymphocyte development and

discern the influence on clinical behavior; (2) gain insights into the pathology of human lymphomas to better understand how these cancers can be treated; (3) define diseases within a disease on the basis of gene expression; and (4) conduct the research in the context of patients who have received standard treatment and for whom clinical records are available to test the validity of the new molecular classifications and their impact on the patient (e.g., response or resistance to treatment).

Dr. Staudt first demonstrated how the technologic tool cDNA microarray analysis of gene expression was applied in this research to define subgroups of cancer patients with related gene expression profiles. He presented the oncologist's view of how B-cells develop, leading to the hypothesis that many of the common non-Hodgkins lymphomas derive in some fashion from a germinal center B lymphocyte or from a cell in a later stage of differentiation. He then described the research stages in his laboratory with collaborators, and across the NCI, to test that hypothesis, including: (1) construction of the normalized cDNA germinal center B-cell library, which was subsequently sequenced deeply as part of the CGAP initiative; (2) creation within the NCI of an informatics platform to analyze germinal center B-cell sequences; and (3) use of cDNA clones from this and other lymphoid cDNA libraries to make a specialized microarray—the lymphochip—devoted to the study of normal and malignant lymphocytes. Dr. Staudt noted that the current version of the lymphochip microarray contains about 18.5 thousand cDNAs, about 3.5 thousand of which are named genes and the rest ESTs from the germinal center library, representing significant growth from the first version of the lymphochip, which contained 6.5 thousand genes. He then demonstrated how experiments are conducted comparing cDNA probes made from clinical samples to a reference RNA sample and to other clinical samples. This methodology was used to systematically analyze gene expression in normal and malignant cells to help in understanding which patterns of gene expression were due to tumor and which to the host response.

Dr. Staudt presented a gene expression map showing their entire data set of 1.8 million measurements of gene expression in samples studied using 126 arrays. This map contained many gene expression signatures (i.e., groups of genes that show coordinate expression having to do with the cells in which they are expressed or the physiological process in which they participate, such as the proliferation cluster signatures) that can be derived from it. He pointed out that hierarchical clustering, which can be accomplished using only the computer, reveals gene expression similarities among malignant lymphocytes in the same diagnostic category, suggesting that the diagnoses made by pathologists can be seen easily through gene expression. Dr. Staudt stated that certain clustering of tumors with normal cells can be instructive; and as examples of this, he used: (1) the proliferation gene expression signature to show that lymphomas vary in their proliferation rate, and (2) the germinal center B-cell signature to show that follicular lymphoma has retained much of the biology of the germinal center B cell. He then described research intended to determine whether: meaningful ways can be found to subdivide one diagnostic category, diffuse large cell lymphoma, on the basis of gene expression. Focusing on the germinal center B-cell signature, these investigators re-analyzed specimens from diffuse large-cell lymphomas and segregated them into two

groups based on the expression of germinal center genes. They were able to show that the two types of lymphomas have a different derivation, seemingly from different stages of B-cell differentiation, and appear to be clinically distinct subtypes of diffuse large-cell lymphoma. Dr. Staudt then described clinical trials conducted in collaboration with the University of Nebraska and Stanford University, that appear to confirm this hypothesis. He noted that application of the international prognostic index (IPI) to the same group of patients suggested that the research described is producing new information in that it appears to be measuring different aspects of the biology of cancer. He stated that a much larger multivariate analysis is needed to prove statistically that gene expression profiles and the IPI are distinct prognostics.

Dr. Staudt listed the following as conclusions to be drawn from lymphochip gene expression profiling of normal and malignant lymphocytes: (1) three groups of diseases—diffuse large-cell, follicular, and chronic lymphocytic lymphoma—can be distinguished using the computer to analyze gene expression; (2) there is considerable heterogeneity in each of the tumors, but the heterogeneity in chronic lymphocytic and follicular lymphomas remains to be dissected; (3) these cancers can be viewed as having separate gene expression signatures that are independently variable and reflect different biological aspects of the tumors; and (4) diffuse large B-cell lymphoma into subgroups that have different clinical behaviors. Future research will focus on molecular signaling pathways and patient response to particular regimens. Dr. Staudt concluded by emphasizing the collaborative nature of this research and naming the collaborators.

Questions and Answers

In the discussion, Dr. Staudt answered questions on the following topics: (1) whether there had been an opportunity to follow progression of a single tumor from therapeutic response to therapeutic resistance; (2) the need to perform gene expression analysis in combination with new clinical trials and new therapies to understand the relationship of signatures to clinical outcomes; (3) whether this technology has been used to find minimum residual disease; (4) how to solve the clinical research enigma created because investigators frequently are not dealing with cancers in untreated states; (5) whether there was any correlation with known cytogenetic abnormalities; and (6) whether malt cell lymphomas and chronic inflammation had been studied.

Dr. Staudt announced that a meeting would be held the next day to plan for extending the use of the new microarray technology to study all non-Hodgkins lymphomas. Invitations have been extended to all clinical researchers around the world who are likely to have clinical data associated with frozen lymphoma samples. An attempt will be made to assimilate all available clinical data for a definitive study of the molecular biology of this one type of cancer. Dr. Klausner added that the initiative will be a model for developing large data sets of clinical information on samples from untreated individuals to begin answering some of the questions raised in the preceding discussion.

**STRATEGIES FOR DEALING WITH LARGE-SCALE GENE EXPRESSION
DATA SETS
DR. RICHARD KLAUSNER**

As background, Dr. Klausner reminded members that the NCI funds many investigators to conduct research similar to Dr. Staudt's in a variety of cancers. Challenges for this type of research include data acquisition and analysis and the potential for sharing data on arrays and clones if similar technologies were being used by the various laboratories. He reported that a project has been started in the context of the Director's Challenge to develop standards to share analytical tools and to establish principles and rules to be used as a community so that data can be optimally analyzed and, ultimately, shared. Dr. Klausner emphasized that the initiative is intended only to develop standards of interoperability and analytical tools that are needed and to provide a forum where data can be compared. Updates on this initiative will be provided to the Board.

**THE NEW CANCERNET
MS. SUSAN HUBBARD, MS. NANCY SEYBOLD**

Ms. Susan Hubbard, Acting Director, Office of Cancer Information, Education and Communication (OCIEC), presented an update on the redesign and launch of the CancerNet Web Site. Extensive in scope, the redesigned CancerNet currently has more than 7,000 static pages; about 1.6 million records that can be created into pages on the fly; 300 peer-reviewed summaries of information on genetics, coping with cancer and cancer treatment, detection, and prevention; 1,800 studies open to accrual, a portion of which are linked to CancerLit; 10,000 closed clinical trials, some also linked to CancerLit; a cancer service provider directory; 300 NCI publications; access to the CancerLit database; a dictionary of cancer terms; and links to more than 100 other cancer-related Web sites. The information summaries and clinical trials are available in two levels of technical detail and are available in some cases in Spanish. Recommendations for the redesign were developed at a requirements analysis meeting held in Chantilly, Virginia.

Ms. Hubbard noted that the challenge in responding to the recommendations were the need to maintain current PDQ, CancerFax, CancerMail, and CancerNet delivery systems; develop the new infrastructure; obtain systematic user input on the logic of the design and ease of use; reorganize the content into a logical and scalable architecture, and integrate content from diverse sources from the Office of Cancer Communications and from the operating divisions; and simplify navigation by users. Principles guiding the redesign were to determine user needs (accomplished through two online surveys); develop simple prototypes for testing by actual users; refine prototypes, retest and deploy the first version; verify usability and user satisfaction; provide multiple paths to the information; make the site flat and broad; and ensure consistent presentation of information throughout the site. Usability was tested by a spectrum of users with varying levels of familiarity with the Web, which resulted in the identification of problem areas, such as the need to eliminate arcane language and switch to text rather than graphic links. Ms. Hubbard noted that usability testing will be an iterative process as new content is added.

Next, Ms. Hubbard presented an online tour of the new CancerNet Web Site and conducted a demonstration colon cancer search, illustrating current features of the search function and plans for future enhancements. She showed how the search function can immediately pull up clinical trials in MedLine form, and noted that it will soon be enhanced to provide hot links from the abstracts of reference publications in CancerNet to the whole article located at the National Library of Medicine's PubMed site.

Continuing the online presentation, Ms. Nancy Seybold, OCIEC, demonstrated features of Cancer Trials, NCI's online magazine, and showed how this site is being realigned to take advantage of enhancements to CancerNet. Work is proceeding on schedule to launch the realigned site within the first quarter of 2000. Some areas of development are additions to the base information with features about vaccine therapy, cancer imaging research, a clinical trials primer, and antiangiogenesis. On the new site, an entire navigational access will be added that will be oriented specifically toward clinical trials information in other NCI Web Sites, to provide easier access. Ms. Seybold concluded by showing how lessons learned in the usability testing of CancerNet have been applied in the Cancer Trials realignment effort.

Ms. Hubbard concluded the CancerNet update with a review of priorities for future enhancements in the order of implementation: (1) develop the infrastructure necessary to support a dynamic Web site; (2) institute a computerized and dynamic authoring system to facilitate the monthly reviews and updates of all peer-reviewed statements in PDQ; (3) develop a universal database (UDB) as a core repository for all information, to permit real-time processing, and to serve as a powerful search and retrieval engine; (4) integrate the CancerNet terminology with the Enterprise-wide Vocabulary, a system being developed in the NCI Office of Informatics; (5) continue to improve internal communication through the E-let system and ListServ; (6) improve communication with users by providing with an update service and ListServ; (7) improve findability by moving to either XML or SGML; and (8) make improvements in searching capability. Specific improvements in the latter include a single-page search form, capability for proximity searching for clinical trials, a link to PubMed, improved indexing and coding for protocols and summaries, open text box capability, smart indexing, and capability for indexing text not on other portions of the NCI and NIH Web Site. Priorities in the area of products and services are a UDB-driven CancerFax, intermediate-level summaries, implementation of ConNCIerge software, development of voice recognition and text-to-speech technology (CancerVoice), and collaborative enhancements with the Clinical Trials Support Unit, Cancer Therapy Evaluation Program, and DCS to provide real-time updates about organizations participating in NCI-supported clinical trials, as well as electronic protocol submissions and processing. In discussion, Dr. Kay Dickersin suggested the need to add epidemiologic information to CancerNet, and Dr. Elmer Huerta advised that future enhancements should provide the capability for animation graphics and sound.

**NEW WAYS OF ANALYZING SPECIFIC CLINICAL TRIALS PORTFOLIO
DR. ROBERT WITTES**

As background, Dr. Wittes noted that clinical investigation is a process of asking the right question in the right setting, and in clinical medicine the relevant setting has traditionally been determined by the state of the patient's disease and state of the patient. Increasingly, patient wishes and target expression are two other considerations that are shaping the way clinicians interested in new therapies think. Other considerations are the shift from the previous emphasis on the empirical process for developing chemical entities to cancer-related science. Dr. Wittes stated that in an attempt to integrate all of these considerations in developing a clinical trials portfolio for specific kinds of cancer, one is confronted immediately with a series of disease settings that are peculiar to each cancer (i.e., a series of clinical states). Innovative matters to address include: (1) issues connected with each disease, (2) obstacles faced, (3) tools needed, (4) molecular targets available, (5) important questions, and (6) other clinical trials already in progress. Dr. Wittes used the example of prostate cancer to illustrate the complexities of designing innovative clinical trials around the joint issues of clinical states on one hand, and targets on the other. He suggested, therefore, that the goal in clinical trials portfolios might be to describe disease-related research opportunities and the protocols that stem from them, in terms of the clinical states in which patients find themselves. This is a medically meaningful approach, and one that is comprehensible to patients and their families. The process could easily be extended to prevention interventions. In the early trial setting, work with new chemical entities would increasingly map to the targets they are intended to intersect; the two descriptions are complementary and eventually converge in the later stages of clinical testing when the intended targets and treatment intentions blend and become the same goal. Dr. Wittes noted that this issue will have an impact on the development of the next generation search engine for the UDB and on planning for ways to exhibit the information. Dr. Klausner emphasized the importance of this issue, made difficult by the implications of changing eligibility criteria and changes in the way prioritization of trials and targets are considered. Ms. Hubbard expressed the view that the state-of-the-art statements on CancerNet and PDQ should be rewritten to reflect clinical questions. Dr. Dickersin suggested that the resources provided by the Cochrane Collaboration should be used. In response to another question, Dr. Wittes promised diligence in attempting to identify gaps in the portfolio and fill them.

SUBCOMMITTEE REPORTS AND NEW BUSINESS

DR. J. MICHAEL BISHOP

Dr. Bishop stated that because of the unexpected absence of Dr. Frederick Li, the report of the Subcommittee on Coding, and a discussion of coding of grants to reflect minority inclusion in the NCI research portfolio, would be deferred until the next meeting. Dr. Dickersin suggested an update on the tamoxifen prevention trial and modeling for the use of tamoxifen in the prevention setting, including a clarification of the intended population as a future agenda item. Members were asked to notify Dr. Kalt if they were interested in serving on the NCAB Subcommittee on Communications.

THE GEOGRAPHY OF CANCER: NEW DEVELOPMENTS
DR. JOSEPH FRAUMENI, DR. SUSAN DEVESA, MR. DAN GRAUMAN,
DR. LINDA PICKLE, DR. IRIS OBRAMS AND DR. BARBARA RIMER

Introduction. Dr. Joseph Fraumeni, Director, Division of Cancer Epidemiology and Genetics (DCEG), presented background information on how NCI's epidemiologic mapping of cancer mortality in the United States has evolved over the years. He noted that, in the 1970s, when there was striking international variation in cancer occurrence and changes in risk among migrant populations, U.S. geographic patterns were largely unremarkable when analyzed by state or region. The decision was made to adopt a more systematic approach using a county-based cancer mortality system, to help detect clustering of the more common tumors. Dr. Fraumeni reviewed the NCI strategy for the geographic studies. The first phase comprised a series of computer-generated color-coded atlases presenting White and non-White mortality rates during the period from 1950 to 1969, an atlas for non-neoplastic diseases, and two atlases that updated the cancer maps through 1980. The second phase involved a series of correlational studies that characterized site-specific cancer patterns in more detail and related them to environmental and demographic data available at the county level. In the third phase, the NCI has collaborated with other research groups in a number of field studies in various parts of the country with high-risk populations, using a case-control approach to identify exposures that might account for the elevated rates. Dr. Fraumeni then gave examples of epidemiologic data that were derived in all phases and showed how the findings prompted: (1) new regulations from the Occupational Safety and Health Administration (OSHA) for workplace exposures to inorganic arsenic; (2) case-control studies that revealed a carcinogenic effect from community as well as occupational exposure to arsenic; (3) congressional hearings, legislation, and public health measures to alert the public to the danger of smokeless tobacco; and (4) case-control studies that uncovered the effects of shipyard exposure to asbestos, particularly during World War II, on the high rates of lung cancer in coastal counties in the southeastern United States.

The New Atlas of Cancer Mortality in the United States. Dr. Susan Devesa, Chief, Descriptive Studies Section, Biostatistics Branch, DCEG, unveiled the new *Atlas of Cancer Mortality in the United States, 1950-1994*. Included in the atlas are more than 250 maps showing variation in cancer rates during 1970 to 1994, and comparisons with corresponding maps from 1950 to 1969; summary tables and figures; accompanying text to describe observed variations for specific cancers and suggest explanations on the basis of known risk factors. Dr. Devesa acknowledged the contributions of coauthors and collaborators in all phases of production and summarized the methods used to calculate mortality data, rank by magnitude and partition the data into ten categories, and color code the information for presentation. Currently, mortality rates are calculated per 100,000 person years and age-standardized to the 1970 U.S. population. Dr. Devesa then showed maps of lung, breast, prostate, cervical, and bladder cancers to illustrate the types of information that can be extracted from the atlas. In some maps, data are calculated according to state economic areas (SEAs)—individual counties or groups of counties that are relatively homogeneous with respect to various demographic, economic, and cultural factors—to highlight regional variations as compared to the more localized variations that

are seen at the county level. Dr. Devesa presented data for bladder cancer in men and women for the early and later time periods that showed elevated rates for bladder cancer among men and women in northern New England. The unusual patterns observed in these maps are regarded as a special research opportunity, and a study has been launched by the NCI in conjunction with the state health departments and academic centers to identify reasons for the patterns.

In summary, Dr. Devesa noted that for the recent time period, the geographic variations in mortality for several cancers are similar to the patterns previously observed and reflect lifestyle and other environmental factors, medical care systems, reporting practices, and other variables depending on the tumor type. The most striking difference over time is seen for lung cancer, the patterns of which track the variations in smoking habits across the country. Dr. Devesa stated that the patterns depicted in the new atlas should provide further clues to areas of the country where epidemiologic studies and cancer control interventions may be warranted.

In discussion, Dr. Freeman asked whether socioeconomic factors could be isolated from race, and what race as a variable means in the atlas. Dr. Devesa responded that future studies can look at correlations with socioeconomic status, which would come from census information. She added that race and gender are used in the atlas as markers of lifestyle, cultural, and occupational exposures, providing opportunities for additional studies to better understand the geographic patterns.

Interactive Mapping on the World Wide Web. Mr. Dan Grauman, Computer Specialist, DCEG, discussed benefits to be derived from publishing the NCI Atlas on the World Wide Web (WWW), costs to date, characteristics of the two Web sites (Atlas On-line and Custom Maps), and future plans. Mr. Grauman cited as benefits the fact that the sites are easy to modify and access, make results and data available, have linking and download capabilities, facilitate presentations, are computer-independent, and are adaptable to many applications. Cost for the two Web sites, including enhancements scheduled for February release, was \$136,000, about \$100,000 of which came from the Information Technology Innovation Fund. Mr. Grauman described the two Web sites as extensions of the Atlas, offering information for the general public, opportunities for research, and tools for educators. Main features are the Atlas text with hyperlinks to more than 460 maps, tables, figures, and graphs. Users can download all of the above and the data and boundary files used to generate the Atlas maps. Mr. Grauman demonstrated the main features of Atlas On-line, highlighting: (1) the home page, which links to user options and to the Custom Maps Web Site; (2) table of contents, consisting of a group of direct links to tables, figures, and maps; (3) direct links to user options; and (4) download capabilities.

Next, Mr. Grauman demonstrated the main features and highlights of Custom Maps, which he described as a dynamic Web site. With this tool, users can control map parameters (number and type of ranges, ranging method, map colors), create thousands of maps, zoom and pan, and view a single geographic region. Mr. Grauman presented an online demonstration highlighting each of these features, using lung, cervical, and breast cancers as examples—the first to illustrate a cancer where mortality has risen

dramatically, the second to show a cancer with decreasing mortality, and the third, one with little change over the early and late time periods. He then reported on enhancements planned for launching within the year: (1) rate calculation program on the Web site; (2) ability to download calculated data; (3) capability for looking at the data behind the maps for a particular entity; (4) multiple maps and time trends with animation; and (5) ability to create multiple maps ranging across time periods to show trends. Projects being considered for the more distant future include adding noncancer mortality rates, other ranging methods, more statistical techniques, and layered maps, the latter to include data such as environmental and industrial exposure.

In response to a question from Dr. Bishop, Mr. Grauman explained that Atlas On-Line and Custom Maps are intended primarily for researchers who wish to analyze the data in a different way; however, the mortality data come from the National Center for Health Statistics (NCHS) and are in the public domain. Dr. Millon-Underwood asked if pediatric data would be separated from that for adults, and was informed that the rate-calculating program to be launched in February would provide the capability for choosing age categories, combining sexes, and using the data to create maps on the fly.

Geographic Information Systems. Dr. Linda Pickle, Mathematical Statistician, Surveillance Research Program, DCCPS, continued the presentation on the geography of cancer developments by showing how data underlying maps like those in the new *Atlas of Cancer Mortality in the United States, 1950-1994* can be used to build a more complex geographic information system (GIS). As background, she explained that a GIS is a computer system that displays a collection of layers of information, each of which has data specific to certain geographic locations. In the public health setting, this capability permits researchers to examine the association between locations of individual cases or high rates of cancer or any other disease and exposures (e.g., environmental and lifestyle) that might have caused the disease. Dr. Pickle reviewed the NCI's long history of producing cancer atlases, which launched the entire field of medical geography and noted that early mortality atlases led to significant advances in understanding the geographic differences of cancer rates in the United States. She showed oral cancer and lung cancer mortality maps from the early *Atlas of Cancer Mortality for U.S. Counties, 1950-1969* to illustrate two primary uses of mortality atlases: (1) to identify specific locations where changes in health policy need to be made or prevention programs started; and (2) to explore more general patterns or geographic patterns in the mortality data to generate etiologic hypotheses, which can be further refined and tested in field studies. The oral cancer maps resulted in policy changes with regard to the sale of smokeless tobacco to minors, and the maps on lung cancer, together with personal knowledge about the high mortality areas, led to the generation of hypotheses that helped focus subsequent studies. Dr. Pickle noted that the GIS now permits a more systematic and efficient approach to etiologic research. She pointed out, however, that the early mortality maps point to areas where an epidemiologist could find sufficient numbers of cases to study but the design does not permit easy exploration of the data. She described how an interdisciplinary working group at the NCHS approached the task of designing a general mortality atlas and arrived at solutions to the problems of basic map style, legend design, color choices, classification of rates into color categories, and indication of unreliable rates. Dr. Pickle

then demonstrated how to build from the basic design a more complex multilayered GIS map, using an HIV mortality map as the base and adding layers of factors (e.g., locations of cities, population clusters) that might help explain the patterns. The example illustrated that patterns in data can be easily explored within the limits of available data. Applications of GIS in public health include hypothesis generation to compare patterns of disease and exposure, as an aid to statistical analysis of geographic patterns, for estimating potential exposures, for surveillance, and for prevention, screening, and treatment. Problems to be addressed before the tools can be utilized to the full extent relate to the confidentiality of case locations and medical information, identifying suitable data for all geographic units, validating available data, and producing small-area data estimates from large-area surveys. In addition, analytical tools need to be added to GIS software for identifying spatial and temporal correlations and trends, automating cluster identification, and validating "hot spots." Work is also needed to extend research on map data visualization to multiple layer GISs of interactive or Web-based systems. Dr. Pickle concluded by predicting that the future of GIS could include better data (e.g., historic exposure information), three-dimensional visualizations, and the ability to take a virtual tour of GIS data.

Update on the Long Island Breast Cancer Project. Dr. Iris Obrams, Associate Director, Epidemiology and Genetics Research Program, DCCPS, stated that the Long Island Breast Cancer Study Project (LIBCSP) was created as a multistudy effort to investigate the causes for the increased rates of breast cancer in the northeastern United States, particularly to emphasize environmental factors. She noted that the project, which has been integrated as part of NIH's overall research into breast cancer, was mandated in 1993 by Public Law 103-43, consists of 10 research studies, and includes a GIS. Its objectives are to develop an effective tool for investigating environmental factors that may contribute to breast cancer and to help share health-related environmental information with the community. Dr. Obrams noted that the GIS for health applications is seen as a model; therefore, staff have worked extensively with advisors and with the community in developing plans and will be working with oversight committees as the GIS progresses. The GIS data layers will include geospatial base maps, demographic data, cancer registry and medical data (e.g., health care facilities), and environmental data (i.e., federal, state, and county data sets, data on land use, hazardous materials, pesticides, chemicals, chemicals, air and water monitoring results, weather and climate information). Dr. Obrams gave an example of the kinds of analyses that could be performed with the GIS, which could lead to further research in a particular area. Data from multiple sources will be linked to account for individual risk factors, for example, looking at environmental data as a possible risk. Important issues are that: (1) data are imperfect; (2) the eye is not a good analytical tool in terms of rate interpretation; and (3) confidentiality aspects require establishing key levels of access. Dr. Obrams discussed strategies for obtaining community input, including a Web site for information dissemination about data in the GIS, town meetings to obtain leads from the community, with an eye to evaluating the completeness of available data that is put into the GIS. Dr. Obrams concluded with a video showing mass media coverage of the town meetings.

Future Directions. Dr. Barbara Rimer, Director, DCCPS, noted that because of the cancer registration system in the United States, cancer is an ideal topic for the use of

GISs and that cross-divisional collaboration is critical to GIS research, both to develop priorities and then to undertake them. She stated that the NCI research agenda is designed to overcome some of the deficiencies, build better GISs, and then use them to understand cancer in the United States. Specific goals are to encourage the development of GIS methodology; foster appropriate use of GIS for epidemiologic behavioral and cancer surveillance research; and facilitate integration of appropriate types and levels of data in program planning, implementation, and evaluation. Intramural and extramural researchers will be encouraged to pursue the following topics: (1) correlate area specific data and generate hypotheses using etiologic and prognostic factors; (2) incorporate area specific cancer incidence and survival data and examine trends within population registries; (3) examine interrelationships of ethnicity, socioeconomic status, lifestyle practices, environmental exposures, and health care delivery systems that contributed to geographic variation in cancer; and (4) refine targets of intervention geographically and for population characteristics. She noted that the GIS data may provide methods for examining the interrelationships between health behaviors and cancer incidence, mortality, and treatment patterns in specific geographic areas and will monitor intervention and emerging trends in those areas. As an example, Dr. Rimer discussed a recent NCI study on trends in mammography, and with a GIS, behavioral and environmental data can be collected and examined as part of future studies. Different software packages can be developed for GIS that will enhance and increase its usefulness. She added that confidentiality will be an issue as smaller and smaller areas are studied.

Questions and Answers

During the discussion that followed, Dr. Fraumeni noted that the data are designed to provide clues to etiologic and prognostic factors and clarify patterns of mortality that may include informative medical care delivery and screening programs. Discussion followed on linking to SEER data and other data gathered by the National Center for Health Statistics (NCHS) earlier.

POLICY UPDATES DR. MARVIN KALT

DHHS Research Integrity Regulations. Dr. Kalt informed the Board that DHHS is reorganizing its research integrity and research misconduct process, and the Office of Science and Technology Policy is taking the lead. The Office of Research Integrity's role will be primarily educational and will ensure that appropriate research integrity processes are available to the research community. Institutes will conduct their own investigations and the inquiry process will be separate from the investigative process. This will create a third party entity for research integrity inquires and for institutions too small for an objective process. He noted that comments from Board members must be received by December 12.

A110 and FOIA. Dr. Kalt stated that final regulations were issued, and DHHS and the NIH will issue information on this that will impact awardees. He noted that the final regulation stated that any published data gathered through any level of federal funding cited in support of a federal regulation qualifies as accessible under the FOIA, but only

data collected following the issuance of the regulation is covered. All requests for information will be submitted to the NIH Institutes, rather than the principal investigator or an awardee institute. The institute will assist the awardee organization with the response and the final communication will be from the NIH. A report will be submitted to the Board when a sufficient number of requests have been received and responses developed.

ADJOURNMENT

Dr. J. Michael Bishop

There being no further business, the 112th meeting of the National Cancer Advisory Board was adjourned at 12:03 p.m. on Wednesday, December 8, 1999.