DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL CANCER INSTITUTE
123rd NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
September 9–10, 2002

Building 31C, Conference Room 10
National Institutes of Health
Bethesda, Maryland

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BETHESDA, MARYLAND
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The National Cancer Advisory Board (NCAB) convened for its 123rd regular meeting on Monday, September 9, 2002, in Conference Room 10 of Building 31, National Institutes of Health (NIH), Bethesda, MD. The meeting was open to the public on Monday, September 9, 2002, from 8:30 a.m. to 3:50 p.m. The meeting was closed to the public from 4:05 p.m. until adjournment at 6:00 p.m. The meeting was reopened to the public on Tuesday, September 10, 2002, at 8:45 a.m. until adjournment at 12:30 p.m. NCAB Chair Dr. John E. Niederhuber, Director, University of Wisconsin Comprehensive Cancer Center and Assistant Dean for Oncology, University of Wisconsin School of Medicine, presided during both the open and closed sessions.

NCAB Members

Dr. John E. Niederhuber (Chairperson)
Dr. Samir Abu-Ghazaleh
Dr. James Armitage
Dr. Moon Shao-Chuang Chen
Dr. Kenneth H. Cowan
Dr. Jean B. deKernion
Mr. Stephen Duffy
Dr. Ralph Freedman
Dr. Elmer E. Huerta
Dr. Susan M. Love
Dr. Larry Norton
Ms. Marlys Popma
Dr. Amelie Ramirez
Ms. Lydia Gonzalez Ryan

President's Cancer Panel

Dr. LeSalle Leffall

Alternate Ex Officio NCAB Members

Dr. Steven K. Akiyama, NIEHS
Dr. Hugh McKinnon, EPA
Dr. Peter Kirchner, DOE
Dr. Richard Pazdur, FDA
Dr. John M. Powers, DOD, OASD, HA
Ms. Raye-Ann Dorn, VA

Members, Executive Committee, National Cancer Institute, NIH

Dr. J. Carl Barrett, Director, Center for Cancer Research
Dr. Joseph Fraumeni, Director, Division of Cancer Epidemiology and Genetics
Dr. Peter Greenwald, Director, Division of Cancer Prevention
Dr. Joseph Harford, Associate Director for Special Projects
Dr. Marvin Kalt, Director, Division of Extramural Activities
Dr. Alan Rabson, Deputy Director, National Cancer Institute
Dr. Barbara Rimer, Director, Division of Cancer Control and Population Sciences
Dr. Dinah Singer, Director, Division of Cancer Biology

Liaison Representatives

Dr. Eve Barak, National Science Foundation
Dr. Margaret Foti, American Association for Cancer Research
Dr. Robert W. Frelick, Association of Community Cancer Centers
Dr. Edward P. Gelmann, American Society of Clinical Oncology, Inc.
Ms. Ruth Hoffman, Candlelighters Childhood Cancer Foundation
Mr. Neil Hoffman, National Science Foundation
Ms. Judy Lundgren, Oncology Nursing Society
Ms. Nancy O'Reilly, The American College of Obstetricians and Gynecologists
Ms. Nancy Riese Daly, American Society of Therapeutic Radiology and Oncology
Ms. Kristin Simonson, American Society of Therapeutic Radiology and Oncology
Ms. Barbara Stewart, Association of American Cancer Institutes
Ms. Julie Taylor, American Society of Clinical Oncology
Ms. Pamela Wilcox, American College of Radiology

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DAY ONE—MONDAY, SEPTEMBER 9, 2002

I. INTRODUCTION—DR. ANDREW von ESCHENBACH

Dr. Andrew von Eschenbach, Director, National Cancer Institute (NCI), opened the meeting by asking the Board and others in attendance to observe a moment of silence in memory of victims of the events of September 11, 2001. He then welcomed the new members of the NCAB: Dr. John Niederhuber, the newly appointed Chair of the NCAB; Dr. Moon Chen, Associate Director for Cancer Prevention and Control at the University of California–Davis Cancer Center in Sacramento; Dr. Kenneth Cowan, Director of the University of Nebraska's Eppley Cancer Center; Dr. Jean deKernion, Chair of the Department of Urology at the UCLA School of Medicine; Ms. Marlys Popma, Executive Director of the Republican Party of Iowa and a breast cancer survivor; Ms. Lydia Gonzales Ryan, Clinical Director for Hematology, Oncology, and Stem Cell Transplantation at Children's Health of Atlanta; and Dr. Franklin Prendergast, Director of the Mayo Clinic Comprehensive Cancer Center.

Dr. von Eschenbach also announced the appointment of two new members to the President's Cancer Panel (PCP): Dr. LaSalle D. Leffall, Jr., a surgeon, oncologist, and medical educator at the Howard University College of Medicine in Washington, DC, who will serve as Chair of the PCP; and Mr. Lance Armstrong, professional cyclist and cancer survivor. Dr. Harold Freeman, President of North General Hospital in New York City, who has served as PCP Chair since 1991, will serve the remainder of his appointed term as a member of the Panel.

II. WELCOME AND ACCEPTANCE OF MINUTES—DR. JOHN E. NIEDERHUBER

Dr. Niederhuber welcomed Board members; representatives of liaison organizations; Dr. Leffall; Dr. Marvin Kalt, Director, Division of Extramural Activities, and Executive Secretary, NCAB; other NCI staff; and members of the public. He invited the public to submit to Dr. Kalt, in writing and within 10 days, comments regarding items discussed during the meeting. He also reviewed the confidentiality and conflict-of-interest practices required of Board members in their deliberations.

A motion was requested and made to approve the minutes of the June 2002 NCAB Meeting. The motion was seconded, and the minutes were unanimously approved by the Board.

III. APPROVAL OF FUTURE MEETING DATES THROUGH 2004—DR. JOHN E. NIEDERHUBER

Dr. Niederhuber called Board members' attention to future meeting dates listed in the Agenda. Dates have been confirmed through 2004.

IV. NCI DIRECTOR'S REPORT—DR. ANDREW von ESCHENBACH

Dr. von Eschenbach stated that, as Director of the NCI, he intends to emphasize three themes: (1) everything the Institute does must be patient-centered; (2) the Institute has an important leadership role to play within the National Cancer Program, which requires full participation of a broad and complex array of organizations and institutions; and (3) this leadership role underscores the importance of collaboration and partnerships. He added that the recently appointed NIH Director, Dr. Elias Zerhouni, also emphasizes the role of the patient and the communities served by the NIH, as well as the role of partnerships.

As an example of partnerships and trans-NIH initiatives enhanced by this approach, Dr. von Eschenbach described efforts to expand NCI research facilities in Frederick, Maryland. Recent discussions have led to plans for a programmatic partnership among the NCI, the Army, and the National Institute of Allergy and Infectious Diseases (NIAID) to create in Frederick, through expansion and rehabilitation of existing resources, a state-of-the-art facility for advanced biomedical and biotechnology research.

Dr. von Eschenbach reported that Dr. Eric Lander, Director of the Whitehead Center for Genome Research, has agreed to act as a Special Advisor to the NCI Director in creating a series of focus groups within the extramural research community to look at the agenda for basic research going forward to 2015. These groups will identify important research opportunities and gaps in knowledge. Dr. von Eschenbach also acknowledged the efforts of Dr. Anna Barker, who has been working as a consultant to the NCI in creating strategies and forging partnerships to accelerate the process of drug development. To examine issues related to translational research, Dr. von Eschenbach continued, Drs. Joseph Simone and Arthur Nienhuis are chairing a series of meetings of a Working Group on Cancer Centers and Specialized Programs of Research Excellence (SPOREs). The Working Group is investigating ways to encourage greater integration and interaction of these two programs, partly because most SPOREs have been established within Cancer Centers. The Working Group is also exploring strategies to promote the interface of the two programs with the greater cancer-related community. Dr. von Eschenbach said he would report to the NCAB on the recommendations of the Working Group at a future meeting.

Dr. von Eschenbach reported that the process of recruiting a new Director for the Division of Cancer Treatment and Diagnosis (DCTD) is nearing completion; he also announced the decision of Dr. Barbara Rimer, Director of the Division of Cancer Control and Population Sciences (DCCPS) to leave the NCI at the end of the year for a position at the University of North Carolina. He said that he hoped to be able to report on progress in filling these positions, as well as recruitment efforts underway in the Office of Communications (OC), at the next NCAB meeting.

Dr. von Eschenbach provided updates on several new partnership initiatives. A collaborative effort with five pharmaceutical companies, the Friends of Cancer Research, the NIH Foundation, and the Association of American Cancer Institutes is focusing on overcoming barriers to early-phase clinical trials. A partnership with the Avon Foundation will soon begin funding grants designed to help close the gap between discovery and delivery with regard to breast cancer, with an emphasis on minority and underserved populations. The National Lung Cancer Screening Trial, which is soon to be launched, has been modified by adding more sites in the American College of Radiology Imaging Network (ACRIN) component to complement the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) sites; there will now be a total of 30 sites across the country. Quality control and coordination issues have been resolved so that there will be uniformity across all study sties.

The NIH, Dr. von Eschenbach reported, will soon convene a major workshop or conference to address issues related to the cessation of the combined therapy arm of the Women's Health Initiative's hormone replacement study. The NCI will play an important role in that meeting. He reminded the Board that Tuesday's NCAB meeting agenda would include a group of presentations concerning hormonal influences on breast cancer. He added that the NCI is involved in the planning of a future scientific meeting that will examine the relationship among breast cancer, hormonal alterations, and reproductive history.

Dr. von Eschenbach announced personnel changes as part of the process of reorganizing the Office of the Director (OD). Dorothy Foellmer, formerly of the Office of Policy Analysis and Response, has assumed responsibility for coordination and integration within the OD. Nora Winfrey has taken on the role of the Director's Executive Assistant. Two special assistants—Susan Persons and Kathleen Schlom—are helping Dr. von Eschenbach deal with external and internal issues, respectively,

Dr. von Eschenbach congratulated Mary McCabe for her ongoing efforts in restructuring the OC. He also announced that the NCI Web site, cancer.gov, has been selected as the 2002–2003 winner of the Golden Web Award by the International Association of Webmasters and Designers.

Budget Update

Dr. von Eschenbach stated that the Board would be provided at its next meeting with a full report on the closeout of the FY2002 budget. The Senate has recommended an FY2003 budget for the NCI of $4.642B, which is close to the amount requested in the President's budget. The House of Representatives will soon prepare its own appropriation bill. There is a good chance, Dr. von Eschenbach added, that a continuing resolution will be passed to continue funding at current levels into the new fiscal year until new appropriations are approved.

The NCI staff, Dr. von Eschenbach explained, is using several modeling exercises to describe the various potential scenarios for the 2003 and 2004 budgets and their implications for current commitments; preliminary discussions have focused on the likelihood that the entire NIH budget will level off with the FY2004 budget. Dr. von Eschenbach explained that several principles are being incorporated into these models: The NCI is committed to supporting Research Project Grants (the RPG mechanism), particularly for new investigators. Some models predict a 6 percent increase in grant applications, while other estimates are as high as 11 percent; this will place significant pressure on the ability to maintain the same payline as in recent years. The NCI, Dr. von Eschenbach said, will continue to do everything possible to protect its ability to fund these grants, and it is working hard to leverage its resources through partnerships and collaborations to support its other commitments and initiatives.

Questions and Answers

Dr. Larry Norton, Director, Medical Breast Oncology, Evelyn H. Lauder Breast Center, Memorial Sloan-Kettering Cancer Center, asked whether the large increase in new grant applications is common across the NIH. Dr. von Eschenbach replied that the increases are higher for the NCI than for other Institutes. He suggested that the availability of support from the Department of Defense and other organizations, both public and private, has contributed to the growth of the pool of qualified applicants. He added that the NCI is working with other Institutes to develop a pilot project for stimulating creativity within the R01 mechanism, perhaps involving a different review process.

Dr. deKernion asked whether strategies are in place to deal with the discrepancy between numbers of applications and available funds. Dr. von Eschenbach explained that the modeling being performed by the NCI is designed to produce such a strategy. He suggested that one approach might be to find ways of cost sharing or cofunding to spread resources more widely to cover a larger number of investigators, even if this means funding at slightly lower levels.

Dr. Ralph Freedman, Professor, Department of Gynecologic Oncology, M.D. Anderson Cancer Center, asked for more information on the role of the private sector in sharing the cost of the National

Lung Cancer Screening Trial. Dr. von Eschenbach expressed the NCI's gratitude to the American Cancer Society (ACS), which has committed to contributing $1M per year for 5 years. The ACS is also mobilizing its network of volunteers to enhance the recruitment, education, and information dissemination components of the trial. Rapid accrual will likely result in significant cost savings, and assistance with dissemination will help save lives. Dr. von Eschenbach added that negotiations are underway with other groups, including the Legacy Foundation, to provide similar support.

Dr. Niederhuber asked whether developing plans for the Frederick facility might result in bringing additional financial and human resources to the NCI. Dr. von Eschenbach said that although this endeavor is still early in the planning process, the NCI is maintaining a broad vision of the opportunity for collaboration to enhance its agenda through partnerships with other NIH Institutes, the Army, academic institutions, and private companies involved in biotechnology. The Frederick facility can be a platform for much of this type of collaboration. Dr. von Eschenbach agreed to consider inviting Dr. Lander or another speaker to a future NCAB meeting to discuss the work of the focus groups that are looking at the agenda for basic research.

V. BYPASS BUDGET UPDATE—MS. CHERIE NICHOLS

Ms. Cherie Nichols, Director, Office of Science Policy and Assessment, NCI, described the Bypass Budget, which is issued each year in a publication entitled *The Nation's Investment in Cancer Research*, as NCI's strategic plan for supporting cancer research and ensuring that discoveries are translated and applied to all people. This document, which was mandated by the National Cancer Act of 1971, is submitted directly by the NCI Director to the President and Congress, bypassing the usual channels through the NIH Directors and Secretary of the Department of Health and Human Services (DHHS).

The Bypass Budget, Ms. Nichols explained, is a blueprint to reduce the burden of cancer, based on professional judgment of needs. It is a communication tool for describing what has been accomplished, what needs to be done, how the NCI plans to proceed, and what resources are required to meet the expressed objectives. The Bypass Budget is used by NCI staff for program planning and by advocates to inform Congress and others about the need to support cancer research.

The current Bypass Budget, which will be available in November, is organized according to the four cornerstones of NCI planning and priority setting: defining and building a research capacity (developing technological and personnel resources); advancing discovery and application (Extraordinary Opportunities to develop profound insights into cancer prevention, control, detection, and treatment); addressing areas of public health special concern (e.g., quality of life, health disparities); and planning national agendas for disease-specific research.

Ms. Nichols explained that Progress Review Groups (PRGs), made up of internal and external experts and advocates, have been one primary mechanism for planning the NCI's disease-specific cancer research agenda since 1998. Examples of recommendations that have appeared in all ten PRG reports and that have been incorporated into the Bypass Budget include enhanced bioinformatics, molecular profiling, and improved imaging. Ms. Nichols reviewed several other PRG recommendations that have been used in developing the Bypass Budget.

In spring 2001, Ms. Nichols reported, a mailing to more than 8,000 people asked for suggestions for Extraordinary Opportunities for the Institute. The resulting 37 suggestions for Extraordinary

Opportunities were discussed by the NCI leadership during a retreat in November 2001. Ms. Nichols reviewed several changes and clarifications in the Bypass Budget based on these ideas.

Ms. Nichols described the external review process through which the NCI solicited input from more than 200 individuals, organizations, Government agencies, professional organizations, advocacy groups, advisory committee members, SPOREs, and others. Changes made in response to this review have included new objectives and milestones, descriptions of relationships among priority areas, and a revised narrative that reflects many of the reviewers' concerns. Suggestions were also received concerning potential partnerships, and the NCI was encouraged to provide strong leadership for technology transfer.

Ms. Nichols displayed a slide depicting the timeline for development of the NCI Bypass Budget. As part of this process, each plan within the Bypass Budget is assigned to one or more "NCI Champions," who are responsible for development of the individual plans and reporting on progress.

Ms. Nichols reviewed suggestions received from the cancer research community on ways to enhance the involvement of those outside the NCI in planning the research agenda. The NCI was encouraged to establish a broad-based systematic process to collect this input; solicit input at the formulation stage (rather than wait for a formal review stage late in the planning process); bring diverse perspectives to the table; and ensure that everyone has ample opportunity to respond. Ms. Nichols listed several potential methods for improving the process of soliciting external input that might be further explored by the NCAB: establishment of an Extraordinary Opportunity-like process for other types of investments; NCI Listens sessions and town meetings; Federal Register notices; sessions at meetings of professional associations; creation of expert panels; and electronic communications.

Questions and Answers

Dr. Amelie Ramirez, Associate Professor, Department of Medicine, and Deputy Director, Chronic Disease Prevention and Control at the Research Center, Baylor College of Medicine, asked about the low number of responses to the invitation to review the Bypass by outside organizations. Ms. Nichols said she would be interested in ideas from the Board on ways to increase the response rate; she emphasized, however, the high quality of the responses that were received.

Dr. Freedman asked how balance can be ensured so that the planning process does not reflect the needs of only organizations with powerful voices. Dr. von Eschenbach replied that the responsibility of the NCI is to manage the distillation of diverse input and make informed decisions, through faithful application of the process described by Ms. Nichols, about what is an appropriate task for the Institute and what is better achieved through collaborations and interactions with outside entities. The NCI, he noted, does not pretend to be all things to all people. Dr. von Eschenbach added that inviting advocates, professionals, and the public to open meetings—perhaps at Cancer Centers—might be a way to excite the country about the progress that has been made against cancer and emphasize the importance of pushing harder now that the "light at the end of the tunnel" is becoming visible.

VI. LEGISLATIVE UPDATE—MS. SUSAN ERICKSON

Ms. Susan Erickson, Acting Director, Office of Policy Analysis and Response, NCI, mentioned that the 107th Congress does not have much time to vote on pending legislation before its target adjournment date of October 4. An emphasis will be placed on appropriations bills and legislation

associated with homeland security. Any pending legislation not acted upon before that deadline will have to be reintroduced in the 108th Congress.

Since the last NCAB meeting, two new bills of interest to the NCI have been introduced. The Cancer Survivorship Research and Quality of Life Act, introduced by Representative Steny Hoyer of Maryland, would establish an NCI Office on Survivorship, to be supported by raising the cancer control budget from 10 to 13 percent of the NCI budget, and create a new position—the Associate Director for Cancer Survivorship. The Patient Navigator Outreach and Chronic Disease Prevention Act, introduced by Representative Robert Menendez of New Jersey, would create two grant programs, to be administered by the NCI and the Health Resources and Services Administration (HRSA), providing prevention, early detection, treatment, and follow-up services for populations with health disparities. The NCI grants would be provided to NCI-designated Cancer Centers, academic institutions, and public and private organizations; the HRSA program would add Indian Health Service Centers and rural Health Clinics to this list of recipients.

Other pending legislation of interest to the NCI includes a collection of women's health bills that may be introduced together in an omnibus bill. Topics include mammography quality standards, breast cancer and environmental health research centers, breast implants, and ovarian cancer.

Questions and Answers

Dr. deKernion asked whether the two new bills described would provide additional funds for grant implementation. Ms. Erickson replied that new funds are not attached to these bills, although appropriation of such funds is authorized.

VII. NEW BUSINESS I—DR. JOHN E. NIEDERHUBER AND NCAB MEMBERS

Dr. Niederhuber opened the floor for new business. Dr. Kalt announced that at its June 2002 meeting, the NCAB approved two new R37 MERIT awards. These are R01s that scored within the fifth percentile or better to continue the work of investigators who have demonstrated continued excellence in science. MERIT awards were made to Dr. Ricardo Dalla-Favera, from Columbia University, for his project on AIDS-associated lymphoproliferative disorders and to Dr. Kenneth Kinsler, from Johns Hopkins University, for his project on genes from the FAP locus.

In the absence of other new business, Dr. Niederhuber requested that the Board observe a moment of silence simultaneously with similar observations being conducted throughout the NCI campus.

VIII. PATIENT PRIVACY REGULATIONS—MS. MARY McCABE

Ms. Mary McCabe, Director, Office of Education and Special Initiatives (OESI), NCI, and Acting Director, Office of Communications (OC), presented an update on the new national Privacy Rule mandated by the Health Insurance Portability and Accountability Act of 1996 (HIPAA). The DHHS drafted a rule and issued it for public comment. The research community responded to provisions in the rule that had unintended consequences for researchers, particularly those involved in epidemiological studies. A final draft of the rule was published in December 2000, at the end of the Clinton administration, but its implementation was postponed by the Bush administration pending receipt and analysis of further input solicited in March 2002 from researchers, health insurance providers, and others. A revised rule was published August 14, 2002, and implementation of the rule will begin April 14, 2003.

Those covered by the rule include health care providers and health care institutions that transmit health information electronically; these electronic communications are referred to as "HIPAA transactions." Researchers whose work includes providing treatment to clinical trial participants are among those covered by the rule. Researchers who are not engaged in HIPAA transactions are not covered by the rule. Cancer Centers are now trying to distinguish between researchers who take part in patient care from those who do not.

Protected health information, Ms. McCabe explained, is defined as identifiable data transmitted in any form, including decedents' health information when used for nonresearch purposes. Human specimens do not come under the rule, although clinical information attached to a specimen that identifies a patient does. "De-identified" information, in which references to specific individuals have been removed, does not come under the rule. De-identified information is not anonymous, because codes can be used to link to identifier data. The fact that de-identified information is not covered by the new rule is very helpful to researchers conducting epidemiological studies.

Ms. McCabe noted that patient authorization will be required for the use or disclosure of protected health information. This applies to research using existing databases or the collection of new data in trials involving treatment of participants. Institutions are allowed to use a single form to obtain permission for all uses and disclosures; this authorization can also be obtained by adding language to a trial's informed consent form. Another change that is very important for the research community is the elimination of the expiration date for authorization to use or disclose data.

Ms. McCabe listed specific elements that must be included in an authorization, such as who may use or disclose the information, the purpose for its collection, and acknowledgment of the right to revoke authorization. It is unclear at this point, she noted, whether researchers can satisfy this requirement by stating that the purpose is cancer research, or whether the form must identify a specific type of research (e.g., breast cancer) or a specific study. The resolution of this question will be of great interest to the research community. The right to revoke authorization also has a potential impact for research; however, any information collected and stored up to the point of revocation can be retained and used.

Ms. McCabe stressed that the new Privacy Rule does not present a conflict with the Common Rule used to protect human subjects in federally sponsored research. Research involving human subjects still requires Institutional Review Board (IRB) review and informed consent under the Common Rule, and use or disclosure of collected data requires patient authorization under the Privacy Rule.

Ms. McCabe described options for conducting research without authorization. A waiver can be obtained from an IRB or a privacy board for studies with minimal risk. Preliminary research using existing data and the use of decedents' data for research purposes can also be conducted without authorization.

Ms. McCabe explained that the rule contains a transition provision for studies in progress on April 14, 2003. Researchers will not be required to obtain authorization for data already collected under informed consent or IRB waivers under the Common Rule.

One item under the previous regulations that created problems for epidemiology research, Ms. McCabe observed, was the accounting provision, which required documentation of each occasion on which a chart was accessed. This has been revised so that researchers are required, upon request, to: (1) account for disclosures made without individual authorization; and (2) for databases with 50 or more

records, list protocols for which patient information may have been disclosed, including contact information for researchers to whom data may have been provided.

Ms. McCabe referred NCAB members to the DHHS Office of Civil Rights Web site at http://www.hhs.gov/ocr/hipaa for information on implementation of the new Privacy Rule. She said that the NCI has been working with the Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDC), and Agency for Healthcare Research and Quality (AHRQ) to develop an education program to assist researchers, both individually and institutionally, in complying with the new rule. She reported that a meeting is scheduled for September 19 to hear from scientists about their needs in this regard. She offered to report back to the NCAB or the Subcommittee on Confidentiality of Patient Data to ensure that the kind of support the research community needs is provided.

Questions and Answers

Dr. Niederhuber asked Ms. McCabe to describe, in general terms, previous activities of the Subcommittee on Confidentiality of Patient Data and the NCAB on the subject of patient privacy. Ms. McCabe replied that the Board has focused in the past on informing institutions about how to implement structures to ensure patient confidentiality. The Subcommittee, she added, was originally intended to play a proactive role in the development and implementation of regulations but has not had many opportunities to meet and explore these issues.

Dr. Niederhuber asked Dr. Norton to comment on activities of the American Society of Clinical Oncology (ASCO) related to patient privacy issues and how the NCAB might be able to coordinate its efforts with those of other groups. Dr. Norton stated that ASCO represents the professional community and reacts to regulations from the point of view of how they might facilitate or restrict research. By comparison, he added, the NCAB represents a more diverse community. He stated that the regulations as described will probably work well, but unintended consequences cannot be revealed until the rule has been applied in the real world. Dr. Norton suggested that the NCAB inquire about provisions for monitoring the impact of the new rule and seek an opportunity to provide constructive feedback after hearing testimony based on experience in implementing the rule. Dr. Niederhuber suggested that this monitoring should include input from Cancer Centers, which are developing broad networks. He expressed his belief that the Subcommittee on Confidentiality of Patient Data should continue to exist; however, since the previous Chair, Dr. Frederick Li, is no longer an NCAB member, new leadership will need to be selected.

Ms. McCabe volunteered to provide the NCAB with an outline of existing and draft educational materials in order to learn whether the NCI is on target and meeting the needs of the research community. Dr. Niederhuber encouraged her to do that, emphasizing the importance of monitoring the impact of the new Privacy Rule and providing educational assistance in its implementation. Dr. Kalt said that each of the NCI's Divisions will be asked to provide anecdotal information on the experiences of the researchers they support in implementing the new rule. In addition, specific human-subject information from applications for continuations of grant awards can be distilled and presented to the Subcommittee. NCAB members, especially new members, will be asked about their interest in serving on the Subcommittee, and an update will be provided at the December NCAB meeting.

IX. KIDNEY/BLADDER PROGRESS REVIEW GROUP—DRS. PETER JONES AND NICHOLAS J. VOGELZANG

Dr. Peter Jones, Director, Norris Comprehensive Cancer Center, University of Southern California, presented to the NCAB the results of a roundtable meeting held last year to discuss key research priorities in multiple scientific and clinical disciplines. Dr. Jones explained that the Kidney/Bladder PRG was divided into four subgroups (Discovery, Translation, Treatment, and Cancer Control), and the group decided to focus on common pathways and what has been learned from basic science over the last few years. Dr. Jones presented the priorities established by the Discovery and Translation subgroups, and Dr. Vogelzang presented those of the Treatment and Cancer Control subgroups.

Dr. Jones began his presentation by emphasizing genitourinary malignancies as a serious cause of death in the United States, drawing attention to the numbers of deaths from prostate (32,000) and kidney and bladder cancers (25,000) relative to the amount of ongoing research on each.

Dr. Jones used a figure (Hanahan and Weinberg [2000] *Cell* 100: 57-70) to illustrate the pathways involved in tumor growth and development. This approach served as a framework to allow the various groups within the PRG to communicate with each other. Dr. Jones explained that tumor cells are self-sufficient in growth signals and insensitive to antigrowth signals; they can sustain angiogenesis, evade apoptosis, and metastasize. Dr. Jones also pointed out the importance of the interaction between tumors and surrounding tissue.

Dr. Jones briefly described kidney and bladder cancers, starting with the frequency and histology of human renal epithelial neoplasms and four genes associated with renal carcinoma. He described in more detail how one of these genes, the *von Hippel-Lindau* (*VHL*) gene, is responsible for both sporadic and nonsporadic forms of clear cell cancer. Clear cell cancer constitutes about 75 percent of cancers of the kidney. A large number of germline and sporadic mutations in the *VHL* gene have been identified and characterized. There is evidence to suggest that mutations in the *VHL* gene result in VHL proteins that are unable to interact with other proteins, causing hypoxia-inducible factors (HIF) to accumulate. This leads to increased angiogenesis, glucose transport, and production of growth factors—and, subsequently, tumor cell growth. Dr. Jones added that although much is known about this process, less is known about other renal cell cancer pathways, and virtually none of this information is used to treat patients.

Dr. Jones explained that the situation with bladder cancers is different, as there is little evidence of an inherited form of the disease. Aberrations have been identified in regions of certain chromosomes—9p and 9q; and 11p and 17p—that are frequently lost in bladder cancer cells and thus, presumably, harbor genes important for carcinogenesis. One example is the INK4a locus on chromosome 9p. Dr. Jones explained how this locus is responsible for two genes, *p16* and *p14*, that are upstream of two of the most important pathways in the cell: the retinoblastoma and the *p53* gene pathways. This is important, as an understanding of the pathways at the molecular level may allow a clinician to predict which cancers will be invasive and which will not.

Dr. Jones added that cancer might also be caused by epigenetic changes in the methylation status of gene promoters. Some 30 percent of kidney cancers do not have a mutated *VHL* gene; instead, the gene is inadequately expressed due to changes in the methylation status of its promoter. Reactivating this "silenced" gene may be a strategy for treatment in the future.

Dr. Jones continued by describing the priorities established by the PRG subgroups. Their focus was on the mechanisms of pathways, particularly molecular markers and the development of new agents and models, followed by clinical trials and tailored therapies. Dr. Jones listed seven priorities that arose from discussions in the Discovery and Translation subgroups: (1) understand the risk factors for bladder and kidney cancer phenotypes; (2) identify epigenetic, RNA expression, and proteomic alterations in these tumors; (3) understand the role of stroma and intercellular signaling; (4) generate mouse models for kidney and bladder cancer; (5) examine blood, urine, and premalignant and tumor tissues to identify and qualify disease and identify targets for therapy; (6) facilitate noninvasive and minimally invasive imaging techniques; and (7) identify and prioritize agents to target known cancer growth and progression patterns.

Dr. Nicholas J. Vogelzang, Director and Professor of Medicine, University of Chicago Cancer Research Center, continued the presentation by discussing the priorities and points established by the Treatment and Cancer Control subgroups. Their first priority is to develop innovative therapeutic strategies that will eradicate disease, preserve organ function, and maintain quality of life. Dr. Vogelzang proposed the use of mechanism-based agents, citing as an example work conducted by Dr. Marston Linehan, NCI, to identify the VHL protein and its role in angiogenesis and the vascular endothelial growth factor (VEGF) pathway. Dr. Vogelzang presented preliminary clinical results from a placebo-controlled trial of anti-VEGF antibody in about 120 patients with kidney cancer. The trial was conducted by Dr. Jim Yang, NCI. A p value of 0.001 was obtained from time-to-progression survival curves for patients receiving high-dose antibody versus placebo, and four patients in the former arm achieved an objective response. Dr. Vogelzang emphasized that while this was a modest response rate, it did indicate that the antibody was having an effect by inhibiting the VEGF pathway, a "proof of principle."

The second priority is to develop and improve approaches to risk assessment. Dr. Vogelzang reminded the Board that there are at least six categories of kidney cancers resulting from unique chromosomal or genetic abnormalities; he emphasized the need for molecular markers to characterize these cancers beyond their histological appearance. Dr. Vogelzang presented the work of Dr. Bin Teh, Van Andel Research Institute, who uses microarrays to distinguish clear cell cancers with low- versus high-risk features and has developed a set of prognostic genes. These could be used to redefine the current metastatic staging system of UCLA.

Dr. Vogelzang discussed how new genetic and protein signals must be correlated with prognostic groupings. Such novel markers and imaging techniques have implications for treatment and, probably, chemoprevention trials in bladder cancer.

Palliative care is another priority for patients with advanced cancer at diagnosis. Some 95 percent of patients with metastatic renal and bladder cancer die—usually with discrete patterns of metastasis. The mechanisms underlying these patterns are not yet known but may be understood with the use of microarray technology applied to primary and metastatic human tumors. Management strategies, especially those involving radiation oncologists, orthopedic surgeons, and neurosurgeons, can be refined to inhibit organ-specific disease. However, there are some areas for optimism in the care of patients with metastatic renal cancer. Dr. Vogelzang mentioned the success of Dr. Rick Childs, NIH, with nonmyeloablative allogenic stem cell transplantation in eradicating the disease in 20 to 30 percent of 55 patients treated to date and the growing use of this procedure at other centers.

Dr. Vogelzang continued by listing the priorities defined by the Treatment subgroup, stating that the PRG felt that quality of life for both patients and patients' families was under-studied. Given the numbers of patients surviving with bladder cancer, this should be given more research weight. Over half

of patients diagnosed each year have early-stage, easily curable disease, but some half million survivors must deal with urinary and sexual dysfunction affecting their quality of life.

Dr. Vogelzang listed other cancer control points, such as: (1) lack of investigators and instruments; (2) need for standardized behavioral interventions to reduce the risk from these two tobacco-related cancers; (3) need for enhanced early detection and the validation of molecular markers; (4) need to explain the increased incidence of kidney cancer over the last 20 years: Is it related to increased obesity in the population? (5) need for screening to reduce mortality from bladder cancer in high-risk current and former smokers; and (6) use of samples provided by "genetically at risk" families, including those with *VHL* mutations, to screen and validate markers for kidney cancer.

Lastly, Dr. Vogelzang expressed concern about the disparate outcomes of three specific groups of patients: women (who are 50 percent more likely to die of bladder cancer after diagnosis), the elderly, and African Americans.

Dr. Vogelzang concluded his presentation by outlining the resources needed for the task. These were: (1) setting up centers of disease-specific research and SPOREs to encourage multi-institutional consortia; (2) developing new animal and cell models; (3) increasing specialist training; (4) providing validated, high-quality throughput technology; (5) conducting large, multifaceted screening and prevention studies; and (6) applying noninvasive imaging modalities to evaluate the efficacy of new therapies.

Dr. Vogelzang reiterated the interdependence of the four PRG subgroups—Discovery, Translation, Treatment, and Cancer Control—and how this should lead to better risk assessment, better staging, better individual treatment, and improved population outcomes. Dr. Vogelzang expressed hope that the death rate from kidney cancer could be reduced in line with that of bladder cancer.

Questions and Answers

Dr. Vogelzang replied to a question from Dr. Norton about specific needs by stating the need to recognize the "orphan," or orphanlike, nature of bladder and kidney cancers. He would like to encourage clinical SPOREs and training. Dr. Niederhuber asked whether the concept of "orphans" could be interpreted as part of a pathway, since SPORE creation based on a disease is problematic, and the budget is limited. Dr. Jones replied that pathway SPOREs are an option, since individual pathways are part of multiple diseases. The angiogenesis pathway is a good example of this.

Dr. deKernion asked whether it was better to invest in bringing investigators and basic scientists into the field rather than "starting at the top." Dr. Vogelzang agreed, saying that the PRG felt it was important to both train urologists in basic science and bring basic scientists more closely into the clinic.

Dr. Jorge Gomez, Executive Director, Kidney/Bladder PRG, NCI, was asked by Dr. von Eschenbach to comment on SPOREs, based on his recent workshop experience. Dr. Gomez explained that a previous PRG on pancreatic cancer had a special initiative to create a pancreatic cancer SPORE; they lowered SPORE requirements without compromising standards. This initiative was received enthusiastically by the pancreatic cancer community.

ANNUAL UPDATE ON CANCER PROFILES AND STATISTICS

X. INTRODUCTION—DR. BARBARA RIMER

Dr. Barbara Rimer introduced the annual update on cancer profiles and statistics by presenting an overview of the topics to be discussed and briefly describing the role of the national cancer surveillance system in the United States.

The national cancer surveillance system provides data that are superior to any other data available for any other disease studied. The NCI's national Surveillance, Epidemiology and End Results Program (SEER) is the centerpiece of the surveillance system, and it is the oldest source of cancer data, with its 30th anniversary being celebrated next year.

Cancer surveillance data are used for tracking cancer, conducting evaluations, performing epidemiological studies, explaining trends, and planning. Dr. Rimer observed that NCAB members would get some insight not only into the overall trends in cancer incidence and mortality, but also into who is benefiting from progress and who is not. Cancer surveillance data also help determine which cancer types need special attention and more study. The Surveillance Research Program (SRP) at NCI not only collects the data and reports the findings, but also tries to interpret those data. . Through the design of new tools, DCCPS staff try to make the data understandable and useful not only to scientists, clinicians, and researchers, but to the advocacy community as well. The data are then used to improve cancer control.

XI. OVERVIEW OF THE NATIONAL CANCER SURVEILLANCE SYSTEM AND THE LATEST STATISTICS—DR. BRENDA EDWARDS

Dr. Brenda Edwards, Associate Director, SRP, DCCPS, NCI, presented an overview of cancer surveillance and the statistics involved. She defined *cancer surveillance* as providing a quantitative portrait of cancer and its determinants in a defined population. The functions of surveillance are the measurement of incidence, morbidity, survival, and mortality for persons with cancer and the assessment of genetic predisposition, environmental and behavioral risk factors, screening practices, and quality of care from prevention through palliation. Cancer surveillance forms the basis for cancer research and interventions for cancer prevention and control.

At the heart of cancer surveillance are population-based cancer registries. In addition to SEER, the National Program of Cancer Registries (NPCR), approved in 1992 by Congress and managed by the CDC, funds registries in all states not covered by SEER. In 2000, SEER was expanded to include more diverse populations, including those in rural areas such as Kentucky and Louisiana and non-Mexican-American Hispanics and other population subgroups in California and New Jersey.

One of the most notable cancer statistics is from *Cancer Facts & Figures 2002*, published by the ACS. It is a projection of the cancer cases and deaths that will occur this year. The data on new cases are based on the 10 percent of the United States covered by SEER. Since much of the cancer data comes from hospitals, the cancer program of the American College of Surgeons, state registries, and the CDC program, the DCCPS was able to report data for 53 percent of the U.S. population for a 5-year period (1995–2000). Data on cancer deaths come from the National Center for Health Statistics (NCHS).

Dr. Edwards discussed how to better describe cancer patterns. DCCPS statisticians employ joinpoint analysis, which involves a series of joined line segments that form trend lines. Each point on a

line represents a statistically significant change in trend. The results of this analysis, as they appear in the 2002 report, show that death rates from cancer have been declining about 1 percent a year since 1993 after several years of increase. This year, the most recent incidence trend has been reported as stable.

Another new feature in the report is age adjustment to the year 2000. Age makes a difference in cancer rates, as rates increase with age. After adjusting for age, there is a net decline in the cancer rate.

Dr. Edwards then discussed three of the four types of cancers responsible for over half of cancer deaths. First was lung cancer. From the joinpoint picture, the incidence and mortality rates for whites were lower than those for blacks. Mortality declined for both black and white men. Trends in lung cancer deaths for both black and white women remained steady.

For prostate cancer, Dr. Edwards pointed out a rapid increase in incidence in the 1980s and a decline in the 1990s; the rate is again on the increase, primarily in men under 65.

In breast cancer, the incidence for both black and white women has been increasing since the 1970s, although the level is much higher for white women. Current mortality rates are declining for both groups, although black women have a higher rate than white women—and the gap is widening.

The greatest increase in breast cancer is among women 50 to 64 years of age. The trends for women 65 and over are steady. Mortality rates have declined in women of all ages except those 75 or more years old. The diagnosis of early-stage disease appears to be driving the incidence rates up. Incidence of regional disease has turned around and begun to increase.

Dr. Edwards then discussed the impact of age and aging on the U.S. cancer burden. Although the age-adjusted cancer death rate is decreasing, the overall population is increasing, especially those 65 years of age and older; it is in this population where two-thirds of the cancer deaths occur, so that has increased the number of cancer deaths. This year, SEER has developed a method for estimating cancer survival rates by racial/ethnic group.

Dr. Edwards questioned how cancer is counted—whether it is enumerated for an individual or a cancer type—knowing that a single person may have more than one type of cancer during his or her lifetime. Another way to calculate is by prevalence. Using SEER data, those who have been living with cancer, and how long they have survived, have been identified.

Dr. Edwards indicated that a global positioning system device provides an image of cancer surveillance. She used the term *ecologic analyses* to describe the study of long-term trends in cancer rates in the context of area—that is, measurements based on census data on area of residence and socioeconomic status (SES).

Dr. Edwards concluded by stating that the cancer surveillance program is emerging and changing. With the registry system and a variety of linked data and special studies, statisticians will be able to do more to explain cancer trends and to make data more available to a broader group of people.

XII. EXPLAINING CANCER TRENDS—DR. ERIC FEUER

Dr. Eric Feuer, Chief, Statistical Research and Applications Branch (SRAB), DCCPS, NCI, reviewed information on understanding cancer trends. He presented two examples: breast cancer and how modeling is used to understand the impact of mammography and adjuvant therapy on mortality, and prostate cancer, and overdiagnosis in prostate-specific antigen (PSA) screening.

Breast cancer mortality rates fell 18 percent from 1990 until 1999. Major reasons for this decrease are the introduction of multiagent chemotherapy in the mid-1970s and tamoxifen in the 1980s. Mammography usage started in the early 1980s and increased dramatically in the late 1980s and early 1990s.

The Cancer Intervention and Surveillance Network (CISNET) is an NCI-sponsored consortium of modelers focused on the impact of cancer control (interventions, screening, treatment, and primary prevention) on current and future trends and optimal cancer control planning. The purpose of CISNET is to learn the reasons behind cancer trends.

In September 2000, nine grantees were funded in breast, prostate, and colorectal cancer research, and in August 2002, eight additional grantees were funded to study prostate, colorectal, and lung cancers. CISNET breast cancer investigators address a broad range of questions, but all groups have focused on the impact of mammography, adjuvant therapy, and the combination of both on U.S. breast cancer mortality between 1975 and 2000. The groups use common population inputs, such as dissemination of adjuvant therapy, dissemination of mammography, changes in background risk, and mortality from other causes, but they will apply model-specific assumptions and inputs, such as tumor growth rates, efficacy of treatment, and screening characteristics. The simulation models can mimic various scenarios and allow for the partitioning of predicted mortality based on: treatment alone, screening alone, and both.

Dr. Feuer then focused on one component, dissemination of mammography, to show how modeling works. This was done in two steps. The first was to input age at the first screening exam. This information comes from cross-sectional national surveys. The second step was to input the interval between consecutive screening exams; for this, a set of linked mammography registries was used—i.e., data from the Breast Cancer Screening Consortium. Next, Dr. Feuer showed the proportion of women born between 1933 and 1937 who had ever been screened and the dates of their first screening exams and then used a statistical model to fit these data into a smooth curve. By the year 2000, 90 percent of these women had had at least one mammogram. Using this method for all the birth cohorts of interest, Dr. Feuer showed that women in the youngest cohorts—those born in the late 1950s and 1960s—were having their first mammograms early in life—some before the age of 35.

To model repeat mammograms, the data were divided into three categories: those derived from women who tend to have annual mammograms, those from women who tend to have biennial mammograms, and those from women who have sporadic mammograms. In this simulation, each woman was assigned a single random number between 0 and 100 to determine group membership, and the probability of belonging to each group at different ages was modeled using the data from the linked mammography registries. Dr. Feuer then presented the screening history of simulated women. This type of modeling can be used to evaluate the impact of observed mammography trends on U.S. mortality and can go even further by varying the model parameters to study the impact of various cancer control strategies and differences among subpopulations.

Dr. Feuer next discussed overdiagnosis in PSA screening. The PSA test was FDA-approved in 1986 for monitoring the relapse of prostate cancer and, in 1994, for aiding in the detection of the disease. By the mid-1990s, about 40 percent of white men and about 35 percent of black men 65 and older had had their PSA tested.

Based on autopsy studies, it is predicted that about 36 of every 100 men will develop prostate cancer at some point in their lives, although many of those cancers would never produce symptoms in the person's lifetime. Before PSA testing, about 9 of every 100 men were diagnosed with prostate cancer; 27 would have had latent prostate cancer. The PSA test was designed to pick up prostate cancers that were destined to become clinical.

Next, Dr. Feuer defined *lead time* as the time a diagnosis of cancer is advanced due to early detection through screening. For example, if an unscreened person had cancer clinically detected at age 72 but would have had the cancer detected at age 67 if screened, the lead time is 5 years.

Overdiagnosis is defined as those cases of cancer detected by screening that would have gone undetected without screening. For a 70-year-old man, the chance of dying of causes other than cancer in 5 years is about 20 percent; for a 75-year-old man, this chance increases to 28 percent. With overdiagnosis, a man is likely to experience the trauma of cancer treatment with no potential gain in life expectancy.

Dr. Feuer commented on the impact of the introduction of screening on population incidence patterns. When introduced into a population, screening always causes an initial bulge in incidence because it detects what would have been undiagnosed cases. As screening stabilizes, later-stage cases that would have been clinically diagnosed occur less often, and overall incidence begins to decline. Finally, incidence stabilizes to the level it was at before screening was implemented. If there is a longer lead time, the incidence has a higher peak and takes longer to return to its prescreening level. In another example with the same pattern of screening, an overdiagnosis of 33 percent was introduced. In this case, there was a more extended incidence peak and no return to the prescreening level of incidence.

The actual incidence seen in SEER data for whites and blacks showed a slight increase from 1975 to 1990, a steep increase from 1990 to 1993, a decline until 1996, and a return to the pre-1990 trend from 1996 on. The incidence for blacks was greater than that for whites throughout. The background trend (in the absence of screening) may actually be declining because the rates of surgical procedures used to treat the symptoms of an enlarged prostate (which sometimes detects prostate cancer as an incidental finding) have been falling. This is due to the medical management of this condition. The observed incidence trends and assumptions about the background trend can be used to estimate the lead time and overdiagnosis associated with PSA screening in the U.S. population.

Various models were projected for prostate cancer incidence to determine the best fit to observed incidence. For white men ages 70 to 84, the best fit was a 5-year lead time, with an estimated overdiagnosis of 29 percent. This means that approximately 4 of the 27 latent prostate cancers—about 15 percent—would be picked up by PSA screening.

Dr. Feuer concluded his presentation by stating that estimates of overdiagnosis are important when weighing the potential mortality gains of screening against the burden of unnecessary treatment. These estimates should be considered "ballpark" estimates only and will be refined as PSA screening trials in the United States and Europe come to fruition. While some see this estimate as representing a lot of unnecessary treatment, others feel the tradeoff is the potential to save other men's lives. In the long

run, the true challenge of screening is to detect factors that determine which men are destined to develop progressive disease.

XIII. NEW TOOLS FOR UNDERSTANDING CANCER PATTERNS—DR. LINDA PICKLE

Dr. Linda Pickle, Senior Mathematical Statistician, DCCPS, NCI, presented new methods for identifying cancer patterns over time and through geographic mapping. She focused on data visualization tools, particularly those useful for exploratory data analysis—referred to as *data mining*. These methods can identify patterns in data and generate ideas for hypothesis testing; these can then be tested using statistical analysis.

The goals of cancer data exploration include identifying broad geographic patterns and clusters of unusually high rates (hot spots), generating hypotheses about the causes of patterns, and illustrating relationships among risk factors.

Visualization tools such as maps or graphs help show how rates may cluster geographically or vary over time, and cancer data exploration can illustrate relationships among risk factors. As the amount of data grows, it is more and more difficult to discern these relationships; visualization tools can focus and speed up this process.

Visualization tools include map smoothing, linked maps and graphs, maps conditioned on levels of risk factors, multivariate plots linked to maps, and animation. The simplest method is map smoothing. This removes most of the day-to-day and place-to-place variation. Maps of cancer rates for small areas can be difficult to interpret because of the high variability of these rates. Previous smoothing methods did not account for varying population size, but new methods can incorporate weights into the algorithm so that stable rates will be smoothed much less than unstable (more variable) rates. These new methods can identify patterns in the data that would be missed by standard methods.

A more complicated graph is a linked micromap plot, which links statistical graphs to maps so that the patterns on both can be seen simultaneously. This can be run on a personal computer or interactively over the Web and can be used for any geographic unit and for different types of statistical graphs. Dr. Pickle showed a linked micromap plot with two panels of statistics from SEER cancer incidence data, one showing rates, the other, counts.

Another type of visualization tool, the conditioned choropleth map, helps explore relationships between cancer rates and potential risk factors. This software allows interactive decomposition of a single color-coded map into a stratified map according to one or two other factors. Slider bars let the user choose how to stratify. As an example, Dr. Pickle showed cervical cancer mortality rates stratified by SES and by percentage of women who had had Pap smears in the previous 3 years. One slider let the user control the definition of high, moderate, and low rates; another represented percent below poverty level status; and a third controlled the stratification of Pap smear use.

Conditioned maps are effective for examining relationships when there are only two factors, but usually, there are more. A visualization tool to examine more complex, multivariate relationships is a parallel coordinate plot linked to a map. The user can highlight data on a map, and the corresponding data will be highlighted on the graph and vice versa. This method can examine relationships among a virtually unlimited number of factors.

Statistical tools can also be added in the background to help sort through the patterns found with the parallel coordinate plot. For example, statistical variable clustering algorithms can find clusters in the data.

Animated presentations can show how cancer patterns change over time. Dr. Pickle presented an example in which the red and blue areas of a map represented high and low cervical cancer rates, respectively. Over 5-year intervals, rates in most places declined (became blue) because of regular Pap smears—except for Appalachia, where rates remained high. This was a "hot spot," and it was clearly illustrated in this animated presentation.

Dr. Pickle concluded her presentation by stating that statistical data visualization is a multidisciplinary area of research in which work is ongoing. Most of the work presented was the result of a Digital Government Initiative grant from the National Science Foundation, the purpose of which was that Government agencies partner with academia to develop better visualization tools. Information on the Digital Government Initiative is available on the Web at diggov.org.

XIV. NEW TOOLS FOR CANCER PLANNING: THE STATE CANCER PROFILE— DR. B. SUE BELL

Dr. B. Sue Bell, Mathematical Statistician, SRAB, SRP, DCCPS, NCI, explained the work being conducted on the State Cancer Profiles Web site. The goal of this site is to make statistics and tool sets used to characterize the national cancer burden available to state and local cancer control planners, policy makers, and advocates to provide them with more information to focus cancer control resources on the persons and places that can benefit most.

Dr. Bell next discussed cancer statistics for researchers. These statistics are delivered to users through SEER*Stat, a compact disk containing a tool to calculate cancer statistics, as well as an extensive database that has been collected from the SEER registries. Individual cancer records can be viewed, and statistics can be produced on frequencies and rates, trends over time, and survival. Cancer query systems are available on the Web. These systems access databases containing statistics calculated using SEER*Stat software and SEER data. When using CanQues, a user constructs interactive queries. When using FastStats, a user picks from the available statistics.

Less-frequent users of cancer statistics often rely on either the CDC State and Territory Cancer Data—a one-page report—or the ACS's *Facts and Figures* booklet. Both are available on the Web.

The Web site integrates the latest data for major cancer sites, area demographics, and behavioral risk factors. It provides dynamic access to graphical and statistical summaries for the cancer control planner to explore opportunities for intervention. The statistical summaries include measures of statistical stability to communicate confidence in rate estimates for small areas or for demographic subgroups.

Some of the challenges for the system include protecting the confidentiality of cancer patients, ensuring that system users do not misinterpret the information, providing graphics that support complex decisions yet are easy to understand, and complying with Section 508 of the Rehabilitation Act for Web accessibility for disabled persons.

Dr. Bell provided a sample scenario using New Jersey breast cancer statistics and demonstrating how these statistics compare with others across geography, over time, and across race/ethnicity, as well as

with statistics for other cancers. She focused on comparisons of mortality rates and mammography usage and on current and long-term trends. In a second scenario, Dr. Bell displayed similar comparisons using county statistics.

In conclusion, Dr. Bell stated that the next steps in the State Cancer Profiles project include conducting usability testing, developing tutorials and interactive help, presenting a preview at the American Public Health Association annual meeting (in November), incorporating cancer incidence data from the CDC's NPCR, and "going live" around the end of the year.

XV. USING CANCER SURVEILLANCE DATA FOR COMPREHENSIVE CANCER CONTROL—DR. JON KERNER

Dr. Jon Kerner, Assistant Deputy Director, DCCPS, NCI, discussed how to bring the latest technology in cancer surveillance into the arena of cancer control planning. The greatest challenge to the NCI is closing the gap between discovery and delivery. In terms of cancer control, those most in need of the benefits of research are often the last to get them. The barriers that prevent these benefits from reaching those who need them must be removed.

Dr. Kerner presented a model of research information dissemination, labeled *passive diffusion*. He asked how NCI can proactively diffuse cancer surveillance information. Dr. Kerner presented a continuum of discovery and delivery, starting with research, leading to dissemination and diffusion research, and from there to dissemination, delivery, and policy influence.

Another model examined the relationship among the CDC, ACS, and NCI in a comprehensive cancer control partnership. NCI is involved primarily in research and development. The CDC is focused on dissemination and diffusion, with links to every state health department in the country. ACS is largely involved in delivery of services, as well as dissemination and diffusion. Each organization does a little bit of everything but has strengths in certain areas.

The CDC has defined *comprehensive cancer control* as "an integrated and coordinated approach to reducing cancer incidence, morbidity, and mortality through prevention, early detection, treatment, rehabilitation, and palliation." The CDC has data on the latest state plans for comprehensive cancer control. The National Dialogue on Cancer, the state cancer planning committee, set as a goal that every state would have a comprehensive cancer control plan drafted by the end of 2003 and that those plans would be implemented by the end of 2005.

The NCI defines *cancer control science* as "the conduct of basic and applied research in the behavioral, social, and population sciences to create or enhance interventions that, independently or in combination with biomedical approaches, reduce cancer risk, incidence, morbidity, and mortality." Dr. Kerner asked how science can inform and influence the practice of comprehensive cancer control. The "push-pull" infrastructure model from the Robert Wood Johnson Foundation was used to examine this question. Science and technology push information out, and the market and demand for intervention pull information out. The critical point to this model is the delivery capacity and what the limitations are.

NCI's Translating Research Into Improved Outcomes (TRIO) program examines delivery limitations. Its three components are: (1) using cancer surveillance data to identify needs, track progress, model and understand trends, and motivate action; (2) developing tools for accessing and promoting the adoption of evidence-based cancer control interventions; and (3) establishing regional and local

partnerships to identify and overcome infrastructure barriers to implementing comprehensive cancer control plans.

Dr. Kerner discussed the partnership tools that have been developed. The first is the State Cancer Profiles developed by NCI and CDC. This system shows where the high rates are, what the trends are, and what populations should be reached.

Another system is the community assessment e-tool developed by ACS. This is a CD-ROM designed to enumerate what organizations are already delivering cancer control services in particular regions.

CDC publishes a *Guide to Community Preventive Services*, which is a summary of intervention approaches that work in community-based cancer prevention and control.

Finally, NCI is working with ACS and CDC to develop an evaluation, called the Plan Link Act Network With Evidence-Based Tools (PLANET), to determine the difference being made by these tools. PLANET provides methods for people to access information. One approach is the traditional way of searching information: going directly to the sites of interest—but users must know what they want. Another approach involves a Web browser system, Ask Jeeves, that will take users to a site by typing in a question.

Dr. Kerner concluded by summarizing DCCPS' next steps. The testing and launch of PLANET is expected by January 2003. Expansion of surveillance and modeling research dissemination and diffusion, support for NCI and NIH dissemination and diffusion research, support for ACS and CDC dissemination and diffusion research, and NCI knowledge transfer teams and interagency partnerships across the discovery/delivery continuum are also planned.

XVI. DISCUSSION

Participants discussed the quality of the work that has been done and the efforts to make a difference in cancer control. Dr. Niederhuber began by stating that in all the presentations, what was missing was the role of Cancer Centers. Dr. Rimer responded by stating that Cancer Centers are one of the greatest potential users of data in the cancer control world. Cancer Centers are also part of the groups developing state plans. Dr. Rimer stated that some training was needed to make sure the Cancer Centers are adept at using the new tools because often the tools the Centers have are no better than those available to the average citizen. Dr. Niederhuber then stated that most often, when people have cancer in the family, they will look to the Cancer Center in their region as a resource, and this should be used to advantage. Dr. Kerner stated that many Cancer Center directors believe they should be regional leaders in closing the gap between discovery and delivery. He believes there is a great opportunity for the NCI to partner with Cancer Centers but that Cancer Centers have not necessarily reached beyond their own research and patient populations.

Dr. Chen asked about trends showing that SES varies with cancer risk and how and why that concept had changed. He also asked how SES is operationally defined. Dr. Edwards responded by stating that there is not one measure that works across all diseases over time, and attempts are being made to define SES in a useful way.

Dr. James O. Armitage, Professor and Dean, College of Medicine, University of Nebraska Medical Center, did not seem to think that the "17 years to get less than 20 percent application of an intervention" applied to medical therapeutic research. He stated that treatment for certain cancers is instantly applied. Dr. Susan M. Love, Adjunct Professor, Department of Surgery, University of California School of Medicine, stated that some treatments are applied before they are proven. Dr. Rimer stated that the reality is that while many treatments are rapidly disseminated in some areas, many parts of the country are slow to adopt them. Dr. Kerner stated that, for some parts of the country, such as Appalachia, the risk of dying of certain cancers—for example, cervical cancer—has not changed in more than 50 years, mainly because a large number of women there have never had a Pap smear. Also, many of the counties in those regions have no hospital, or their hospitals lack therapies available elsewhere.

Dr. Armitage stated that one interpretation is that oncologists are slow to adopt new therapies when they become available, which he believes is untrue. Another interpretation is that the people in those regions are too poor or lack insurance and, thus, cannot avail themselves of the health care system—or that there is no health care system where they live. Dr. Rimer stated that some interventions have been slower to diffuse than is ideal. Dr. Edwards stated that part of the work in which she is involved is the selection and tracking of certain treatments through patterns-of-care studies. Dr. Feuer mentioned that dissemination of treatments outside of Cancer Centers is not optimal.

Dr. Norton asked how it is being addressed the fact that Americans move so much geographically. Dr. Edwards stated that she has hired a geographer to help address that issue and tailor some of the data for population change, but it is a challenge to keep track of that information. Dr. Ramirez asked how the data looked in terms of breakdown of racial and ethnic groups into subpopulations. Dr. Edwards replied that the data are currently not very good because they are incomplete. She said that this information needs to be collected in local hospitals. Dr. Ramirez responded by saying that this creates disparities and that help is needed at the national level to get the message to the regional level. Dr. Rimer also mentioned the role of the Special Populations Network in collecting the needed data.

Dr. Ramirez asked Dr. Kerner whether a feedback system could be designed so that when a user gets information from a Web site, he or she can get information back to NCI. Dr. Kerner replied that the NCI is working with the Office of Communication and with the Office of Education and Special Initiatives to develop some guidelines and implement some sort of feedback system.

Dr. Norton asked what provision is available to prevent misinterpretation of cancer data by the public (users). Dr. Rimer replied that data are "suppressed" in areas where people could really come to misconceptions. There are also caveats about how to use the data. Dr. Bell said that that is one of the reasons that confidence intervals are presented with the data. Dr. Edwards noted the difficulty in preventing people from making the wrong interpretations, and work is being conducted on the way information should be presented to try to avoid this problem. Dr. Kerner stated that this is a major role of the Cancer Centers and other partners, providing ways for these issues to be addressed locally. Dr. von Eschenbach commented that the DCCPS has worked very hard to reach out and get broad inputs from the community.

CLOSED SESSION

This portion of the meeting was closed to the public in accordance with the provisions set forth in Sections 552b(c)(4) and 552b(c)(6), Title 5 U.S. Code and 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. appendix 2).

Members were instructed to exit the room if they deemed their participation in the deliberation of any matter before the Board to be a real conflict or that it would represent the appearance of a conflict. Members were asked to sign a conflict of interest/confidentiality certification to this effect.

The en bloc vote for concurrence with all other IRG recommendation was affirmed by all serving Board members present. During the closed session of the meeting, a total of 1,472 applications were reviewed requesting support of $482,585,996. Funding for those 1,472 applications was recommended at a level of $482,449,646. The subcommittee meeting adjourned at 5:50 p.m.

DAY TWO—TUESDAY, SEPTEMBER 10, 2002

MINISYMPOSIUM—HORMONAL INFLUENCES ON BREAST CANCER OVER THE LIFE COURSE

XVII. INTRODUCTION—DR. LESLIE FORD

Dr. Leslie Ford, Associate Director for Clinical Research, Division of Cancer Prevention (DCP), NCI, introduced the topic of the minisymposium: the influence of hormonal exposure on the incidence of breast cancer. Epidemiological studies have determined that hormonal exposure correlates with the incidence of breast cancer. However, these studies have not determined how hormones influence a woman's risk of developing breast cancer. Evidence-based medicine has provided insight into the molecular mechanisms altered by hormonal exposure. Dr. Ford noted that a workshop addressing the effects of hormonal exposure during the reproductive years would be held in the winter of 2002. She commented on the estrogen-plus-progestin hormone replacement therapy (HRT) clinical trial halted earlier this summer. This study, organized by the Women's Health Initiative (WHI) in 1990, investigated the benefits of HRT in postmenopausal women. The study determined that the risk of developing both cardiovascular disease and breast cancer due to the use of HRT far exceeded any benefits attributed to improvements in osteoporosis and colon cancer. Even though this clinical trial was halted, Dr. Ford observed, these studies should be looked upon as a triumph for clinical trials and evidence-based medicine, especially with respect to studies on hormonal influences on breast cancer. Dr. Ford introduced the distinguished speakers participating in the minisymposium.

XVIII. THE HORMONAL EPIDEMIOLOGY OF BREAST CANCER—DR. ROBERT HOOVER

Dr. Robert Hoover, Director, Epidemiology and Biostatistics Program, Division of Cancer Epidemiology and Genetics, NCI, discussed past and present epidemiological studies focused on elucidating the hormonal etiology of breast cancer and the future of such studies. In the eighteenth century, Amazini observed that breast cancer mortality was related to hormonal exposure. Over the next 200 years, other scientists determined that reproductive factors—specifically estrogen produced by the ovaries—played a critical role in the development of breast cancer. Since the 1930s, numerous hormonal risk factors have been identified that either increase the risk for breast cancer or play a protective role. The most recent risk factors identified include high birth weight, which predisposes a child to breast cancer, and maternal preeclampsia, which protects the child against breast cancer. Progress made in identifying risk factors far exceeds knowledge of the mechanism of action of these hormones.

Dr. Hoover explained that the majority of people identify estrogen as a carcinogen and the root of all hormonally based risk factors. Dr. Hoover focused on time factors in relation to estrogen exposure: specifically age, duration, and currency of exposure. In the 1990s, Oxford University studied the relative risk of breast cancer in women receiving estrogen replacement therapy. These studies determined an increased risk for breast cancer when estrogen therapy was used within 5 years of diagnosis, regardless of the number of years the women were on the hormone therapy. These data indicated that the effects of estrogen use were not cumulative but, rather, were time-sensitive. Dr. Hoover noted that HRT became popular in the United States in the 1980s after estrogen hormone therapy was associated with increased incidence of endometrial cancer. Progestin used in conjunction with estrogen lessened the risk of endometrial cancer. Dr. Hoover explained that progestin acts as a differentiating agent on endometrial tissue and as a proliferating agent on breast tissue. This difference in mechanism of action led to questions on the effect of HRT on the incidence of breast cancer. One study conducted several years ago

concluded that women who used HRT were at higher risk of developing breast cancer; the same results were found by the HRT study organized by the WHI.

Dr. Hoover discussed several other studies that identified relationships between the time estrogen exposure occurred and the incidence of breast cancer. Postmenopausal obesity has been identified as a risk factor for breast cancer, with peripheral fat acting as the main source of estrogen. Several studies, including one by Dr. Regina Ziegler at NCI, have determined that obesity is a risk factor only when weight gain occurred within 10 years of diagnosis. A number of studies on pregnant women have concluded that pregnancy is protective against breast cancer, but protection occurs 5 to 10 years after pregnancy. These studies suggested that the risk of breast cancer due to estrogen exposure is related to the time of exposure relative to the time of diagnosis and not to cumulative estrogen exposure. Dr. Hoover commented briefly on the tamoxifen prevention studies performed by Dr. Ford. Tamoxifen has been used to prevent breast cancer in high-risk women because it blocks estrogen. Tamoxifen almost completely prevented the occurrence of breast cancer during the first year of treatment, but the level of protection dropped to 50 percent by the second year. These data indicated that 1 year of blocking estrogen cannot completely negate the times the women were exposed to estrogen, both before and after menopause.

Dr. Hoover discussed the protection provided by a pregnant women's age at first birth. It is an accepted fact that women who have their first birth before the age of 18 have a lower risk of breast cancer than women who have their first birth at age 35. The rate of breast cancer mortality over the past century directly correlates with the change in fertility patterns related to age at first birth. The ability of pregnancy to protect against breast cancer is not fully understood, but protection by pregnancy requires that the child be carried to term. A recent linkage study from Scandinavia indicated that a longer length of gestation provided more protection against breast cancer. Dr. Hoover commented that these results demonstrate that the protection provided by pregnancy is based on a critical period of hormone exposure.

Dr. Hoover reviewed a number of studies that questioned the importance of estrogen exposure alone with respect to breast cancer. *In utero* hormone exposure appears to alter a child's risk for breast cancer as an adult. In preeclampsia, the drop in the mother's levels of urinary estradiol would predict decreased estrogen exposure to the fetus, thus providing protection later in life. However, a recent study found that women with preeclampsia had normal circulating estradiol levels. Dr. Hoover commented that high birthweight children are at higher risk of developing breast cancer, apparently due to increased exposure to estrogen—but this is only a hypothesis. Dr. Hoover discussed studies on women exposed to diethylstilbestrol (DES) during fetal development; DES was used to prevent miscarriages from the 1940s through the 1960s. Ten years ago, NCI performed a follow-up study on the daughters of women who had used DES and found no correlation between exposure and incidence of breast, uterine, or ovarian cancer. Dr. Hoover remarked that these data indicate that other hormones need to be evaluated when investigating hormonal risk factors.

Dr. Hoover suggested a number of candidate hormones, including insulin-like growth factor (IGF) and insulin growth factor, that affect the incidence of breast cancer. Epidemiological data indicate that many hormones, even when they are not typical reproductive hormones, affect breast cancer. Dr. Hoover commented on one study that found a decrease in levels of serum prolactin each time a woman had a child. This decrease in prolactin may explain the protective value of parity at an early age. Dr. Hoover concluded the discussion on past studies of estrogen and hormone exposure by stating that while estrogen is the most studied breast cancer-related hormone, cumulative lifetime exposure to estrogen does not explain the mechanism for all of the hormonally related risk factors associated with breast cancer.

Dr. Hoover discussed new challenges and opportunities for hormonal epidemiology research. The major challenges for estrogen studies include the current inability to accurately measure circulating estrogen levels and to detect the correct form of estrogen at the appropriate times. In addition, there is a basic lack of understanding regarding what defines a normal mechanism of action for estrogen compared with an abnormal mechanism. Dr. Hoover explained that advances in molecular biology have revolutionized the ability to measure exposures, outcomes, and susceptibility in relation to epidemiology, as well as expand knowledge of basic cancer research. A major advancement in molecular epidemiology includes the ability to profile women according to genetic variations related to specific hormones, especially estrogen.

Dr. Hoover commented on the current challenges facing molecular epidemiology. Studies based on genetic effects require large numbers of subjects from diverse populations. The type of risk evaluated determines the populations that need to be investigated and requires studies that are rigorously conducted, analyzed, and interpreted. In addition, polymorphisms in genes demand that more than one study be performed to ensure that the appropriate gene is identified. Dr. Hoover pointed out that NCI has developed the infrastructure to meet these demands through the creation of Cohort and Case Control Consortia. The Consortia are composed of groups of researchers conducting large cohort studies that involve both the collection of biological specimens and the tracking of risk factors. Epidemiologists, clinical scientists, and molecular scientists work in collaboration to produce common protocols and methods to perform coordinated, paralleled, and pooled analyses that can be used to test hypotheses in the scientific community. Presently, the Consortia include representatives from 22 of the largest cohorts that work with both biospecimens and risk factors.

The initial study conducted by these Consortia included cohorts located throughout the world and investigated breast cancer in 8,000 patients, with an equal number of controls. Dr. Hoover explained that the scientists involved in the Consortia are attempting to conduct a study that is on the cutting edge of both epidemiology and genomics research. The proposal, presently under review by NIH, will investigate a number of risk factors associated with breast cancer, including hormonal risk factors. The study will investigate candidate polymorphisms and haplotypes in more than 50 genes. Dr. Hoover concluded his talk by reiterating that future studies on hormones must take into account the biological mechanisms that influence how hormones increase the risk for breast cancer.

Questions and Answers

Dr. Freedman commented on the low incidence of breast cancer in countries where the level of breast feeding is higher in comparison with that in Western countries and inquired whether lactation would be protective in women who used estrogen therapy later in life. Dr. Hoover responded that the studies on breast feeding have found that significant levels of protection are found only when women lactate for over 5 years. In Western countries, it is difficult to find women who breast feed for over 2 years. However, understanding the mechanism of protection provided by long-term lactation would be useful in creating therapies that would mimic the protection without requiring women to lactate for 5 years.

Dr. Chen asked what is presently being done to study the protective and risk factors associated with breast cancer among westernized Asian-American women. Dr. Hoover discussed the difficulty in ascertaining the factors that are specifically protective among traditional Asian women compared with westernized Asian women. Initial studies found that women living in rural Asia had levels of estradiol 25 percent lower than those of Caucasian women living in the United States. However, when the estradiol

levels were compared between the most and least acculturated Asian women living in the United States, no significant difference was found. Dr. Hoover commented that current studies on migrant populations are focused on traditional and high-soy diets; he recommended that other questions be asked to determine the differences in genetics and/or lifestyles among these populations.

Dr. Love commented that the incidence of breast cancer in Taiwan is, overall, lower than that in the United States; that the average age of onset is 47, compared to 69 for women in the United States; and that the continued increase in postmenopausal breast cancer seen in the United States does not seem to exist in Taiwan. Dr. Hoover added that Taiwanese women have a lower rate of premenopausal breast cancer as well. In addition, the rate of breast cancer continues to rise as American women progress through menopause, while the rate of breast cancer in Taiwanese women levels out after they reach age 40. Dr. Hoover noted that he did not have an explanation for these differences, but he stated that postmenopausal risk factors alone could not explain the differences. Dr. Hoover asked for advice on new hypotheses to explain these differences.

XIX. OVERVIEW OF MECHANISMS OF HORMONE ACTION ON BREAST CANCER INFORMATION SERVICE—DR. J. CARL BARRETT

Dr. J. Carl Barrett, Director, Center for Cancer Research, NCI, reported on the different mechanisms of action that estrogen has on breast cancer. Dr. Barrett described how levels of ovarian and uterine hormones fluctuate dramatically during adolescence, remain relatively cyclic during the reproductive years, fluctuate slightly during the perimenopausal years, and remain low through postmenopause. Conversely, hormones produced by the pituitary gland and hypothalamus remain relatively high throughout postmenopause. These changes in hormonal levels, especially during pregnancy, must be considered when studying any disease, especially breast cancer. Dr. Barrett commented that estrogen affects the brain, immune system, liver, and bone in addition to the mammary glands and the reproductive organs of both females and males. Therefore, the whole system needs to be studied when determining how a hormone affects disease development.

Dr. Barrett described the complexity of the signaling pathways regulated by estrogen. The estrogen receptor (ER) is a dimer composed of two subunits, with each subunit stimulating very different downstream responses. In addition, there are other estrogen-related receptors that can influence the downstream effects activated by the ER, as well as other receptors that can bind estrogen and influence which genes are “turned on and off." Dr. Hoover explained that the traditional model for estrogen’s action involves the dimerization of the ER upon ligand binding, interaction of the receptor with other estrogen-responsive elements, and activation of the transcriptional machinery of various genes—including prolactin—that could be equally important in cancer development.

Dr. Barrett discussed six different potential mechanisms of action by which estrogen might influence the development of breast cancer. Estrogen can directly stimulate proliferation or inhibit cell death of a target cell. It can also indirectly stimulate target cell proliferation via autocrine or paracrine growth factors. Dr. Barrett focused the rest of his talk on the remaining four mechanisms of action: synergistic activity with other growth factors, induction of mutations in target cells, hereditable reprogramming of gene expression, and alterations in the adult stem cell compartment.

Estrogen works intricately with other hormones and growth factors in regulating a number of different biological processes. Various hormones are regulated by the progression of the menstrual cycle, but the menstrual cycle itself is regulated by environmental influences, such as diet and lifestyle.

Dr. Barrett explained that hormones work in concert with growth factors to stimulate mammary cell growth and differentiation. These effects induce genetic changes that can result in the manifestation of cancer. Dr. Barrett commented that the hormones to which mammary cells are exposed during fetal development or puberty influence mammary cell growth and differentiation later in life.

Dr. Barrett discussed the interactions between the estrogen system and IGFs. The IGFs and IGF receptors (IGF-Rs) comprise a complex network of signaling pathways critical to the development of cancer by influencing the rate of cell proliferation and the inhibition of cell death. Dr. Barrett stated that blocking this signaling pathway results in the failure of cells to undergo transformation by oncogenes. He discussed a number of lifestyle factors capable of regulating the circulating and tissue levels of IGFs. These lifestyle factors also place an individual at increased risk for developing cancer. A cascade of proteins regulates the level of circulating IGFs. Chemopreventive agents, as well as antiproliferative signals, can activate these proteins. Dr. Barrett described some studies that found a correlation between increased levels of circulating IGFs and premenopausal breast cancer, as well as prostate, colon, lung, and other cancers.

Dr. Barrett explained how the cross-talk between the IGF-1 and estrogen pathways affects breast tissue development and breast cancer. Normal breast tissue development requires estrogen-stimulated IGF-1 production. A number of risk factors for breast cancer—such as high birth weight and high premenopausal breast tissue density—correlate with increased levels of IGF-1. In addition, low levels of IGF-1 in women with preeclampsia correlate with a decreased risk of breast cancer, while high levels of IGF-1 in premenopausal women correlate with an increased risk of breast cancer. Dr. Barrett noted that estrogen and IGF-1 are capable of activating other signaling pathways. Treatment of animals with estradiol results in increased phosphorylation and upregulation of IGF-R, and IGF-1 activators can stimulate the ER in the absence of estrogen. Because of these interactions, Dr. Barrett stressed, estrogen should not be evaluated in isolation as working independently of other physiological regulators but, rather, should be examined along with other environmental risk factors that can alter the estrogen system and other growth factor systems associated with cancer development

Regarding estrogen's ability to induce mutations in target cells, Dr. Barrett indicated that eight estrogen metabolites have been shown to have mutagenic activity. The mutagenic metabolites can have plastogenic or aneuploid effects on cells that are ER-negative. Dr. Barrett discussed certain polymorphisms in a class of enzymes associated with either an increased or decreased risk of breast cancer, depending on the enzymes' rates of metabolite inactivation. Dr. Barrett commented on two different agents presently in clinical trials: one estrogen metabolite that acts as an anticarcinogenic agent by blocking angiogenesis, and an aromatase inhibitor that blocks estradiol production more effectively than antiestrogens. While these compounds affect the metabolism of estrogen, they most likely are not directly involved in the cancer process.

With respect to the concept of inheritable reprogramming of gene expression, Dr. Barrett commented how DES exposure during fetal growth causes persistent alterations in DNA methylation that have been associated with the regulation of estrogen-dependent genes. He then described mechanisms that could potentially explain the protective effects of pregnancy, focusing on alterations in the adult stem cells. A recent paper published in the September issue of *Development* demonstrated the fate of mammary epithelial cells that have differentiated as a result of lactation into a new population of cells that are less responsive to carcinogenic insult. At the molecular level, there are also several mechanisms that could account for the protective effect of pregnancy, including: increased levels of BRCA1 and BRCA2, which remain high after pregnancy and lactation; reduction in the number of epithelial cells that express

estrogen and progesterone after pregnancy; and increased levels of nuclear *p53* in hormone-treated mammary cells. All of these changes that occur after pregnancy are capable of protecting against breast cancer.

Dr. Barrett closed by discussing research from Dr. Jeff Rosen's laboratory. The studies applied differential gene analysis to cells treated with estrogen and progesterone and identified a number of unregulated genes involved in the regulation of differentiation and expression of transcription factors. One of the genes was a retinoblastoma-associated gene that encodes a protein that regulates chromatin remodeling. Dr. Barrett stated that this was an example of an inherited gene that was potentially changed by pregnancy or other physiological processes, but did not involve a mutational mechanism. He summarized by stating that estrogen acts through a variety of biological pathways and that all pathways should be investigated when attempting to understand estrogen's role in breast cancer.

Questions and Answers

Dr. Love requested that Dr. Barrett comment on why pregnancy at a late stage in life is not protective. Dr. Barrett stated that the explanation is complex, but that changes occur in the cells of the breast tissue, and these changes are a function of age and occur independently of pregnancy.

XX. NORMAL BREAST DEVELOPMENT AND THE ORIGINS OF BREAST CANCER—DR. ROBERT A. WEINBERG

Dr. Robert A. Weinberg, Member, Whitehead Institute, and Daniel K. Ludwig and American Cancer Society Professor, Department of Biology, Massachusetts Institute of Technology, described the composition of breast tissue. He explained that breast tissue is composed of epithelial cells that line the milk ducts and stromal cells that create an environment for normal epithelial cell proliferation and growth. During adolescence, the milk ducts undergo branching and invade the mammary fat pad, or stroma. Early during pregnancy, side branches develop, and small lobules, called alveoli, arise along the milk ducts. Breast milk fills the alveoli late in pregnancy. Dr. Weinberg stressed that understanding the hormones that act locally on mammary gland development would provide some insight into the etiology of breast cancer.

In normal morphogenesis, growth hormones, estrogen, progesterone, and prolactin all regulate the differentiation of the epithelial cells. These same hormones affect the pathogenesis of breast cancer. Dr. Weinberg explained that his laboratory used mouse models to understand how systemically circulating hormones act locally on epithelial cell development. The model involved removing epithelial cells from the fat pad of the mouse while leaving the stroma intact, and vice versa. Epithelial cells from progesterone-receptor knockout mice were then grafted into the fat pad, and development of the epithelial cells was analyzed. The transfer of epithelial cells that lacked the progesterone receptor resulted in the complete absence of ductal branching during adolescence, as well as side branching and alveoli development during pregnancy. Transfer of stromal cells lacking the progesterone receptor into mice with normal epithelial cells resulted in normal milk duct development. These data demonstrated that normal breast development required that the progesterone receptor be expressed on the epithelial cells but not on the stromal cells. Dr. Weinberg observed that these data indicated that progesterone is required for branching of the milk ducts and formation of alveolar precursors.

Dr. Weinberg described similar experiments that transferred prolactin receptor-negative epithelial cells into normal mice. Early in development, there were no differences in ductal branching in the virgin

mice. Once these mice became pregnant, the side branches developed normally, but no alveoli developed; the absence of alveolar cells also resulted in no milk production. The transfer of prolactin receptor-negative stromal cells into normal mice produced no difference in breast development. Dr. Weinberg commented that these data indicate that prolactin regulates precursor alveolar development and side branching, alveolar development, and milk secretion.

Dr. Weinberg mentioned that the role played by estrogen in mammary gland development is limited to influencing the initial branching of the ducts. However, in breast cancer cells, estrogen can stimulate cell growth through induction of the ER. Dr. Weinberg noted that a number of other growth factors play critical roles during different stages of mammary gland development.

Dr. Weinberg described experiments performed in his laboratory that explored, at the molecular level, potential mechanisms for the growth-stimulatory effects of prolactin. These studies showed that IGF-2 was produced in large amounts in epithelial cells that expressed the prolactin receptor. He proposed that IGF-2 leaves the cell in which it was produced and stimulates nearby cells to proliferate, resulting in alveoli formation. These data lead to the hypothesis that prolactin, which is normally produced by the pituitary, is aberrantly produced by breast cancer cells, resulting in increased IGF-2 production, which, in turn, induces autocrine growth of mammary epithelial cells. Experiments are presently underway to test this hypothesis.

Dr. Weinberg described the growth stimulatory factor wnt-4, another factor that induces cell proliferation. He explained that normal mammary cell development occurred in a mouse model in which progesterone receptor-negative epithelial cells were commingled with wildtype epithelial cells. The progesterone receptor-negative epithelial cells proliferated in response to wnt-4 released by the wildtype cells in response to progesterone. Other studies have shown that when epithelial cells are unable to produce wnt-4, they lack the ability to branch, similar to what is observed in cells that do not express the progesterone receptor. Conversely, Dr. Weinberg added, progesterone's effects were mimicked when cells overexpressed wnt-4.

Dr. Weinberg stated that his laboratory was recently able to induce transformation of normal human mammary epithelial cells into breast cancer cells. Human normal cells require at least five genetic changes to be transformed into cancer cells, whereas mouse cells require only two to three genetic alterations. The human epithelial cells could be transformed only when grown in the presence of stromal cells, indicating a collaborative interaction between these cells. Dr. Weinberg explained that mouse stromal fat pads could not support human epithelial cell grafts. However, humanized mouse stromal fat pads—consisting of human stromal cells grown with mouse stromal cells—have been generated that support human epithelial cells. This has allowed a mouse model to serve as a model for studying human breast tissue. Dr. Weinberg reported that this model developed normal ductal tissue and alveolar lobules and produced milk once the mice were pregnant. In addition, the human mammary epithelial cells expressed the ER on the ductal tissue.

Dr. Weinberg closed by discussing preliminary data from a recent experiment performed in his laboratory. Epithelial cancer cells mixed with stromal fibroblasts isolated from patients who underwent reduction mammoplasty induced formation of breast cancer at a low rate when transferred into mice. Conversely, epithelial cancer cells grown in the presence of carcinoma-associated stromal fibroblasts resulted in a significantly higher rate of breast cancer formation. Dr. Weinberg commented that future studies will investigate the role of stromal cells in inducing epithelial cells to form carcinomas.

Questions and Answers

Dr. Love noted that although large-breasted women are not at increased risk for developing breast cancer, they may not have normal breast tissue in terms of growth hormone levels. Dr. Weinberg responded that while those women may not have normal breast tissue because of increased levels of growth factors, the work he discussed focused on women who had undergone reduction mammoplasty, and that stromal fibroblasts isolated from those patients did not strongly support carcinogenesis. He also mentioned that in a separate study that used epithelial cells from patients who underwent mammoplasty and who had histopathologically normal breasts, one of ten of the samples placed in stromal fat pads developed into invasive carcinomas. This method could be useful in revealing "hidden" breast cancers by transferring the cells to the humanized stromal fat pads.

Dr. Love mentioned work by Dr. Mina Bissell that had shown that breast cancer cells grown in the presence of normal stromal cells respond normally. Dr. Weinberg noted that those experiments were performed *in vitro,* while the experiments in his laboratory used a physiological system that attempted to replicate normal breast development.

Dr. Norton commented that metastatic cells are usually morphologically similar to the primary lesion and asked whether Dr. Weinberg had looked for the presence of fibroblasts at metastatic sites. Dr. Weinberg indicated that metastasized epithelial cells recruit stromal fibroblasts from the primary organ site; however, his laboratory has not investigated metastasis in the humanized mouse model.

Dr. von Eschenbach acknowledged Dr. Weinberg's contributions to NCI. He then remarked on the dissimilarities between breast and prostate cancer and wondered how comparative oncology could provide some insights into other carcinomas. Dr. Weinberg responded that any advances in the understanding of breast cancer development would have implications for other carcinomas. Breast cancer is, experimentally, a more malleable and trackable carcinoma than others. Dr. Weinberg emphasized that the original tumor reconstitution experiments were performed using prostate cancer stromal cells, and these indicated that the stromal interactions would most likely be reiterated in other carcinoma systems that involve epithelial and stromal cells.

XXI. EXTRAMURAL RESEARCH GRANT PORTFOLIO ON HORMONES AND BREAST CANCER—DRS. DINAH SINGER, DEBORAH WINN, PETER GREENWALD, AND ELLEN FEIGAL

Dr. Dinah Singer, Director, Division of Cancer Biology (DCB), NCI, explained that the DCB supports basic research in cancer biology and etiology. She highlighted how grants and grant dollars were distributed among different areas of research, focusing on the endocrine component of cancer. Dr. Singer briefly reviewed the stages of normal breast development, which can be divided into three phases: differentially regulated in large part by estrogen, progesterone, and prolactin. DCB is following the breast cancer PRG's recommendation to increase its research efforts to understand early mammary development, and these efforts are complemented by research at the National Institute of Child Health and Human Development (NICHD) and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

Dr. Singer focused on the role of estrogen in normal breast development and breast cancer, drawing particular attention to the interaction between the stroma and the epithelium. Dr. Singer reminded the Board that the effects of the ER are actually mediated by coactivators, thus, determining

how the cell will respond to estrogen. Understanding this response will help with the design of better selective ER molecules (SERMs). Because overexpression of estrogen affects both normal and cancer cell growth, DCB supports research on estrogen biosynthesis and metabolism.

Dr. Singer briefly mentioned the role of the progesterone receptor in normal mammary development and tumorigenesis before presenting the complex relationship between pregnancy and breast cancer. She outlined two approaches to the problem. The first is to support research into understanding the molecular effects of hormones, while the second involves developing appropriate animal models. Dr. Singer gave two examples of the molecular approach. Prolactin has a role in the production of milk proteins during pregnancy, while the prolactin receptor is expressed on breast cancer cells. Likewise, two new protein kinases have been identified that are unique to epithelial cells in pregnancy and cancer. Such cell surface markers can be developed as potential molecular targets.

Dr. Singer described an animal model that is being used to look at hormonal effects on tumor development during pregnancy. Rodent susceptibility to chemically induced cancer decreases during pregnancy, correlating with p53 induction. Artificially elevating levels of p53 confers the same kind of resistance seen during pregnancy. It is known from mouse models that targeted inactivation of p53 in the breast results in 100 percent incidence of breast tumors. Not only do these tumors metastasize, but they also progress from being ER-positive to ER-negative.

Dr. Singer then talked about how growth factors also impinge on the epithelial cells and influence the development of breast cancer. Tumor growth factor (TGF)-β interacts with parathyroid-like hormone in a positive feedback loop, inducing breast cancer cell proliferation and bone degeneration. This emphasizes the complexity of TGF-β's effects, which differ according to whether TGF-β is acting as a tumor suppressor or a promoter.

Dr. Singer presented a slide of the roles of different hormones at various stages of cancer development, followed by one illustrating the numbers of grants and amounts of research funding dollars at each of these stages. DCB supports 116 grants in the area of hormones and breast cancer out of a total of 400 grants in the area of breast cancer. About 60 percent of the 116 "hormone" grants are focused on early breast cancer (both ER-positive and ER-negative), 20 percent are for early-phase and normal development, and 20 percent are for metastatic progression. Dr. Singer concluded by saying that the Division was aware of gaps in the distribution of support and is working to rectify this by increasing the portfolio.

Dr. Deborah Winn, Acting Associate Director, Epidemiology and Genetics Research Program (EGRP), DCCPS, NCI, gave a presentation on reproductive hormones and cancer. This area encompasses not only levels of endogenous hormones, but also exogenous hormones from HRT oral contraceptives, phytoestrogens, and environmental chemicals. She drew attention to the fact that DCCPS is also interested in other types of cancer, noting that estrogen has a protective effect on colorectal cancer, and is also concerned with issues like breast density and mammography performance.

Dr. Winn explained the distribution of DCCPS research grant projects in hormones and cancer. Thirty-five grants deal with prevention, 33 of which focus on epidemiology and the etiology of cancer or related conditions. Twenty-two grants focus on hormone therapy. Dr. Winn explained that 13 of the HRT studies just collect information about HRT history and do not include measurements of hormone levels or hormone-related genes. Dr. Winn believes this trend is changing to provide a balance of information about various aspects of hormone-related cancer.

Dr. Winn listed details of several ongoing studies. The first was the compilation of a multiethnic cohort of 29,000 people in Hawaii by Dr. Lawrence Kolonel, University of Hawaii. Participants were interviewed at baseline, gave blood and urine samples, and completed extremely detailed questionnaires on characteristics such as dietary factors and phytoestrogens. The aim of the study is to measure the interaction of multiple growth factors, hormones, and chemicals on the risk for breast and prostate cancers.

Data were also presented from a study by Dr. Greendale at UCLA, who investigated breast density changes in 875 postmenopausal women in relation to serum estrone levels from HRT.

The New Hampshire Mammography Network contains 74,000 women, 26,700 of whom are currently receiving HRT. Participants are being followed to measure the impact of HRT on mammography performance, breast cancer incidence, and prognostic indicators such as stage at diagnosis.

Dr. Winn discussed several studies of survival after breast cancer. One study involves physical activity as part of a trial examining morbidity after breast cancer. The Breast Cancer Case-Control Study in Long Island was concerned with the association of estrogen-like environmental chemicals and breast cancer risk. Although no definitive association was determined, this population is being reexamined to assess the effects of other chemicals, such as polychlorinated biphenyls (PCBs), chlordane, dieldrin, and dichlorodiphenyldichloroethylene (DDE) on breast cancer survival.

The extended use of hormone medication is also under DCCPS review in conjunction with the NCHS. Health information on HRT and contraceptives comes from the National Health Interview Survey (NHIS) (39,000 households) and the California Health Intervention Survey (CHIS).

Dr. Winn announced a potential future project based on the impact of HRT use following the recent announcement from WHI. DCCPS is considering supplementing the cancer research network to measure the rate of initiation or discontinuation of HRT among women in health maintenance organizations (HMOs), before and after the announcement, and how clinical HRT guidelines might change in response to such initiation/discontinuation..

Finally, Dr. Winn described the cohort consortium as a valuable opportunity for collaboration across NCI divisions, with extramurally funded programs, and with international associations.

Dr. Peter Greenwald, Director, DCP, NCI, explained that grants supported by DCP fall into 3 categories: clinical trials of SERMs, hormone measurement as biomarkers for breast cancer risk, and studies of dietary influences.

Dr. Greenwald began by describing clinical trials of SERMs. In 1998, the National Surgical Adjuvant Breast and Bowel Project (NSABP) and NCI reported that tamoxifen reduced the risk of invasive and noninvasive breast cancer and bone fractures, but increased the risk of endometrial cancer and vascular events. Genomic analysis of BRCA1 and BRCA2 was subsequently performed on 288 women who developed breast cancer after entry into this trial. Dr. Mary Claire King, University of Washington, and others showed that tamoxifen decreased breast cancer incidence among healthy BRCA2 carriers but did not decrease the incidence among women with inherited BRCA mutations. The promising results obtained from breast cancer prevention trials led to the Study of Tamoxifen and Raloxifene (STAR) trial, which has accrued 14,000 of a targeted 22,000 patients. Dr. Carol Fabian, University of

Kansas, is conducting a Phase II trial of third-generation SERMs in high-risk women by using fine-needle aspirate to look for cytological evidence of hyperplasia.

Dr. Greenwald continued by discussing the second category of supported grants: hormone measurements as biomarkers. Dr. Craig Jordan, Northwestern University Medical School, is validating a method of determining levels of estradiol and progesterone in the saliva of women taking the SERM raloxifene. Saliva is an excellent medium to measure steroids, and it is hoped that this method will make it easier to monitor the drug's effects. Two other studies are analyzing pregnancy hormone profiles as breast cancer risk factors. One is comparing levels of various hormones across different breast cancer risk groups, while the second is examining whether high dietary fat intake and weight gain cause increased estradiol levels.

The third category of grants concerns phytoestrogens in the diet. Dr. Greenwald discussed two ongoing, randomized clinical trials testing the hypothesis that dietary modification as an adjuvant to standard breast cancer therapy will reduce recurrence and increase survival in women with localized breast cancers. The Women's Intervention Nutrition Study (WINS) uses a low-fat diet and has completed accrual of 2,400 patients. The Women's Healthy Living Trial (WHEL) uses a plant-based diet and has completed accrual of 3,100 patients. The dietary modification component of the WHI clinical trial is being used to test the hypothesis that adoption of a low-fat diet is associated with a reduced risk of proliferative forms of benign breast disease.

Two studies are being conducted on soy proteins. Dr. Krischer, of the University of South Florida, has a pilot program to treat premenopausal women with isoflavones prior to surgery for breast cancer. Dr. Schilsky, University of Chicago, is trying to determine whether soy protein reduces the symptoms of postmenopausal women taking tamoxifen for breast cancer. Dr. Greenwald reported that DCP is also supporting a study examining the effect of a low-fat diet on the IGF-1 axis, as well as a study of the effect of soy on mammographic density.

Dr. Greenwald cautioned the Board that news of the risks associated with HRT might boost use of inadequately tested botanical medicines, presenting as an example published work from Dr. Janet Rowley's lab at the University of Chicago showing that maternal ingestion of dietary flavonoids could contribute to infant leukemia.

Dr. Greenwald concluded his presentation with a slide showing how the $30M total budget for DCP grants was allocated; approximately two-thirds was for grants for clinical trials of SERMs. Dr. Greenwald finished by mentioning that the report from an NIH workshop on SERMs, jointly sponsored by NCI, the NIH Office of Research on Women's Health, and the National Institute on Aging (NIA), had just been published.

Dr. Ellen Feigal, Acting Director, DCTD, NCI, presented a summary of grants at DCTD involving the hormonal aspect of breast cancer. About $85M was allocated to 241 grants in breast cancer in FY2001. Of this, $6.5M (7.6 percent) went to 26 grants on breast cancer and hormones; $5.8M (6.8 percent) went to 22 grants on breast cancer and imaging; and $8.3M (9.8 percent) went to 30 grants on breast cancer and radiation. Clinical trials were also conducted in U10 cooperative groups and at other sites in the United States and overseas. Drug development was also conducted through contract resources at NCI.

Dr. Feigal described the clinical trials of breast cancer and hormones. It is known that chemotherapy, tamoxifen, and ovarian suppression are individually effective adjuvant treatment modalities in women under 50 with ER-positive breast cancer. One trial is determining whether ovarian suppression improves the survival of premenopausal women receiving tamoxifen and whether an aromatase inhibitor can be substituted for tamoxifen when ovarian suppression is used. The North American Intergroup and Breast International Group are conducting the trial. Patients will be randomized to one of three arms: (1) tamoxifen for 5 years; (2) tamoxifen for 5 years and ovarian suppression (using a gonadotropin-releasing hormone analog for 5 years, oophorectomy, or radiation); and (3) the aromatase inhibitor exemestane for 5 years and ovarian suppression as in arm 2.

Dr. Feigal described three other clinical trials. The first, conducted by the North Central Group and the NSABP, is looking at the timing of primary surgery in 1,000 premenopausal women in relation to their menstrual phase (follicular versus luteal). A second trial, Arimidex (anastrozole) and tamoxifen alone and in combination (ATAC) in postmenopausal women, involves treatment with the aromatase inhibitor anastrozole, either alone or in combination with tamoxifen. While efficacy has been demonstrated, and anastrozole has recently received FDA approval, the side-effect profiles of anastrozole and tamoxifen are different.

Dr. Feigal reported that a third trial, treatment with IGF-1 plus somatostatin as adjuvant in breast cancer pathogenesis was halted due to gallbladder toxicity. Four additional trials are ongoing to examine aromatase inhibitors as adjuvant therapy in patients with stage 1 and 2 breast cancers and ductal carcinoma *in situ* (DCIS).

Dr. Feigal then discussed grants for breast cancer and imaging. Researchers at Washington University School of Medicine in St. Louis and the University of Illinois are using positron emission tomography (PET) imaging technology to help diagnose hormone-responsive tumors. Fluoroestradiol (FES), a derivative of estradiol, is used as a marker. FES uptake correlates with ER expression in ER-positive tumors, while patients with ER-negative tumors show no FES uptake when scanned. Dr. Feigal showed PET scan images of patients receiving treatment with tamoxifen; the absence of FES uptake indicated that tamoxifen has bound to the ERs. Dr. Feigal presented images to illustrate how FES is used to measure the heterogeneity of ER expression in breast cancer and consequent bone metastasis.

Dr. Feigal continued by discussing drug development and breast cancer, specifically anti-HER2 immunoliposomes. These were designed by Drs. John Park and James Marks at UCSF to provide maximum efficacy via receptor-targeted internalization. Anti-HER2 immunoliposomes bind to, and are internalized by, HER2 overexpressing cells *in vitro,* resulting in intracellular drug delivery.

Dr. Feigal reviewed a number of promising new molecules under investigation. The aryl hydrocarbon receptor (AHR) modulator is a potent inhibitor of carcinogen-induced breast tumor growth. AHR is active against ER-negative tumors and exhibits synergistic activity with tamoxifen. NCI is conducting tumor xenograft studies and is working on AHR formulation and pharmacology. The next molecule presented by Dr. Feigal was a SERM with potential for use both as a preventive and therapeutic agent. This molecule, LY353381-HCl, may be active in tamoxifen-resistant patients, and NCI will be conducting clinical trials. The molecule 17-AAG is a drug of Japanese origin that binds to the cellular chaperone protein hsp90. It has the potential to downregulate hormone receptor- and growth factor-modulated signaling and is currently in clinical trials in the United States and United Kingdom. Finally, a selective inhibitor of the SRC family of kinases is also under investigation through a molecular drug discovery grant. SRC kinases couple the endothelial growth factor (EGF) receptor and HER2/Neu to Stat

activation in breast cancer. They also interact with BCR-Abl in chronic myelogenous leukemia (CML). Dr. Thomas Smithfield at University of Pittsburgh has been funded to identify novel inhibitors that might target specific SRC kinase isoforms and oncogene-signaling pathways.

XXII. SUMMARY DISCUSSION—DR. SUSAN M. LOVE AND NCAB MEMBERS

Dr. Love opened the minisymposium for discussion by stating that the previous paradigm of thought, which focused on estrogen as the pivotal hormone to induce breast cancer could be replaced by a more complex picture involving a number of other hormones, as evidenced by the presentations. She stressed the importance of the role of stromal cells in breast cancer development: Cancer targets epithelial cells, but stromal cells, which determine the density of the breast tissue, obviously play a critical role and may explain why breast tissue density correlates with an increased risk of breast cancer.

Dr. Love affirmed the importance of estrogen exposure at critical timepoints during the lifespan of a woman. As an example, she noted Dr. Richard Love's data that oophorectomies performed in premenopausal women at the same time as a mastectomy were beneficial only when the carcinoma contained ER-positive cells. In addition, oophorectomies performed during the luteal phase of the menstrual cycle resulted in a 30 percent improvement in survival rate compared with the same surgery performed during the follicular stage. These studies, combined with the data presented at the minisymposium, indicate that local levels of hormones play a critical role in breast cancer development.

Dr. Love emphasized that another breast cancer research area that should be studied further, and which involves local hormone levels, is the contents of breast ductal fluid. Estrogen levels in breast ductal fluid in postmenopausal women are 40 times higher than they are in the blood. In addition, a number of other chemicals can be detected in this fluid, including prolactin, testosterone, nicotine, and pesticides. The breast ductal fluid bathes the epithelial cells, and the contents of the fluid may directly correlate with increases in breast cancer. Dr. Love observed that macrophage levels in breast ductal fluid are high, suggesting that some viruses may be involved in an increased incidence of breast cancer.

Regarding the results published on the WHI HRT study, Dr. Love remarked that the data proved the hypothesis on HRT and breast cancer risk to be correct. In terms of how to counsel patients, Dr. Love recommended that in addition to incorporating healthy lifestyle changes, patients should start diminishing HRT after they have been on it for 5 years. Short-term use of HRT for symptom relief, however, is relatively safe, as long as a woman is not at high risk for heart disease or thrombosis. Dr. Love concluded by listing a number of critiques on the WHI study: The HRT study investigated only Prempro and assumed that it was safe; and the results of the study suggest that all bioidentical hormones, including the so-called bioidentical ones, be considered harmful until proven safe. When a woman completes her reproductive period, the body gradually reduces sexual hormone levels. Perhaps other therapies that mimic this physiological state should be investigated.

Dr. Norton remarked that the research presented at the minisymposium promoted collaborations among clinicians, laboratory scientists, and epidemiologists. Further steps are needed to ensure that this exchange of ideas, as well as education, is extended to scientists in other fields, both at NIH and in the extramural research community.

Dr. Love responded that a conference organized by the Susan Love MD Breast Cancer Foundation on the Intraductal Approach to the Breast Cancer will be held next spring in Santa Barbara, California. In addition, as a result of a multidisciplinary Think Tank held by the Foundation on Hormones

and Breast Cancer, a Basic Breast Cancer course will be held in the spring. The purpose of the conference is to bring together clinicians, epidemiologists, and basic researchers in an effort to expose them to concepts outside their basic field of research.

Dr. von Eschenbach emphasized that this minisymposium served to update all NCAB members on the breast cancer research currently ongoing at NCI. The research presented will continue to unfold, and new data will be discussed at future NCAB meetings.

Dr. Ford described an NIH-wide conference that is in the planning stages. The goal of the conference is to interpret the data from the WHI-sponsored HRT study with the objective of addressing how to provide women with the information they need to make informed decisions on pre- and postmenopausal treatments. The conference will include scientists involved with all aspects of the study, as well as advocacy groups.

XXIII. NEW BUSINESS II AND FUTURE MEETING TOPICS—DR. MARVIN R. KALT

Dr. Kalt explained to new NCAB members that the December 2002 meeting would not include a grant review cycle; rather, it would be a programmatic review of specific areas, concentrating on the intramural program.

There being no further business, the 123rd meeting of the National Cancer Advisory Board was adjourned at 12:30 p.m. on Tuesday, September 10, 2002.