NATIONAL CANCER ADVISORY BOARD

convenes at the:
National Institutes of Health
9000 Rockville Pike
Conference Room 10, C Wing, Building 31
Bethesda, Maryland 20892

ATTENDEES

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The National Cancer Advisory Board (NCAB) convened for its 103rd regular meeting at 8:30 a.m., September 24, 1997, in Building 31, C Wing, 6th Floor, Conference Room 10, National Institutes of Health.

NCAB MEMBERS

Dr. Barbara K. Rimer (Chairperson)
Dr. J. Michael Bishop
Dr. Richard J. Boxer
Mrs. Zora K. Brown (absent)
Dr. Pelayo Correa
Dr. Robert W. Day
Dr. Kay Dickersin
Mrs. Barbara P. Gimbel
Dr. Alfred L. Goldson
Dr. Frederick P. Li
Dr. Sandra Millon-Underwood
Dr. Ivor Royston (absent)

Dr. Philip S. Schein
Dr. Phillip A. Sharp
Dr. Ellen V. Sigal
Ms. Ellen L. Stovall
Dr. Vainutis K. Vaitkevicius
Dr. Charles B. Wilson (absent)

President's Cancer Panel

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

Alternate *Ex Officio* NCAB Members

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

Members, Executive Committee, National Cancer Institute, NIH

Dr. Richard Klausner, Director, National Cancer Institute
Dr. Alan Rabson, Deputy Director, National Cancer Institute
Mr. Philip D. Amoruso, Associate Director for Extramural Administrative Management
Ms. MaryAnn Guerra, Associate Director for Intramural Administrative Management
Dr. Faye Austin, Director, Division of Cancer Biology; Chairperson, Extramural Advisory Board
Dr. Joseph Fraumeni, Director, Division of Cancer Epidemiology and Genetics
Dr. Peter Greenwald, Acting Director, Division of Cancer Prevention
Dr. Marvin Kalt, Director, Division of Extramural Activities
Dr. Edison Liu, Director, Division of Clinical Sciences
Dr. Robert Wittes, Director, Division of Cancer Treatment and Diagnosis
Dr. Margaret Tucker, Chairperson, Intramural Advisory Board, Board of Scientific Counselor
Dr. Edward Harlow, External Advisor, Office of Science Policy; Member, Massachusetts General Hospital
Dr. Martin Abeloff, External Advisor and Co-Chair, Clinical Sciences Subcommittee A of the NCI Intramural Board of Scientific Counselors; Professor and Director, Johns Hopkins Oncology Center
Dr. David Livingston, External Advisor, Chairperson of the NCI Extramural Board of Scientific Advisors; Professor of Medicine, Dana-Farber Cancer Institute
Dr. Matthew Scharff, External Advisor and Co-Chair, Basic Sciences Subcommittee A of the NCI Intramural Board of Scientific Counselors; Professor, Albert Einstein College of Medicine
Dr. Alfred Knudson, External Advisor, Special Advisor to the NCI Division of Cancer Epidemiology and Genetics; Acting Director, Intramural Genetics Program; Senior Member, The Institute for Cancer Research, Fox Chase Cancer Center

Dr. Maureen O. Wilson, Executive Secretary of the President's Cancer Panel

Liaison Representatives

Ms. Kerrie Wilson, American Cancer Society
Dr. Stanley Zinberg, American College of Obstetricians and Gynecologists
Dr. Bernard Levin, American Gastroenterological Association
Dr. John Currie, American Association for Cancer Education, Inc.
Dr. Margaret Foti, American Association for Cancer Research
Dr. Marc E. Lippman, American Association for Cancer Research
Dr. Robert Martuza, American Association of Neurological Surgeons
Dr. Edwin Mirand, Association of American Cancer Institutes
Dr. Robert Frelick, Association of Community Cancer Centers
Ms. Laura Liebermann, Candlelighters Childhood Cancer Foundation
Dr. Lovell Jones, Intercultural Cancer Council
Ms. Jean Ard, Leukemia Society of America
Ms. Dorothy Lamont, National Cancer Institute of Canada
Dr. Margaret Foti, National Coalition for Cancer Research
Dr. Tracey Walton, National Medical Association
Dr. Eve Barak, National Science Foundation
Ms. Pamela Haylock, Oncology Nursing Society
Dr. Jeffrey Norton, Society of Surgical Oncology, Inc.
Dr. Marston Linehan, Society of Urologic Oncology

CALL TO ORDER, OPENING REMARKS, AND CONSIDERATION OF MINUTES OF PREVIOUS MEETING
Dr. Barbara Rimer

Dr. Rimer called to order the 103rd meeting of the National Cancer Advisory Board (NCAB) and introduced guests representing cancer education and research associations as well as advocacy organizations. She welcomed members of the public and the press and invited them to submit in writing, within 10 days, any comments regarding items discussed during the meeting. A motion was requested and made to approve the minutes of the June 1997 meeting. They were approved by the Board unanimously.

FUTURE BOARD MEETING DATES
Dr. Barbara Rimer

Dr. Rimer asked Board members to review the 1999 meeting dates as listed and report any conflicts.

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

Dr. Klausner announced that Dr. Rimer would be resigning her position as NCAB chair at the end of the current meeting, and he acknowledged Dr. Rimer's leadership in this role. Dr. Rimer will assume a position within the National Cancer Institute as Director of the newly organized Division of Cancer Control and Population Science (DCCPS). Dr. Klausner next reported on the status of the FY97 budget and some of the distribution highlights.

Research Project Grants (RPGs). By successfully maintaining the R01 payline at the 23rd percentile, the NCI was able to fund 673 competing R01s in FY97, an increase of 35 and 167 grants over the numbers funded in FY96 and FY95, respectively. Total FY97 funding for R01s in the NCI portfolio is expected to be about $575M for a total of 2,192 grants. The payline for the FIRST award (R29) was maintained at the 30th percentile,

resulting in about 110 new awards totaling almost $12M. About 450 FIRST awards are currently being funded. Competing program project grants (P01s) were funded through a priority score of 140, including 13 new (type 1) P01s, for a total of 41 competing awards for more than $55M. Overall, the P01 dollar line increased from about $183M in FY96 to more than $200M in FY97, a 10 percent increase.

The NCI also funds grants through several exception-type processes that add to the direct rank order funding based on meeting paylines and peer review. Two examples are the Accelerated Executive Review (AER) and the bridge funding awarded by the Divisions. The NCI spent $20M (or 4%) more in exceptions (including AERs) in FY97 than in FY96, a level that maintains exception funding at approximately 10 percent of the RPG pool. Twenty-six grants (for $6.6M) were funded through the AER mechanism in FY96, and an additional $1.3M was obligated in FY97. About 54 percent of AER applications were funded in FY97, an increase from the 50 percent success rate in FY96.

Cancer Center Grants. New cancer center grants were awarded in FY97 to the University of New Jersey and the Oregon Cancer Center. Overall, the core center program increased by 3.5 percent over FY96. A 17 percent increase in funding for the Special Programs of Research Excellence (SPORE) allowed an increase in support of the existing breast, lung, and prostate SPORES and the funding of a new gastrointestinal SPORE, for pancreatic cancer, at the University of Nebraska Medical Center. The overall SPORE program is currently undergoing an internal review.

Other Research Grants. Clinical cooperative groups received a 6 percent increase in FY97, when adjusted for one-time funding in FY96 for items such as tissue banks and correlative laboratory sciences. New training initiatives in FY97 included the Career Program, the Howard Temin Award, and the Minority Mentored Career Development Award. Under the first, career award positions increased by 20 percent (35 new positions) since FY95. The Temin Awards have been attracting significant interest. In the first year, 32 applications were received during the two cycles, and 20 applications have been received to date for the first of 3 cycles in FY98. This program provides transitional funding for postdoctoral candidates as they move to institutions to begin independent, unmentored research. Awards have been made in this highly competitive program only to those who received outstanding ratings in peer review, and the success rate is currently 20 percent for this program, compared with 35 percent and 40 percent in other career-type programs. The new Minority Mentored Career Development Awards also provide support during the transition from mentored to independent status. The $1M in funding allocated to this award in FY97 enabled the support of 10 cancer researchers who previously had been recipients of Minority Supplement Research Project Awards.

Through the Cancer Education Program, the NCI funds and supports cancer prevention training, end-of-life-cancer education, outreach activities, and a variety of oncology curricula proposals for medical, nursing, and public health schools. This program received a 12 percent increase in FY97. The National Research Service Awards (NRSA) Program received an 8 percent increase in funding and now supports 1,600 NRSA training and fellow positions, an 8.3 percent increase since 1995. One new institutional career award, the K12, has been announced in the area of AIDS oncology through a Request for Applications (RFA). In addition, a Program Announcement (PA) was recently advertised for an initiative in genetic epidemiology. Responses to both of these announcements are pending.

Dr. Klausner noted that all NCI training programs have been integrated under the Office of the Deputy Director for Extramural Science (ODDES) and will undergo a comprehensive review, ultimately with the help of the NCAB. Recommendations from

NCI's program review groups have consistently identified the need for increased training, in particular, to meet the need for new types of multidisciplinary expertise.

Other Budget Lines. Research and development contracts for FY97 are estimated to total about $180M, which is about 7.5 percent of the NCI budget. About 17 percent of the NCI budget (approximately $410M) was spent for the Intramural Research Program (IRP), down from 18 percent in FY96 and between 20 percent and 22 percent in FY95. Research management and support was maintained for another year at about $100M. Although the institute has grown in terms of the variety and array of its programs, NCI objectives are to maintain at current levels or even decrease this budget line. In this regard, a discussion will be held on the Arthur Anderson report based on a request from Representative Porter's committee to take an overall look at NIH management practices and benchmarking against other agencies.

In FY97, the new Office of Cancer Survivorship used approximately $2M to fund 19–20 supplements to support specific research concerning long-term cancer survivors. A total of 49 applications had been received. The supplements included 3 awards to existing cooperative groups, 2 to the Surveillance Epidemiology and End Results (SEER) program registries, 12–13 to cancer centers, and 2 to other cooperative agreements. Two of these awards were funded by the Susan G. Komen Foundation, and two were funded through the NIH Office of Women's Health. These awards were intended to promote new research in this important area and to begin developing needed research infrastructure.

Dr. Klausner reported that the FY97 budget also contains $15M emergency supplement given to the Secretary, Department of Health and Human Services (DHHS), as part of the Flood Relief Bill. The money is earmarked for innovative and interdisciplinary studies of environmental causes of breast cancer, combining the expertise of the NCI, Centers for Disease Control and Prevention (CDC), and National Institute for Environmental Health Sciences (NIEHS). Development of an infrastructure is planned that will enable researchers to work through the complexity of determinants of cancer that result from the interaction of exogenous and endogenous factors. Advances in exposure assessment methodologies and laboratory aspects relating to the biochemistry of exposure as well as molecular genetics and genetic technology are expected to be useful tools in these studies. Major considerations in planning include confidentiality, informed consent, and privacy-related issues. The goal is to develop a population-based, multicenter case control study incorporating state-of-the-art laboratory analysis and rigorous epidemiologic approaches. This approach, if it is successful for breast cancer, can be used to formulate paradigms for studies of the future that couple the new technologies with genetic and molecular analysis.

FY98 Budget. Dr. Klausner projected that with an FY98 budget for the NCI is expected to fall between the House and Senate marks of $2.513B and $2.558B, respectively, the NCI would be able to raise the R01 payline to the 24th or 25th percentile. Exact numbers will be announced as soon as the exact budget figure is known. AERs would be funded up to 10 percentile points from the payline for patient-oriented research and 5 points for all others, increasing the effective paylines to the 34th –35th percentile for patient-oriented research and 29th–30th percentile for all other investigator-initiated research. The priority score for P01s is expected to begin at 135–140 and will be reevaluated based on the number of applications received.

Dr. Klausner commented that the Small Business Innovation Research (SBIR) line represents a significant challenge each year across the NIH. By law, the Institutes are required to set aside 2.5 percent of the extramural portion of their budgets for grants and contracts awarded to small business institutions or collaborations between small business and academic institutions. In FY97, this amounted to $48M for the NCI. Although NCI's

advisory groups have been consistent in indicating the need to link whole varieties of developmental technology with science, the NCI has funded SBIRs at paylines that are significantly higher than those supported through the rest of the RPG pool. An internal task force has been discussing the issue of strategic technologies and the SBIR, and a coordinator for SBIR has been appointed. Dr. Klausner suggested that the problem of attracting the best SBIR proposals and applications should be revisited by the Board later in the year.

Dr. Klausner presented an update on the allocation of $17M (6%) of the $270M in new funding in the RPG line that was set aside to fund RFAs. Three of the new funding initiatives were related to specific recommendations of the NCI program review and working groups or advisory boards. One RFA published in March 1997 for funding in FY98 called for chemoprevention studies in genetically identified high-risk groups and had a set-aside of $3M for cooperative agreements. Another RFA in the developmental therapeutics area, with an initial set aside of $3.75M, will try to capitalize on dramatic changes in chemistry based on the biologic principles of diversity generation and selection; P01s will be awarded. The third was an RFA for the Cancer Genetics Network, with a $5M set-aside for the first year for successfully competing grants. Twenty-nine applications have been received in response to this RFA.

Dr. Klausner discussed two other issues that relate to RPGs. The first dealt with concern for the clinical researcher and the real or perceived problems clinical R01 grants have in negotiating study sections. Dr. Klausner noted that the AER was an attempt by the NCI to address this issue in part. Following extensive discussions at the Board of Scientific Advisors (BSA) meetings, the NCI Executive Committee formulated a proposal for transmittal to Dr. Elvira Ehrenfeld, Director, Center for Science Review (CSR)—formerly the Division of Research Grants, NIH. The NCI has proposed that efforts be initiated to consider the construction of a clinical oncology study section for cancer-related, patient-oriented research. Dr. Klausner reported real progress toward an agreement. Updates of NCI and CSR negotiations in this regard will be communicated in memoranda to Board members.

The second issue related to the R29 or FIRST award. Dr. Klausner recalled that the NIH developed the R29 award to provide a specific mechanism for individuals applying for their first NIH award. However, a major concern has been that this 5-year award, which is capped at $350K total direct costs, may not be providing sufficient funding to enable the young scientist to launch a successful research career, as measured by their success in winning subsequent awards. An NIH committee chaired by Dr. Marvin Cassman and Dr. Ehrenfeld reviewed and attempted to answer frequent questions related to this issue. The Cassman-Ehrenfeld study found that: (1) the number of scientists applying for their first R01 has remained constant since the early 1980s, but the median age has increased from 35 in 1981 to 39 in 1994; (2) new investigators did not appear to be selectively disadvantaged as success rates decreased; (3) applicants for R29s have consistently had a higher success rate than those applying for first-time R01s; (4) new awardees with R01s have a greater probability for success on competitive renewal than those with R29s, although the extent of the advantage is not clear; (5) between 1993 and 1995, 58.6 percent of all new R01 grantees and 53.2 percent of all R29 grantees received their awards based on the original unamended application, a significant decrease from the period from 1980 to 1983; (6) the success rate for new M.D. and Ph.D. investigators is virtually identical; and (7) more than two-thirds of first-time applicants use the R01 mechanism rather than the R29, reportedly for reasons of funding amount and prestige associated with the R01.

Dr. Klausner suggested that these data raise a question about continuing the R29 and posed a challenge to combine a funding approach for new investigators with measures to

optimize their chances of success. One possibility is to have all new investigators apply for R01s, with applications flagged as such for Institute and study section consideration. The Institute would then have the option of funding them to a different success rate by exceptions or through a specifically targeted AER. The AER, however, has the benefit to the new investigator of merging an expedited receipt of response with the ability to look at and respond to critiques that are part of the response. The cost to fund all new applicants to a 25 percent success rate, converting R29s to peer review-recommended funded R01s, has been estimated at an additional $2.2M–$5.5M per year iin each of the next 5 years. Dr. Klausner asked for Board discussion on this issue.

NCI Extramural Research Program. Dr. Klausner announced the reorganization of the NCI Extramural Research Program (ERP) and the appointment of Dr. Robert Wittes to the newly created position of Deputy Director for Extramural Science (DDES) within the NCI. The Office of the DDES (ODDES) has the charge of providing integration, communication, and oversight to the three major planning processes in place within the NCI as they relate to the functioning of the extramural program. In its new configuration, the ERP will have four program divisions under the ODDES—Division of Cancer Treatment and Diagnosis (DCTD), Dr. Wittes, Director; Division of Cancer Biology (DCB), Dr. Faye Austin, Director; Division of Cancer Prevention (DCP), Dr. Peter Greenwald, Acting Director; and Division of Cancer Control and Population Science (DCCPS), Dr. Rimer, Director. In the new structure, the two new divisions replacing the former Division of Cancer Prevention and Control will allow a strengthening of NCI activities in population science, cancer control, and cancer prevention. Programs such as training, the cancer centers, and construction have been consolidated within the ODDES, and extramural activities from the Division of Cancer Epidemiology and Genetics (DCEG) have been moved to the DCCPS. These changes complete the NCI response to recommendations contained in the Bishop-Calabresi report for separation of the extramural and intramural programs. The Division of Extramural Activities will remain independent from Program and will continue to report directly to the Director, NCI.

REPORT OF THE DIRECTOR, NATIONAL CANCER INSTITUTE
Questions and Answers

In answer to Dr. Michael Bishop's question about broadening the mandate of the proposed clinical oncology study section across the NIH, Dr. Klausner replied that the CSR is considering this direction, and the changes effected for NCI's clinical trials will be part of the broader system. Dr. Rimer asked that the updates to the Board include mention of the indicators of success to be used in deciding whether the ET-2 as proposed becomes a permanent study section.

Dr. Kay Dickersin asked whether the planning structure for the interagency study on the interaction of genes and the environment in cancer causation would include extramural advisors and consumers. Dr. Joseph Fraumeni, Director, DCEG, responded that intramural and extramural collaboration will be necessary because of the multicenter and transnational nature of the study. A meeting of the steering committee composed of representatives from the NCI, NIEHS, and CDC will be held to form an advisory group.

Dr. Phillip Sharp referred to Dr. Klausner's comment that the success of the first-time R01 applicant in receiving a grant on the basis of an unrevised application had dropped from 90 percent in 1980 to 50 percent at present. He emphasized that the 1.5-year delay caused by revision and reapplication has an impact in terms of research development that puts the new investigator into another time slot for promotions. Dr. Sharp favored the proposal for AER first-time applicants.

EXTRAMURAL REORGANIZATION
Dr. Robert Wittes

Dr. Wittes explained that, in the reorganization, the new Deputy Director position was created with the objective of promoting optimal functioning within a hierarchical organization. He noted that the organizations of the DCP and DCCPS are provisional on the recruitment of a permanent DCP director and on Dr. Rimer's assessment, as incoming Director, of the needs in the DCCPS. Operating out of the ODDES, the new Centers, Training, and Resources Program (CTEP) has the following Branches: Cancer Centers, Research Facilities, Organ Systems Coordinating (with responsibility for the SPORE program), and Cancer Training. This configuration acknowledges the fact that these programs and functions serve the needs of the entire IRP. The effectiveness of this infrastructure depends on effective internal interactions between the CTEP and the operating divisions, and the extent to which the divisions use the infrastructure components as tools in planning initiatives and running scientific programs.

Dr. Wittes reviewed the status of activities within the CTEP Branches. The Cancer Centers Branch is in the first year of implementation of the Interim Cancer Center Guidelines, which were developed in response to recommendations of the Cancer Centers Program Review Group. A more definitive assessment of their effectiveness will be possible after the completion of three or four additional review cycles. Within the Cancer Training Branch, Dr. Vincent Caroli, Chief, has been asked to convene a series of internal meetings as the first step to determining whether the mechanisms in place and allocation of NCI training dollars and mechanisms are appropriate for the task of meeting the opportunities of the contemporary scientific world. The advisory board structure of the NCI will be involved very early in the process. Within the Organ Systems Coordinating Branch, a staff review of the SPORE mechanism is planned and will be on the agenda of the November meeting of the BSA. Also under consideration within this Branch is the possible use of the interinstitutional consortia mechanisms for supporting multidisciplinary scientific and translation research, which may not form along specific organ or disease lines.

Dr. Wittes next discussed other new components of the ODDES. The Office of Clinical Cancer Research Promotion is an organizational expression of the recent work of Ms. Mary McCabe and Dr. Wittes in educating physicians, the lay public, payers, and managed care organizations about the value of clinical research and why they should be involved. Having this office as a formal entity headed by Ms. McCabe and located centrally in the ODDES expresses the fact that this activity is related not just to treatment but to all of the interventional components of the NCI's Extramural Program. This office will be the focus for further promotional efforts for managing the interagency agreements such as those with the Department of Defense (DoD) and Veterans Administration (VA), and for creating a World Wide Web (WWW or Web) site for clinical trials. Dr. Wittes announced the recruitment of Ms. Nancy Seybold, creator of ASCO Online for the American Society of Clinical Oncology, for the latter effort. Another new component of the ODDES is the Office of Information Architecture headed by Dr. John Silva. Dr. Silva, a surgical oncologist, is currently acting in a dual capacity as program manager for informatics at the Defense Advanced Research Projects Agency and consultant with various NCI components on informatics issues to create the cancer information infrastructure. Other ODDES units still under consideration are an Office of Industrial Relations and an Outcomes Branch. Dr. Wittes noted that issues related to the organization of the ODDES for the future include determining which functions in the Extramural Program do or could service more than one division and could be more effective as a core function organizationally and which functions should remain in the Divisions.

EXTRAMURAL REORGANIZATION
Questions and Answers

In response to a question from Dr. Ellen Sigal, Dr. Wittes stated that NCI staff have consistently

consulted with extramural organizations, Board members, and consumers about the promotion of clinical trials, and the discussions are intensifying.

Dr. Sharp asked whether the Office of Industrial Relations would deal primarily with intellectual property rights issues or with more active promotional issues and whether it would be involved with the SBIR program. Dr. Wittes replied that the decision to establish that office is pending, but the original intention was that the office should serve as a point of entry, providing orientation and education for companies wanting to do business with the NCI. He acknowledged that although intellectual property rights issues and active promotion are not part of the proposed office, they are envisioned as part of the ODDES agenda because of the growing complexity of arrangements for establishing an industry-investigator-NCI interface and the importance of rapid translation to the public health sector of new drugs and devices. Dr. Philip Schein urged that an Office of Industrial Relations receive high priority consideration over the next year.

In response to Dr. Rimer's question about NCAB involvement in the staff review of the SPORE mechanism, Dr. Wittes explained that the BSA normally oversees the scientific programs of the NCI Extramural Program, but that the SPORE review could also be brought to the NCAB. Dr. Rimer suggested this as an agenda item for the Subcommittee on Cancer Centers.

In response to a question from Dr. Dickersin, Dr. Wittes explained that the proposed Outcomes Branch would create a group with responsibility for assessing outcomes in all of the NCI's intervention programs. It would attempt to promote the use of patient-centered outcomes, such as quality of life and economic issues, in clinical trials to make the results maximally relevant. The decision is pending as to whether the Branch should be established or whether this function should be subsumed in the activities of an existing unit. Dr. Dickersin urged that the NCI collaborate with extramural organizations involved in the promotion of clinical trials.

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

Dr. Freeman reported on deliberations at a recent Panel meeting on Cancer and the Aging Population, the second of four meetings to pursue concerns of special populations in the National Cancer Program. The first meeting was entitled "The Meaning of Race in Science — Considerations for Cancer Research." The final two meetings will address the real impact of reduction of cancer mortality and review the health care system and its responsiveness to special populations.

At a meeting hosted by the University of Michigan's Turner Geriatrics Center, the Panel heard from experts in the fields of cancer and gerontology on critical issues shaping research and policy in this area. Statistics for overall incidence, incidence in major sites of malignancies, incidence of gender-specific malignancies, and cancer mortality show that age is the single greatest risk factor for cancer. Other data show that the elderly are expected to comprise 20 percent of the population by the year 2000, up from 12 percent at present, yet a national research agenda combining oncology and geriatrics does not exist. Many speakers noted that the challenge is to plan now to better inform dialogue and policy in this cancer area. A critical question to address is why cancers occur frequently in the elderly. One concept presented dealt with the question at the molecular biologic level showing that part of the tumor cells overcome the normal cell aging process of replicative senescence and are able to divide indefinitely. How and why this occurs is under investigation. There is some indication that viral and cellular oncogenes act against cells beyond the point of normal senescence. Another theory is that senescent cells accumulate with age and express molecules that may disrupt the microenvironment of various organs, leading to cancer. Various animal models are being used to examine the molecular biology of aging, in particular, looking for markers that might predict

lifespan. The Panel believes that more studies are needed on how the process of aging can elucidate the process of cancer.

One of the major issues and recommendations was the need to examine the pharmacologic properties and toxicity of cancer drugs given to older patients as well as to individualize drug therapy to address the diversity and changes in physiological functioning that occur with aging. In this regard, molecular techniques for characterizing the ability of individuals to handle various drugs are being developed and will become important in the future. Because pharmacologic studies of unique issues related to drug interactions with aging physiology do not fare well in study sections, targeted funding may be needed to promote the necessary commitment in this research area. A related issue was overmedication in the aging population and the use by this age group of a variety of nonprescribed compounds without full knowledge of their interactions and effects. The Panel believes that better strategies for pharmacologic management are needed.

> In the area of cancer prevention, detection, and treatment in the elderly, the Panel heard about the need to develop effective cancer detection strategies, particularly in women and minorities. Rates of screening remain lower among the elderly where the risk is higher according to the evidence. This was attributed partly to lack of communication and knowledge about the benefits of screening in this age group and partly to a lack of understanding about the health care benefits provided under Medicare. Another factor mentioned was the inability of the cancer establishment to come to a clear consensus regarding appropriate screening guidelines for older women. The Panel heard testimony that benefits can accrue from lifestyle changes at any age.

In the area of cancer treatment for the aging, the point was made that physiological status should be the determinant when making treatment decisions and not chronological age. Based on data presented, the Panel recommended that clinicians carefully analyze individual patient physiology and response as the basis for seeking the most appropriate and effective treatments. Interesting developments in the use of hemopoietic growth factors to mitigate toxicity and enable better cancer treatment with less morbidity were presented, including the availability of more and better growth factors, better and less expensive cardio- and neuroprotective agents, and affordable and effective antinausea agents.

In the area of clinical trials, speakers emphasized to the Panel that physicians should treat elderly patients on an individual basis so that they may be included in research protocols based on physiology not chronology. This may require changing thought processes and overcoming barriers to clinical trial access such as cost, transportation, and the patient's own prejudices. The Panel believes that this group, which comprises 50 percent of the cancer patients, should be targeted for clinical research. Special ethical considerations that exist in doing clinical research among older patients were mentioned, including ensuring informed consent among patients who may be faced with sensory impairments or mental instability.

Health advocacy and issues of survivorship, supportive care, and education were the final topics of the meeting. Speakers noted the unique challenges that face elderly cancer survivors, including issues of empowerment, measuring and addressing the quality of life, and long-term care. The Panel heard that management of critical symptoms, such as pain and fatigue, can strongly influence mental and physical recovery and that control and palliation may be as important as eradication of cancer for older patients. The importance of providing clear information was addressed, in particular with data that are more individualized and with information on where to seek appropriate care and treatment.

Based on evidence presented at this Panel meeting, there appeared to be many opportunities for collaborative research, education, and training between the disciplines of oncology and geriatrics and among many organizations invested in supporting advances in these areas. The

Panel supports the position made clear in this meeting that older Americans can and should be able to look forward to improved health outcomes in the same way that younger Americans can. The Panel recommends strengthened and expanded collaborative efforts between geriatrics and oncology. Dr. Freeman concluded that excluding the expanding population of people at highest risk for cancer from clinical trials because of age raises deep philosophical and practical questions about the relationship between aging and cancer. He suggested that answers to the questions related to carcinogenesis and aging might help all people, not just the elderly. Panel member Dr. Paul Calabresi pointed out that the median age for cancer is now 70 years, indicating that overall cancer statistics will never improve unless that part of the problem is addressed. The study of cancer in the aging, therefore, is a research area for the future.

REPORT OF THE PRESIDENT'S CANCER PANEL
Questions and Answers

In response to questions, Dr. Freeman stated that the Panel had not planned to prepare a separate report for this meeting. It will be covered in the annual report to the President. Dr. Calabresi added that the October issues of *Cancer* and the *Journal of the National Cancer Institute* will feature cancer in the elderly.

NEW BUSINESS I
Dr. Barbara Rimer

Dr. Rimer asked for suggestions as to items to be addressed as new business during the second day of the meeting. She called attention to the September/October 1997 issue of *Preventive Medicine,* which features a report of the NCI conference on behavioral research priorities in cancer control.

NCAB Policy Statement--Dr. Schein presented for approval a draft of the NCAB policy statement, Impact of Managed Care on Cancer Clinical Investigations. The statement was developed by an *ad hoc* group of seven Board members and was based on NCAB discussions of the issue and testimony from a broad range of constituencies, notably the President's Cancer Panel. Dr. Schein commented that the definition of managed care was broadened over time to include both the private and public sectors, most notably Medicare. He commented that the report of the Clinical Trials Program Review Group (CTPRG) would further reinforce the message that managed care poses a threat and is becoming a serious obstacle to clinical cancer research. Dr. Schein emphasized the importance of placing NCAB concerns about this issue in the public record. Two major elements of the draft statement are: (1) that, at a minimum, participation in a cancer clinical trial, assuming the study was well- designed and appropriately reviewed, represents an acceptable standard of care at the present time; and (2) that managed care organizations, including Medicare, are among the principal beneficiaries of such clinical investigation and that it is appropriate for these organizations to make investments and contributions to the clinical trial cost in the form of reimbursement for basic clinical care that must be provided in the setting of clinical investigations.

In response to a question about how the statement would be implemented in terms of communication after it becomes official Board policy, Dr. Schein suggested the following: (1) continued championing of the issue by the Panel through its channels of communication with the President; (2) use of the statement in channels available to the NCAB as a whole and to individual members; and (3) use of the statement by NCI staff in discussions with Congress and the administration and in dealings with the managed care industry. The periodic column that NCAB has been invited to write for Cancer was suggested as another venue for communication. Dr. Schein acknowledged the need for more data as the situation evolves, in particular, to determine some method of measuring the impact on existing clinical trials by the barriers imposed by managed care. This will be on the agenda of the Subcommittee on Clinical Trials.

After further discussion, a vote on the statement was postponed to the following day, pending the incorporation of revisions suggested by various members of the Board.

NCI SCIENCE INFORMATION SYSTEM
Dr. Frank Hartel, Ms. Sherri de Coronado

In introducing this presentation, Dr. Klausner noted that although much of what the NCI does relates to information, accessing the massive amount of information that encompass the activities and work of the NCI has been difficult. Moreover, it has became increasingly evident that much of the larger extramural scientific and lay community are unaware of the work of the NCI or are experiencing similar difficulties in accessing information. To remedy this situation by tapping into the emerging scientific field of data management and linguistic analysis, Dr. Klausner asked the Office of Science Policy (OSP), to develop a comprehensive Science Information System (SIS) that would enable searches through many different databases and types of machines. Dr. Klausner introduced Dr. Frank Hartel to describe the rationale for and architecture of the system, progress in developing the first modules, and plans for the future.

Dr. Hartel stated that planning and team assembly for the SIS project began in the current fiscal year and software development shortly thereafter. As an applied research effort, the project is expected to continue for several years. Goals of the project are to make it possible for people to deal with data bases in terms of scientific concepts; to overcome barriers created by the multiplicity of sources on the Internet and within the NCI with their unique terminology for identical concepts, idiosyncratic commands, and complexity; and to give NCI managers new tools for analyzing the NCI's extramural and intramural research portfolio as well as for accessing information on other extramural research to identify opportunities and needs.

The OSP approach was to build the SIS as modules, each to address a specific user task or general need, then develop a unifying framework in which all modules operate similarly. The modules fall into three broad categories, those that: (1) hide complexity from the SIS user, (2) help users do their job more easily by putting scientific information into a more accessible form, and (3) help users analyze by scientific concept and question. Dr. Hartel emphasized that SIS is intended to be a resource that facilitates access to information where it is already stored and that organizes the information for easier use. The SIS will be a repository only for information not available elsewhere. In addition to successfully developing the technology, the project depends on NCI staff and the extent to which they use the modules that are built, so that valuable scientific management information is stored in a way that will enable staff to share and locate the information. Dr. Hartel pointed out that systems of this type have an impact on how people see themselves, their jobs, their organizations, and their relationships with other people. The OSP, therefore, will begin an initiative to determine the social implication of this type of change.

Ms. Sherri de Coronado then demonstrated prototypes of two modules in progress--the Intramural Research Database and the Scientific Reports Database. The Intramural Research Database contains information on staff, laboratories, and projects. This module combines the full-text searching capability with that of online data entry to facilitate more frequent updates of the information. Ms. de Coronado demonstrated several important features of the module. Plans are to add more tools to provide reporting capability and to fully extend the online data editing. The OSP intends to transfer responsibility for operating the system to the division staff who are using it after the system has undergone the necessary modifications to make it operational and robust. In response to a question, Ms. de Coronado clarified that the Intramural Research Database is a stand-alone module for intramural use only, but the SIS as envisioned will encompass the whole portfolio of research and be accessible by the external community.

Ms. de Coronado summarized features of the Scientific Reports Database. Full reports and brief

summaries of all NCI meetings will eventually be available in this database, with links to Web sites that use the information and to a module called the Document Store that resides on the SIS server. Using a standard or an *ad hoc* query, searches can be conducted by meeting type, sponsor, topic, title, or key word. Although the prototype of this module was demonstrated as a resource for science management, a longer term goal is to make the module useful for the conduct of research. A module known as the Coding Engine is being developed to standardize the coding and indexing of all types of scientific information with the same set of NCI terminology and definitions. This module will be accessible from multiple applications.

Dr. Hartel emphasized that the OSP approach to developing the SIS has been to determine specific needs from NCI staff, build a unitary bit of software, and have it tested by the users before designing the final module. Although the Scientific Reports and Intramural Research Database prototypes were done in Web browsers, OSP plans to create a desktop application that will be downloaded into staff computers and maintained by the OSP. Currently, about 10 modules have been defined. SIS modules under development, in addition to the two demonstrated, are the SIS Navigation Module, Document Store, Biotechnology Database, Query Translator, and Coding Engine. Development of the latter two will be driven by the Library of Medicine's Unified Medical Language System (UMLS). The UMLS has a data structure that maps individual scientific terms, words, and phrases to underlying scientific concepts and categorizations of scientific inquiry and knowledge. The Coding Engine module will use the UMLS as an information resource to create a coding list that can be used throughout the Institute. The Query Translator module will use the UMLS to access all of the sources of information in the biomedical knowledge space, where a particular kind of term is used, to enable the user to retrieve information from all of those sources without accessing them individually. Ultimately, the system will build a body of scientific information describing all aspects of Institute operations in a form that is accessible and can be brought to bear on conceptual questions.

NCI SCIENCE INFORMATION SYSTEM
Questions and Answers

Dr. Sharp asked if the SIS would ultimately provide the capability for real-time interactions among laboratories and investigators, and if so, would the modules be developed on machines and servers that are typical of a university. Dr. Hartel stated that such a module has been discussed, and the software used would be readily available and would crosscompile on any platform. In addition, the completed NCI modules will be available for use by other institutions.

CLINICAL TRIALS PROGRAM REVIEW GROUP (CTPTG)
Dr. James Armitage

By way of introduction to the report of the CTPRG, Dr. James Armitage emphasized the size of the clinical trials establishment with the involvement of people at all levels throughout the cancer treatment community. The question posed to the CTPRG by Dr. David Livingston, BSA Chair, early in the process was to determine whether the clinical trials establishment had consolidated to the extent that bureaucratic problems were slowing the process of translational science, and if so, how to invigorate the program. The CTPRG came to recognize that recommendations could be made on two levels—as suggested tactics or as structural changes that might dramatically alter the efficiency and output of the clinical trials enterprise. The Review Group's overall viewpoint of the clinical trial entity was that cooperative groups are necessary for a number of reasons. They constitute the Nation's laboratory for clinical science, provide a way to support clinical scientists, facilitate translational research, and provide a way to focus the expertise and efforts of clinical scientists on problems of translation.

Dr. Armitage reviewed questions included in the charge to the CTPRG and the process

established for gathering information and considering the broad issues implicit in the charge questions. The report is structured on the basis of those issues as follows: retention and recruitment of clinical scientists; recruitment of participants to clinical trials; improving clinical trials methodology; increasing collaboration and cooperation in clinical trials; and the organizational framework and structure for implementation of clinical trials at the NCI. Each of these chapters contains recommendations specific to the issue. At the end of the process, a number of recommendations were identified by vote of the committee for special emphasis, and these were included in the Executive Summary. Of that number, the recommendations to establish a patient-oriented clinical research study section and to increase funding for the cooperative groups to recommended levels produced the strongest consensus among members. Dr. Armitage then reviewed the specific recommendations included in each chapter of the report.

Retention and Recruitment of Clinical Scientists in Oncology. Major retention issues heard in the testimony related to the investigators' belief that a successful career were possible. Recommendations were to establish a patient-oriented clinical research study section in the CSR and emphasize salary in awards to mid-career and senior scientists to ensure protected time to devote to clinical investigation. Recommendations for training new clinical scientists were: (1) to add clinical investigator salary lines of 3–5 years duration to cancer center core grants; (2) to expand K12 and T32 awards and direct K08 awards to patient-oriented research; and (3) to establish at least 10 fellowship programs to provide a formalized academic degree program for clinical scientists.

Recruitment of Participants in Clinical Trials. Recommendations were: (1) to continue improving efforts to recruit and retain minorities, underserved populations, and the elderly in clinical trials and to tailor approaches to address linguistic and cultural differences; (2) to increase funding for cooperative groups to ensure adequate patient accrual; (3) to design clinical trials that reduce the amount of data collection and focus on large, fairly simple trials to establish treatment differences definitively; (4) to simplify and broaden entry criteria; consider a range rather than an absolute set of parameters; (5) to encourage NCI-designated cancer centers to participate in cooperative group research; ensure that participation is viewed favorably in the cancer center review process; (6) to develop strategies to convince payers that clinical trials are the preferred way to care for patients; (7) to initiate a high-quality patient-oriented public awareness campaign presenting the value of clinical trials; (8) to integrate representatives of patients and high-risk communities in the decisionmaking process; and (9) to modify and simplify the informed consent process; work with the Office for Protection from Research Risks (OPRR) to develop a template for widespread distribution.

Improving Efficiency in Clinical Trial Methodology. Recommendations for harmonizing methodology among cooperative groups conducting clinical trials were: (1) use the same protocol guidelines; (2) simplify eligibility criteria for all cancer clinical trials; (3) standardize definitions for study endpoints; (4) reduce the number of study parameters required; (5) expedite the protocol development process in the groups; (6) use the same common data collection forms in the cooperative groups and cancer centers; (7) develop common toxicity criteria; (8) develop common biostatistical principles; (9) develop common and simplified procedures for adverse drug reaction and adverse event reaction reporting; and (10) simplify informed consent documents.

To improve the intergroup study process and meet the goal of cost-effectiveness in the clinical trials system, the Review Group recommended the following: (1) investigator initiative should be the basis for the decision to conduct an intergroup trial, and the intergroup process should be harmonized and simplified; (2) extra funds should be provided to the coordinating group to cover additional expenses; (3) systems should be

developed for awarding proper credit and funding to each participating institution; (4) all participating groups should be able to conduct direct registration and submit forms directly to the coordinating group; and (5) tissue samples and related clinical data should be stored and maintained by the coordinating cooperative group. The Review Group believed that electronic transfer of communication could occur among the groups, cancer centers, and the NCI if the recommendations pertaining to standardization and harmonization of data collection were implemented. These considerations led to the recommendation that all NCI-funded cooperative groups and cancer centers should be provided with the means to access all relevant electronic databases, and they should be primary participants in the development and testing of the new NCI informatics system.

Increasing Collaboration and Cooperation in Clinical Trials. Recommendations of the Review Group were as follows: (1) the NCI should urge the Food and Drug Administration (FDA) to form a single oncology advisory committee; (2) the NCI should enlist the clinical trials and patient advocacy communities and the pharmaceutical industry to work with the FDA to address the issue of uniform standards and reporting requirements; (3) legal templates should be developed for interactions between universities, cooperative groups, and industry for material transfer agreements, clinical cooperative agreements, and Cooperative Research and Development Agreements (CRADAs); (4) the public should have access to all information about ongoing clinical trials, except for those funded totally by private interests; (5) cooperative group grants should include a salary commitment to the responsible committee chairs to ensure that time and effort are matched by salary support in the planning, implementation, and review of trials; (6) the cooperative groups and CTEP need well-defined time lines for protocol development, approval, and activation, with clearly stated consequences of not meeting those time lines; (7) the NCI Decision Network needs to be publicized and would benefit from external input; and (8) the NCI should work with other agencies and private organizations to determine the actual costs associated with Phase I through Phase IV clinical trials.

NCI Administrative Structure and the Clinical Trials System. Recognizing that responsibility for the administration and coordination of NCI extramural clinical trials resides largely within the Cancer Therapy and Evaluation Program (CTEP), DCTD, the Review Group recommended the following specific actions: (1) for Phase III studies and Phase II studies not involving new drugs, the CTEP should approve concepts and collaboratively establish research priorities, and its authority should be otherwise limited to regulatory and safety issues and prevent unnecessary duplication; (2) the cooperative groups should be provided with the authority to establish priorities and conduct studies for most prevention and control trials; and (3) amendments and addenda to the trials should become the full responsibility of the group conducting the study; amendments should be filed with, but not require, the approval of the NCI.

Recommendations relating to relationships with the NCI were: (1) the separate protocol review process of DCTD and Division of Cancer Prevention (DCP) should be combined; (2) if legislatively possible, the interval for funding established cooperative groups should be lengthened from the current 5 years to 8–10 years; (3) cooperative groups should be engaged as early as possible in CRADAs negotiations that will require group participation; (4) funding for cooperative group operations should be based on the costs of performing as a headquarters office and should be proportional to Community Clinical Oncology Program (CCOP) membership; and (5) therapeutic trials conducted through the CCOP mechanism should be transferred to the DCTD.

Dr. Armitage noted that the questions about the number and configuration of groups in the clinical trials system were not addressed in the Review Group's report. The experience

of the Group in attempting to reach a consensus on this issue suggested that recommendations about the optimal number of cooperative study groups will only be achieved by the identification of a small committee of individuals with no vested interest in the existing groups. The charge of that committee should be to review numbers and performance of existing groups and base recommendations on issues of quality not process, emphasizing the goals and values desired in the clinical trials program. In closing, Dr. Armitage observed that major advances in common diseases have come from studies in the clinical cooperative group setting, and that the intergroup process provided an even more effective mechanism for focusing the efforts of many on problems of particular importance. However, the most efficient targeting of resources and effort would be possible if specific practice problems in ongoing clinical trials could be identified quickly (registries provide this type of data for specific procedures like bone marrow transplantation) and addressed. Dr. Armitage posed the challenge of developing the necessary mechanisms to do this. In summary, Dr. Armitage stated that the clinical trials system, which is peopled with dedicated NCI staff and excellent clinical scientists, needs to be modified remove obstacles from the path of efficiency and productivity. Clinical trials funding should reward desired ends, and all participants should recognize that the enemy is cancer.

CLINICAL TRIALS PROGRAM REVIEW GROUP (CTPTG)
Questions and Answers

Dr. Klausner thanked Dr. Armitage and members of the Review Group on behalf of the Institute and noted that an implementation group will be assembled to address the NCI response to the recommendations. Dr. Rimer extended thanks to the committee on behalf of the NCAB. She asked Ms. Deborah Collyar and Dr. Charles Coltman to comment as members of the Review Group. Ms. Collyar noted her support of the report as an expression of the first step to improving the existing clinical trials system. She stated, however, that the clinical trials process should be improved to incorporate the new therapy approaches, because the existing process was based primarily on the chemotherapy model. Ms. Collyar noted that the infrastructure also should be reviewed and expanded to reflect more closely the fact that the majority of patients are diagnosed and treated in community settings, not academic centers. Dr. Coltman stated that although uniform conformity of opinion was not possible, the report reflects a high level of consensus among the 29-member group. Recognizing that a larger clinical trials program was needed if improvements in the basic science laboratory were to be translated into humans, the Working Group's recommendations, nevertheless, focus only on ways to improve the efficiency of the current system. Dr. Coltman commented that the issue of the uniformity of management of data and aspects of the conduct of the clinical trials should not be construed to inhibit the intellectual property of clinical investigators in how they design clinical trials, which can be quite diverse even when using the same tools.

Ms. Ellen Stovall emphasized the need in a review process such as this to hear from people who have been on clinical trials. Dr. Frederick Li asked if the Review Group had considered the relative merits of highly targeted groups such as the National Surgical Adjuvant Breast and Bowel Project (NSABP) versus the more general groups like the Eastern Clinical Oncology Group (ECOG) as measured by citation, index, publications, and other objective measures. Dr. Armitage reiterated that reaching consensus on the issue of numbers and structure of the groups was not possible. The Review Group's attempts to gather data on objective measures retrospectively was not successful. Dr. Armitage agreed that such output information will be important if the system is to be improved and that a prospective plan for collecting that information will be needed. Dr. Richard Boxer observed that additional funding applied to help retire the education debt of the young physician considering a specialty in clinical science would make a significant impact on recruitment. Dr. Pelayo Correa expressed concern that moving prevention trials to the treatment arm of the NCI would be detrimental to the prevention

trials. Dr. Armitage commented that treatment and prevention trials must have access to the one clinical trials system built to test their ideas, but a matrix system could be developed so both types of trials could be administered differently. Dr. Coltman noted that therapeutic groups have demonstrated the ability to enroll patients into large cancer prevention trials.

Dr. Schein commended the work of the Review Group in assessing the status of the clinical trials program and synthesizing the recommendations. He pointed out that an underlying theme of the report was the frustration felt by clinicians at the length of time from conception of the idea to completion of the statistical report for the trial. The process should be greatly truncated, including heavy involvement in the design phase by the FDA so that regulatory requirements are ultimately satisfied. Dr. Schein asked if the Review Group believed the clinical trials system in place was ideally suited for the amount of translational research needed to validate the new research ideas that are being generated. Dr. Armitage pointed out that the cooperative groups are the Nation's laboratory for clinical research and are the place where translational ideas are tested. However, the challenge will be to bring the appropriate basic and clinical scientists together to work on them. Dr. Dickersin expressed concern that the clinical cooperative groups are not flexible enough to respond quickly to new ideas. She favored revising the recommendation related to exempting industry trials from public disclosure in light of the current negotiations between the NCI and FDA as part of the National Action Plan. Dr. Dickersin approved the general concept of the large, simple trials but expressed concern that breast cancer outcomes of importance to patients are in danger of being overlooked in such studies. Similarly, the benefits of using standardized data forms must be balanced with the potential benefits to be derived from the additional data produced by asking questions in different ways in different trials.

Dr. Vainutis Vaitkevicius expressed strong support for the principal recommendations, particularly those with the potential to simplify and expedite patient recruitment, to reduce the number of exclusion criteria that tend to reduce the patient pool, and to simplify data collection. Dr. Alfred Goldson commended the report, particularly those recommendations that would make the system more user friendly and therefore more accessible to physicians caring for underserved groups. He pointed out the need to wipe out the 15 percent difference in survival rates among African Americans by recruiting them to clinical trial protocols. Ms. Frances Visco expressed concern that the recommended changes might facilitate the initiation of trials with unimportant questions and poor designs. Dr. Alison Martin, FDA liaison representative, stated that the FDA shares the concern about facilitating new and easier ways to find better cancer treatments. As a point of clarification, she noted that FDA's multiple advisory committees are rooted in institutional history, and the reasons for the routing of drugs to one or the other may not be obvious. The FDA has heard from some communities on this issue and is open to opinions, data, and working relationships. Discussions with CTEP have already been initiated, and an international harmonization effort is under way. As a point of information, Dr. Wittes stated that studies to ascertain the cost per patient of clinical trial care versus the standard of care are in progress, and the issue would be discussed at the meeting of the Subcommittee on Cancer Centers.

The vote on a motion to accept the report as the beginning of the process was postponed until the following day.

LEGISLATIVE UPDATE
Ms. Dorothy Tisevich

Ms. Dorothy Tisevich reported that the House and Senate versions of the Labor/HHS bill are headed for discussion and resolution by the Conference Committee. Scheduled future hearings include testimony by Dr. Klausner on the NCI report on exposure to Iodine-131 from the Nevada Atmospheric Test Series. The NCI has been conducting studies under a mandate from

Congress to address both the dose estimate and estimates of risk of thyroid cancer from exposure. Legislation recently enacted includes the Balanced Budget Act/Taxpayer Relief Act and the Stamp Out Breast Cancer Act. The latter provides for the sale of first-class postage stamps with an alternative rate up to 25 percent higher than regular first-class postage. The revenue that is generated will be divided between NIH and the DoD (70% and 30%, respectively) for breast cancer research. The Government Accounting Office will report to Congress after 2 years on the effectiveness of the program. The One-Stop Shopping Bill was folded into the FDA Modernization and Accountability Act, and the provision to develop a centralized database of clinical trials information for life-threatening diseases was modified to make it subject to the availability of appropriations. The administration has issued a statement about cloning research and is expected to develop a legislative proposal. In the area of genetic privacy, a number of bills have been introduced since June addressing various aspects of the issue such as health insurance considerations, prohibition of discriminatory practices in the workplace, use of genetic information by life insurers to deny coverage, and prohibition of discrimination in hiring. Tobacco legislation targets deterrents to tobacco use by minors, a ban on smoking in federal buildings such that designated smoking areas would cease to exist, and increased assessments on participants in federal support programs for tobacco. The Senate has repealed the provision in the tobacco settlement legislation that would have provided a tax break to tobacco companies to help offset the cost of the settlement.

LEGISLATIVE UPDATE
Questions and Answers

In response to Dr. Goldson's question about the prospects for change in prostate cancer funding, Ms. Tisevich noted that this year's appropriation reports from the House and Senate contain very few directives and are encouraging in certain areas such as prostate cancer in minority populations.

CANCER CONTROL PROGRAM REVIEW GROUP REPORT
Dr. David Abrams

Dr. David Abrams presented the report of the Cancer Control Program Review Group (CCPRG) for Board approval and acceptance. By way of introduction, he described the deliberative process undertaken by the Review Group, including the solicitation of information from NCI staff and the extramural research community, review of NCI cancer control program documentation, and eight open and closed meetings during an 8-month period. He then presented some of the background rationale for the report in terms of definition, organization, and scope of the evolving cancer control program. In attempting to define the area, the Review Group decided to assess the current status of cancer control research and concentrate on defining the area for the short term, recognizing that the division's scope and boundaries can and should change as new knowledge and innovation evolves from various resources. The Review Group began by defining the background contexts and implicit paradigms that have driven this research in the past. The natural course of cancer was viewed as a continuum progressing from youth and low-risk status, through high-risk by virtue of genetic susceptibility or the various environmental exposures, through the transition from disease-free to cancer status, through cancer treatment, and finally through rehabilitation and survivorship, with many opportunities for cancer control. In addition to the primary prevention opportunities of lifestyle and behavior change and environmental management, opportunities for cancer reduction at every level of society now exist for biomedical preventions and chemopreventions. Given what is already known today, many of the most prevalent cancers could be dramatically reduced if only the optimal lifestyle, environmental, and biomedical practices could be implemented in every level of society. This goal can be achieved by investing in both basic and applied research on behavior change, broadly defined as individual, collective, and policy changes. The Review Group, on the basis of existing knowledge and emerging technologies, believed strongly that a

partnership combining the best of behavioral social, population, and public health science with the best of biomedical science, innovations in diagnostics, and therapeutics, would result in a powerful multiplicative or synergistic armamentarium for cancer prevention and control. In the end, the Review Group merged the vertical and horizontal dimensions of the Greenwald-Cullen and Bypass Budget definitions and added the third dimension of translational research to define cancer control research as "the conduct of basic and applied research in the behavioral, social, and population sciences that, independently or in combination with biomedical approaches, reduces cancer risk, incidence, morbidity, and mortality." To accomplish a partnership between the biomedical and sociobehaviorial paradigms, the NCI must make a long-term commitment to balance resources investments in the basic and applied aspects of both paradigms.

Dr. Abrams noted that the Review Group then addressed the issue of organizational structures within the NCI to optimize the full range of opportunities to reduce the cancer burden on society as rapidly and efficiently as possible, based on what is currently known. The Review Group endorsed the creation of the separate DCCPS and the position of DDES in the July 1997 reorganization of the NCI as conforming closely with its principal recommendations. The Review Group identified areas of research that should be emphasized in the new Division: (1) create a unit focused on basic behavioral and social research in cancer control; (2) create a research focus in informatics and communication; (3) establish programs that recognize the role of behavioral prevention across the lifespan; (4) increase integration of and support for cancer screening research; (5) create a research focus on rehabilitation and survivorship; (6) establish research links to various health care delivery systems; (7) expand cancer surveillance and produce a "cancer report card;" (8) maintain strong support of biometry and applied research within the new Division; (9) focus research efforts on underserved populations and those with a disproportionate cancer burden; and (10) expand training in cancer control research. Specific recommendations for NCI action within each research area are included in the full report.

Within the recommendation to establish programs that recognize the role of behavioral prevention across the lifespan, the Review Group specifically identified a need to address the role for government and research in ensuring that biomedical and behavioral interventions are disseminated to every level of society. Also included in the specifics for this research area were recommended methods and parameters for conducting large-scale cancer control trials. The Review Group also believed that pure dissemination or services without a research agenda are not in the scope of the new Division. Recognizing the importance of disseminating empirically validated "best practices" to the entire Nation, however, the Group recommended that the NCI create a unit with the role of transferring the findings of cancer control research to public health practice and evaluating the effects. Tracking the fidelity and population impact of proven intervention should become an expanded role of SEER Program, resulting in the production of new and timely "report cards." Such report cards could then be employed to identify gaps and successes to inform the planning of future research priorities at the highest levels of NCI leadership.

In summary, Dr. Abrams stated that the Review Group recommends creating a basic behavioral science mechanism to drive applications research to complement the basic biomedical science model. The Group advocates synergistic interaction that will have an impact at every level—societal, environmental, community, organizational, group, and individual--to reduce the burden of cancer and use the funds invested for that purpose for the long-term good of society.

Asked to comment as members of the Review Group, Ms. Stovall, Dr. Li, Dr. Sandra Millon-Underwood, and Dr. Robert Day acknowledged the leadership of Dr. Abrams, Dr. Paulette Gray, Dr. Marvin Kalt, and Dr. Kathi Hanna and the contributions of NCI staff and contractors in producing the report. Dr. Li observed that the strength and weakness of cancer control is the breadth of the subject area and that the challenge will be to encourage the necessary collaboration among people from the various disciplines. Dr. Millon-Underwood emphasized

the focus of the report on the need for additional support for training and for interdisciplinary and multidisciplinary research as well as a focus on at-risk and underserved populations.

CANCER CONTROL PROGRAM REVIEW GROUP REPORT
Questions and Answers

Dr. Bishop asked whether the need for recruitment of people into cancer control training had been considered, pointing out that the field is not sufficiently visible to undergraduates and those contemplating graduate work or postdoctoral training. Dr. Abrams noted that the intent of the recommendation was to assemble a critical mass of new scientists by making a long-term commitment to the field and by ensuring that research opportunities exist. Dr. Peter Greenwald added that a strong national organizational effort will be needed with the leading academic research institutions to develop the necessary faculty, research programs, and endowed professorships.

To a question from Dr. Sharp, Dr. Klausner noted that responsibility for population-based environmental carcinogenesis is one of the research areas that cannot uniquely sit in any one division but requires multidisciplinary integration and communication within the NCI and with other agencies such as the CDC, FDA, National Institute of Occupational Safety and Health (NIOSH), National Institute of Environmental Health Sciences (NIEHS), and the Environmental Protection Agency (EPA). Dr. Sigal asked what mechanisms would be developed to engage other agencies in the implementation of the cancer control program envisioned in the report. Dr. Rimer noted that these mechanisms will be identified over the coming months and years as the NCI identifies the boundaries of its mission. The NCI will be building on the research that already is in progress and the work that has been done. Dr. Freeman commented on the need to consider the role of government in solving the problem of the 40M uninsured and 55M underinsured in relation to NCI's responsibility for implementing the goals of the National Cancer Program. Dr. Calabresi suggested that the President's Cancer Panel could plan future conferences to raise the level of national awareness to specific issues that need emphasis and then bring them to the attention of the White House. Dr. Gerald Poje, NIEHS, pointed out that coordination among NIH Institutes is improving but that moving to include interfaces with all of DHHS and beyond to other departments will require a new paradigm of how to engage each other in the monumental task outlined in the report. Dr. Vaitkevicius recommended the program undertaken by the NCI in the past to solve the problem of a lack of clinical oncologists as a model for implementing the training recommendation. Asked to comment from her perspective as newly appointed Director, DCCPS, Dr. Rimer noted that the report is consistent with the kind of programs, policies, and directions envisioned for the Division, and Dr. Susan Sieber, Acting Director, DCCPS, has been working on those issues since October 1. She acknowledged the contributions made by the chair and members of the Working Group and by NCI staff and contractors.

A motion to accept the report of the Cancer Control Program Review Group on behalf of the NCAB was seconded and approved unanimously.

COLORECTAL CANCER SCREENING
Dr. Bernard Levin

To put this topic in context, Dr. Rimer noted that mounting evidence on screening for colorectal cancer (CRC) and the recommendations by a number of organizations suggested that the time had come for the NCAB and NCI to consider the evidence and decide on an appropriate course of action. She introduced Dr. Bernard Levin, Vice President for Cancer Prevention, M.D. Anderson Cancer Center, and most recently the Co-Chair for the American Cancer Society's (ACS) National Conference on Colorectal Cancer Screening. Dr. Levin stated that he would be presenting a particular viewpoint on CRC screening based on the work of many investigators,

but that the issue is surrounded by a number of different opinions. Important questions to consider focus on the tools that should be applied, the strategy (e.g., intervals, diagnostic evaluations) to be implemented following positive tests, and the personnel requirements and costs.

To demonstrate the importance of the issue, Dr. Levin noted that colorectal cancer accounts for approximately 55,000 deaths per year, is the second leading cause of cancer death (the most common cause among nonsmokers), and affects men and women similarly. Since 1973, the CRC death rate has decreased by 17 percent, partially due to an increase in screening, some benefit of adjuvant treatment, and better surgery. However, the mortality rates are differentiated and are increasing for African American men and are only stable for African American women for reasons that are not known. Dr. Levin noted that the process of colon carcinogenesis is better understood at the molecular level than almost any other benign to malignant transformation. Investigators have expanded the body of knowledge to include an understanding of the chromosal location of alterations, mutations, of oncogenes and tumor-suppressor genes, the role of mismatch repair genes in sporadic lesions and in hereditary nonpolyposis colon cancer, and the role of growth factor receptors in the neoplastic transformation. Vital information also exists on the time for transformation in the average risk population from no neoplasia to adenomas to cancer, and this provides multiple windows of opportunity for early detection and screening.

Dr. Levin made the case that colorectal cancer is suitable for screening because of the step-wise progression of events in tumorigenesis, the protracted process (between 10 and 20 years) with multiple windows of opportunity, and definable levels of risk based on age, disease history, and familial occurrence. Moreover, CRC screening meets the World Health Organization's (WHO) basic requirements for screening. About 75 percent of colorectal cancer falls into the so-called sporadic or average-risk category, and this group is the focus of much of the screening activity and many of the guidelines. The concept for CRC screening is to use a simple, affordable, and acceptable test to identify a subgroup more likely to have a significant lesion, in whom it is justifiable to perform an invasive diagnostic test, ideally colonoscopy. Dr. Levin reviewed the characteristics of available screening tests (i.e., fecal occult blood tests [FOBT], flexible sigmoidoscopy, double contrast barium enema (DCBE), and colonoscopy) according to performance, complexity, effectiveness, levels of evidence, and risk. He then described guaiac FOBT methodology, which involves a complex series of interactions requiring scrupulous attention to detail to provide the optimal performance.

Dr. Levin reviewed the results from various screening studies. Randomized controlled trials at the University of Minnesota; Funen, Denmark; Nottingham, England; and Gothenburg, Sweden demonstrated reductions in incidence ranging from 15 percent to 33 percent, improved survival, and shift changes to earlier stage disease. To address the question of cost-effectiveness, the Office of Technology Assessment conducted a series of analyses based on the cost per added year of life. The cost for annual screening using the FOBT was shown to be in accordance with estimates for mammographic screening and end-stage renal dialysis, both of which have been accepted as valuable for public health benefit. Randomized controlled trial data are not available for screening sigmoidoscopy, but two case control studies indicate a 70 percent reduction in fatal cancers and a 75 percent reduction in CRC death risk, respectively, within the reach of the instrument, contributing to an overall 30 percent reduction in colorectal cancer. Two large-scale, randomized controlled trials are in progress—the U.S. Prostate, Lung, Colorectal, Ovarian (PLCO) Trial and the United Kingdom Trial--which will provide data in the future on the positives and negatives of CRC screening by sigmoidoscopy. The National Polyp Study has verified the importance of the adenoma to carcinoma sequence and the potential value of removing adenomas at the stage prior to their developing invasiveness. A National Colonoscopy Screening Trial has been proposed with the primary objective of evaluating colonoscopy and its impact on CRC mortality and the secondary objective of collecting family histories, diet information, and tissue and blood samples.

Coincident with the clinical trials and studies, guidelines have been issued by the U.S. Preventive Services Task Force (1995), the Agency for Health Care Policy and Research (AHCPR) and Gastroenterologic Societies (1997), and the ACS (1997). Dr. Levin noted that the guidelines are remarkably concordant in their recommended (and practical) strategies for evaluating individuals at high, moderate, and low risk for colorectal cancer. He concluded that CRC screening has come of age and will be increasingly important as colorectal cancer becomes a major international health problem due to the globalization of diets and behavior, as suggested by various immigrant studies. Moreover, the evidence for the effectiveness of screening is consistent and compelling, and federal reimbursement has recently been approved. Dr. Levin noted that partnerships have been developed among the ACS, CDC, and the Digestive Health Initiative of the American Digestive Foundation Association to begin addressing the issues. Tasks for the future include: (1) the reduction of barriers to adherence through education of the public and health care system and creation of incentives for the health care system, (2) improved imaging and molecular diagnostics for average-risk individuals, and (3) improved genetic testing for high-risk individuals.

COLORECTAL CANCER SCREENING
Questions and Answers

In response to a comment about perceived problems with fecal occult blood testing, Dr. Levin agreed that the technology needs improvement. For example, the development of immunochemical tests to circumvent the issue of compliance with diet would be a substantial improvement. About 20 percent of the population undergo screening, but screening by FOBT and flexible sigmoidoscopy is as high as 70 percent in groups promoting compliance such as Kaiser Permanente in Northern California. Increasing the proportion overall will require the commitment of health care providers and the construction of an efficient mechanism. Findings from focus groups indicate that individuals who manage the large groups, with notable exceptions, are interested in widespread screening but face real implementation problems. Demonstrations of feasibility are needed.

Dr. Freeman asked what can be done to elevate CRC screening to the importance that it deserves on the basis of incidence and mortality figures. Dr. Levin agreed that the issue needs widespread public promotion of the type successfully accomplished by breast and prostate advocacy groups, including the identification of prominent spokespersons. Dr. Freeman suggested that the NCAB should consider assuming a greater leadership role in this disease, and Drs. Sigal and Schein endorsed this position. Asked about the reason for the differential mortality rates among African Americans, Dr. Levin suggested that a combination of access problems due to socioeconomic status and cultural beliefs, diet, and lack of diagnostics probably accounts for the differences, and further study is needed to answer that critical question and to confirm preliminary findings in an ACS study of a biologic difference.

Asked about the cost of routine screening over the lifetime of a patient of average risk relative to the cost of a later diagnosis and the associated medical care, Dr. Levin reiterated that the Office of Technology Assessment (OTA) estimates put routine screening within the same range as other usually acceptable screening or interventions. Viewed as a national expenditure, costs were estimated for Medicare coverage at about $500M per year. Dr. Levin noted that data are available to support the position that early cancer detection or the removal of adenomas may be a highly cost-effective strategy.

In response to a question about the availability of doctors to perform flexible sigmoidoscopies to the extent that would be needed, Dr. Levin noted that the issue could be solved by using physicians assistants and nurse practitioners, as is already happening in a number of centers. He suggested that establishing screening centers is another possible solution, with crosstraining for the staff in all types of screening procedures. In conclusion, Dr. Rimer recommended the topic

of CRC screening for continued attention by the NCAB and as a focus for discussions of evidence-based medicine.

NIH AND MANAGED HEALTH CARE ORGANIZATIONS
Dr. Edward Wagner

Dr. Rimer introduced Dr. Edward Wagner, Director, Center for Health Studies and the Sandy Macoll Institute for Health Care Innovation. Dr. Wagner is currently serving a year as advisor to Dr. Harold Varmus in the NIH Office of Science Policy. Dr. Wagner announced that he would bring the Board up to date on the NIH initiative on managed care under the direction of the Director and the OSP. The initiative arose out of concerns related to the apparent adverse effect of managed care on clinical research in general and cancer trials in particular. As part of the NIH initiative, the OSP and the American Association of Health Plans (AAHP) have been exploring attitudes about clinical research within the broad range of managed care organizations. Findings indicated that: (1) managed care CEOs, medical directors, and boards were supportive of greater involvement of health plans in clinical research; (2) the current debate has overlooked the 40-year history of HMO-based research and a series of accomplishments; (3) concerns among managed care organizations relate to financial exposure that exceeds usual patient care costs (the autologous bone marrow transplant [ABMT] legacy) and to clinical research protocols laden with unnecessary procedures and visits. Dr. Wagner stated that the OSP has been attempting to deal with those concerns. He noted that managed care's interest in clinical research is deeper than its public relations problem and stems from the commitment of not-for-profit and many for-profit organizations in that clinical research is a common good and that health plans have an obligation to support it. Clinical leaders also understand that optimal patient care for conditions without definitive therapy includes access to approved, peer-reviewed clinical trials. Moreover, findings from health plan-sponsored focus groups have indicated that patients value research and research organizations.

Based on a recommendation of the NIH Clinical Research Panel, the Office of the Director, NIH, is coordinating all NIH managed care initiatives in the OSP, with the goals of (1) increasing the involvement of health plans and their patients in NIH-approved clinical research and (2) developing health plans as active laboratories for clinical and related research. Dr. Wagner reviewed the status of HMO research programs to show that 20 of the largest health plans, from among 30 that were interviewed, had public domain research programs and had made significant contributions in many areas. The 20 health plans represent 30M Americans in their enrollment and have a combined research budget of $80M, more than 50 percent from the federal government, mainly the NIH. Outside funding is a necessary prerequisite of doing public domain research; prevention and cancer are areas of high investigator interest. Dr. Wagner explained that the NIH initiative involves a partnership with the AAHP. NIH efforts include: (1) coordinating all NIH managed care initiatives, (2) establishing an NIH-wide Managed Care Working Group, (3) stimulating and developing substantive managed care initiatives within all institutes, centers, and divisions (ICDs), based on the NCI model, (4) sponsoring a senior advisor on managed care, and (5) encouraging NIH involvement with HMO researchers through their meetings. Negotiating teams have been formed by both parties of the partnership to work on an affiliation agreement, and the partners are cosponsoring a Senior Advisor to the NIH on Managed Care Initiatives. Efforts by the AAHP have included: (1) developing a public statement in support of greater health plan involvement in clinical research with a commitment to cover patient care costs, (2) cosponsoring an annual conference on HMO research with the AHCPR, and (3) developing a clinical research support unit at the AAHP Washington, DC, office as a vehicle for communicating between the NIH and individual health plans.

Dr. Wagner emphasized the need to be aware of barriers to greater health plan involvement, despite the expressed support of clinical research. These barriers relate to the lack of a research infrastructure, the fear of exposure to high-cost experimental treatments, and concern about the

continuity, coordination, and control of patient care when involved with clinical studies. Addressing these issues will be among the challenges for the NIH initiative on clinical research and managed care.

NIH AND MANAGED HEALTH CARE ORGANIZATIONS
Questions and Answers

Points made in discussion included the observation that the NIH initiative does not deal with the infrastructure problems of academic medical institutions and that the managed care definition of clinical research is not sufficiently broad. Dr. Wagner agreed that another initiative may be needed to address the financial health of academic medical centers. He pointed out that leaders of managed care organizations have accepted the definition of clinical research developed by the NIH Clinical Research Panel. A comment was made on the low level of commitment represented by the $20M investment by managed care organizations in clinical research compared with the potential profits of the 20 companies. Dr. Goldson observed that the initiative as proposed appears to represent a viable mechanism for merging well-designed treatment trials with the HMO infrastructure of patients, providers, and funding.

HIV DRUG RESISTANCE PROGRAM
Dr. Richard Klausner, Dr. John Coffin

Dr. Klausner reviewed the changes to the NCI AIDS program effected over the past 2 years of reorganization and restructuring. The NCI budget of about $224M in FY97 for research on HIV and AIDS represents the second largest commitment among the Institutes, exceeded only by that of the National Institute of Allergy and Infectious Diseases (NIAID). One new area of emphasis in the NCI has been the AIDS-related malignancies program, headed by Dr. Ellen Feigal. Cancers that complicate the clinical course of about 30 percent of the individuals with AIDS present an opportunity for research into the unique issues raised by this viral disease and associated with immunodeficiency and immune stimulation, toward increased understanding of AIDS-related cancers and cancers in general. The NCI also has a long-standing commitment to studies in virology and HIV biology, which has resulted in two new initiatives. The first is a collaborative effort within the NCI, with other institutes, and with the extramural community to deal with the issue of viral evolution and resistance biology. Dr. Klausner introduced Dr. John Coffin, Professor of Biology and Microbiology at Tufts University Medical School, who is also working part-time at the NCI, to present his vision of the new program that is being developed.

Dr. Coffin explained that the problem of drug resistance will be addressed in the new program particularly in the context of HIV, although findings will be relevant to other problems in infectious disease and in cancer in general. Relevant issues include: (1) the mortality potential in the United States and worldwide unless effective long-term therapy can be found, (2) the possibility that the suppression of viral diseases, achieved with the combination antiviral therapies, will fall short of providing a long-term solution, and (3) the fact that a fraction of patients fail to show complete suppression of virus load in this therapy or fail at some time after suppression is achieved. Dr. Coffin pointed out that the cause of failure of the therapy in virtually all cases is the appearance of a drug-resistant virus and subsequent development of cross-resistance to all other protease and nonnucleoside reverse transcriptase inhibitors. Transmission of resistant mutations of the virus among patients is a potential problem. The variety of scientific issues to be addressed in the HIV drug resistance program involve structural biology, molecular and clinical virology, epidemiology, and chemistry and will require coordinated thinking about many inter-related problems. The new program will also include animal model studies of population dynamics and resistance mutations, mathematical modeling to develop population biology and, ultimately, translation of the developments into clinical care. Dr. Coffin briefly described studies leading to an understanding of HIV population structures, which will be undertaken as soon as possible. Answers to questions posed in these

population genetics studies will be important in addressing practical issues such as whether anti-HIV therapies can be developed that are resistant to crossresistance, whether treatment strategy (even using available compounds) can be modified for greater efficacy, and how to deal with problems of transmission of already resistant virus.

Dr. Coffin summarized the plans made to date. The HIV drug resistance program will operate out of the Office of the Director, NCI, but will cut across all divisions, as well as major contractors. The program will be centered in laboratories at the Frederick Cancer Research and Development Center (FCRDC). Existing intramural programs will be involved through an internal grant mechanism, and new research groups will be recruited. An advisory committee of extramural experts will be assembled. Planning is in progress for a kick-off meeting for the program and for an Institute-wide meeting to bring together investigators whose research touches on areas that are relevant to the new program. Recruitment is under way for six investigators from among the following areas: biochemistry, mechanisms of genetic variation, molecular virology, virus host-cell interaction, mathematical modeling, clinical studies, animal models, and chemistry.

AIDS VACCINE PROGRAM
Dr. Anthony Fauci

Dr. Klausner introduced Dr. Anthony Fauci, Director, NIAID, to describe the second new NCI initiative, the AIDS vaccine program, which will be a joint venture with the NIAID. As rationale for accelerating HIV research efforts, Dr. Fauci presented data comparing projected annual HIV infections through the year 2000 to show that the number of new cases plateaued in North America at an unacceptably high level, and that the epidemic is still at the peak in sub-Sahara Africa and continuing to accelerate in Asia. Moreover, sub-populations in the United States continue to be at high risk. Dr. Fauci reviewed the evolution of vaccine development in the NIH intramural and extramural programs. Challenges to HIV vaccine development have been the inapplicability of classic vaccine paradigms, unique social and ethical considerations, and unfavorable market forces due to the lack of scientific information. However, reasons do exist for optimism that the development of a HIV vaccine is feasible: (1) vaccine-induced protection has been seen in chimpanzee models; (2) the immune system may be capable of complete control as demonstrated by babies with aborted infection and long-term nonprogressors; (3) mucosal transmission is relatively inefficient; (4) candidate HIV vaccines have proven safe and immunogenic in Phase I and a few Phase II studies; and (5) efficacy trials among high-risk volunteers appear feasible.

Added to the increasingly optimistic scientific picture, research resources for HIV vaccine development have increased in amount and as a portion of NIH funding for HIV-related research (from $111M and 7.9% in 1996 to an estimated $162M and 10% in 1998). The vast majority of NIH AIDS vaccine funding is in extramural projects. Intramural vaccine funding, which accounted for 13.4 percent in FY96, will receive a one-time increase in FY98 to about 17.6 percent to provide base money for the new vaccine center. Taken together, the NIAID and the NCI account for 83 percent of NIH AIDS vaccine funding, intramurally and extramurally. Intramural programs include the NCI peptide antigen vaccine research and the adenovirus vector project and NIAID studies on SIV infection in macaques, the molecular biology of retroviruses associated with AIDS, and vaccines against retroviruses in leukemia and AIDS. Extramural vaccine projects, which are sponsored largely by the NIAID, include the AIDS Vaccine Evaluation Groups (AVEGs) and a variety of other mechanisms that will be coordinated with the new vaccine center. An example of the latter is the AIDS vaccine innovation grants program that funds basic research. The AVEGs will constitute a network for international efficacy trials. Some of the vaccine concepts currently under study are recombinant subunits, live vectors, peptide epitopes, pseudovirions, DNA immunization, and whole-killed or live-attenuated. Dr. Fauci noted, however, that the lack of knowledge of correlates of immunity

and related concepts is a major barrier.

NIAID sponsors an extensive network of domestic and international HIV vaccine and prevention sites for research in the areas of molecular and classical epidemiology and immunology. These sites will provide an already established venue for testing candidates in appropriate areas of the world. The NIAID philosophy in AIDS vaccine research has been and will continue to be maintaining a balance between basic and empiric approaches and involving the NIH, community participation, industry partnerships, and organizational collaborations.

Dr. Fauci explained that acceleration of the national vaccine effort evolved from the idea that a concentrated effort was needed that could capitalize on the talents of intramural scientists and the ability to recruit top scientists from throughout the Nation. An Oval Office discussion with the President of the concept for a NIH Vaccine Research Center led to the May 1997 announcement by the President at Morgan State University that such a center would be established. Funding for construction in the amount of $20M has already been earmarked in the FY98 budget, divided equally between the NCI and NIAID, and a national committee has begun the search for a center director. A facility of about 50,000 square feet will be constructed on the NIH campus, estimated for completion in the year 2000. Currently, the "center without walls" is involving a core of NIH scientists in the integration of modern immunological science with pathogenesis research, the development of immunogens and vectors, and novel creative approaches to vaccines. The NIH Vaccine Research Center will function according to the classic intramural process of proceeding through the scientific directors to the Institute directors, except that in this case the NIAID and NCI will function as if they were a single Institute. The goal of the Center is to stimulate multidisciplinary research in basic and clinical immunology and virology, leading to HIV vaccine design and production.

AIDS VACCINE PROGRAM
Questions and Answers

Dr. Li asked what kind of model would be produced if population genetics were applied to the worldwide pandemic of AIDS, how virulent would the virus become, and whether a vaccine can be produced against the virulent strains that might develop in the future. Dr. Coffin reported much activity extramurally related to modeling of the virus populations of infected individuals and to studying the transmission of the virus, particularly useful in following the spreading epidemic in places like Thailand. He noted that this has been and continues to be an important area for HIV research. Regarding evolution of virulence, the theoretical issues are complicated, and modeling and epidemiologic observation do not appear to have helped address that question. In response to an observation by Dr. Sharp, Dr. Fauci agreed that development of the HIV vaccine will ultimately be done through industrial partners, but the basic science and initial pilot will be a collaborative effort involving government and academic research. As a final note, Dr. Klausner reminded the Board that NIAID and the NCI are collaborating on HPV vaccine approaches for a mucosally transmitted virus in hopes of developing prophylactic viruses for cervical cancer, with the potential benefit of understanding more about immunity that affects mucosal transmission.

NEW BUSINESS II: Subcommittee Reports
Dr. Barbara Rimer

Recognition of the Outgoing Chair. Dr. Kalt, Dr. Sigal, and Dr. Klausner, speaking on behalf of the Board and the Institute, commended Dr. Rimer's ability to inspire confidence, capacity for hard work, energy, fairness, vision, and even-handed and inclusive approach to leadership as Chair of the NCAB. Dr. Rimer was presented a certificate of recognition with the inscription: "This is presented to Barbara Rimer in recognition of her exemplary leadership and service as chairperson of the National Cancer Advisory Board, 1994–1997." In her remarks of acceptance,

Dr. Rimer expressed appreciation of her associations with Board members and NCI staff in grappling with the variety of social, medical, and ethical issues. She acknowledged the support and help received from members of the Board, Dr. Kalt and his staff, her husband, and her staff at Duke University and looked forward to working with colleagues at and around the table as well as in the community in implementing a cancer control program.

Activities and Agenda. Dr. Rimer listed proposed agenda items for the coming year: (1) cross-divisional examination of training; (2) followup on the reports of the Program Review Groups; (3) followup on colorectal cancer screening; (4) cancer genetics (informed consent, confidentiality, social, and counseling issues); (5) the future of cancer surveillance; (6) evidence-based medicine, (6) manage care and followup to the issue of payment for clinical trials; and (7) issues of race, culture, class, and use of health care services in relation to NCI research programs.

Report of the Subcommittee on Planning and Budget. Dr. Sigal presented the minutes of the subcommittee meeting for Board approval. A motion to approve the minutes was seconded, and the vote to approve was unanimous.

Report of the Subcommittee on Clinical Investigations. Dr. Schein presented the revised draft of the NCAB Policy Statement: Impact of Managed Care on Cancer Clinical Investigations and requested a motion for approval. A motion to approve was made, seconded, and passed, with one vote in opposition (and is attached to the these minutes as Attachment 1).

Dr. Schein next presented the following resolution for Board vote: "The National Cancer Advisory Board accepts in principle the findings and recommendations of the National Cancer Institute Clinical Trials Program Review Group. The Board supports the recommendation that the NCI conduct a strategic assessment of the numbers, configuration, and admission of the Cooperative Groups Program." A motion to approve the resolution was seconded and passed by unanimous vote.

As a followup to the subcommittee discussion of the Clinical Trials Program Review Group report, Dr. Wittes outlined the steps to be taken in response to the request for a strategic assessment. A broadly representative implementation group will be empaneled to interact with NCI staff in reacting to and in generating various models for improving aspects of the present clinical trials system. The agenda will include revisiting the goals of a clinical trials program and working on solutions to the question of how to optimize the program and position it for the coming decades. Dr. Wittes listed the key barriers to interventional research as follows: (1) science, its relationship to clinical trials; (2) development, making the program optimally available to the community of scientists; (3) peer review; (4) consensus development; (5) simplification of trials; (6) streamlining procedures; (7) informatics; (8) information dissemination; (9) reimbursement for participation; (10) broadened access; (11) partnership formation, with payers, health care delivery organizations, advocacy groups, industry, and the FDA; (12) human subjects protection (interactions among OPRR, NCI, FDA, investigators, and IRBs); and (13) translational interface and adequacy of the measures in place. Dr. Wittes concluded by noting that NCI's internal implementation committee will complete a series of proposals for many of these issues by the time the advisory group meets for the first time. He emphasized that, while the NCAB has prepared an important Policy Statement regarding the impact of managed care on cancer clinical investigations, more quantitative data and continued surveillance are required.

Dr. Schein then summarized other presentations to and deliberations of the subcommittee. Ms. McCabe described four studies that are attempting to quantitate the additional costs of conducting clinical research relative to standard care and how important a barrier they are for

physician and patient participation. Results of those studies will be available in mid-1998. The subcommittee also addressed the issue of barriers to patient and physician participation in clinical investigations as indicated by the finding that only 2 percent to 3 percent of available patients now participate. The subcommittee plans to quantitate and prioritize the individual issues in terms of their importance as barriers to the process. The subcommittee discussed the need for better public information about the importance of clinical trials and the possibility of some type of announcement, perhaps in the form of an RFA, that the NCI is interested in research to obtain hard data on these barriers as a basis for action.

UPDATE ON CANCER PREVENTION PROGRAM REVIEW GROUP RESPONSE
Dr. Peter Greenwald

Dr. Greenwald acknowledged the receipt earlier in the meeting of the reports of the Clinical Trials and Cancer Control Program Review Groups and noted that responses to all of the Program Review Group Reports will be integrated across the Institute. He referred Board members to his written report of the NCI response to the report of the Cancer Prevention Program Review Group (CPPRG) and highlighted some of the actions planned or that are already under way in response to a number of the recommendations.

Prioritization of Prevention Trials. Dr. Greenwald reported on plans developed during the past year to expand the process for setting priorities for prevention trials using subcommittees of extramural experts, including BSA members. After dissemination of the CPPRG Group report, the decision was made to amplify the scope to engage the larger research community. Three subcommittees are envisioned to: (1) help in developing an informed decision process coordinated across the NCI and involving all the important disciplines; (2) review and advise on drug discovery, animal models, intermediate biomarker evaluation, and (3) clinical trial design.

Community Clinical Oncology Program (CCOP). A number of recommendations focused on the CCOP, including a recommendation to evaluate the CCOP. An evaluation by Kaluzny and Warnecke was published in 1996. The program, begun in 1983 to provide access for community oncologists to NCI treatment trials, was successfully expanded in 1987 to include prevention trials. Consistent with the CPPRG discussion of early detection in the context of genetic predisposition and the detection of precancerous lesions, the Division has initiated planning for systematic development of the Early Detection Program with short- and long-term goals. Over the coming year, an action plan of programmatic concepts and priorities will be developed to take advantage of research opportunities in the areas of biomarkers, imaging, modeling, and clinical trials. All efforts will involve crossdivisional planning and extramural review.

Biorepositories. Crossdivisional planning will be involved in developing and expanding biorepositories as recommended. Issues to be addressed are the need to initiate a decision process for investing, developing, and granting access to biorepositories, the need to develop metrics to measure their utility, and the need to integrate the information into the cancer informatics system. Original plans for the PLCO repository to contain red blood cells, buffy coat, and serum donated under informed consent by PLCO participants has been expanded to include DNA collections and urine specimens. The reconsenting process is under way.

Training. In response to the recommendation for an increased effort to train health professionals, the Division is working with the Cancer Training Branch to use existing mechanisms such as the Career Transition Awards (K22), to provide continued support outside of the NCI for Cancer Prevention Fellowship Program fellows in the early post-training period. A national conference on the Future of Cancer Prevention and Control is

planned to define the new scientific paradigm on how training will impact the future of the field.

Diet and Cancer. Methodologic research responsive to the CPPRG report is currently being conducted under a program announcement for culturally sensitive dietary interventions for African Americans in a small number of investigator-initiated projects. The Division is considering the use of set-aside funds as an effective mechanism for stimulating investigator-initiated research in the field and encouraging interdisciplinary collaboration to move the field forward. Strong relationships already exist with other federal agencies and private and professional organizations working in areas of nutrition and other fields.

Dr. Greenwald concluded that the NCI cancer prevention efforts can have a strong impact in six major areas and all should be pursued: tobacco control, nutrition and physical activity, the use of hormonal agents, intervention against infectious agents such as HPV or H. pylori, chemoprevention interventions for high-risk individuals, and environment.

INTRODUCTION TO NCI CALENDARING SYSTEM
Dr. Marvin Kalt, Dr. Robert Hammond, Ms. Susan Feldman

Dr. Kalt explained that the NCI Calendaring System has been developed as a comprehensive event-scheduling system to help NCI staff and the public track the large number of NCI meetings and other activities. He introduced Dr. Robert Hammond, Chief, Office of Advisory Activities (OAA), to describe the features of the new Web site and demonstrate how it can be used. Dr. Hammond noted that the NCI Event Calendar was created under the direction of Ms. Susan Feldman, Senior Program Analyst, OAA. The system permits users to view calendars by day, month, or year and to search for specific events (past and future) by title, keyword, or multiple criteria. The system will be linked to the Science Reports Database in the NCI Science Information System to provide access to minutes and reports of the various advisory groups. Reports will be searchable through a common thesaurus and key words developed in coordination with the OSP. The system is part of the greater cancer information system and will continue to evolve in coordination with other NCI offices and through user feedback. With the help of Ms. Feldman, Dr. Hammond demonstrated the ease with which the calendar can be viewed and searches can be conducted.

Dr. Hammond described the plan for handling information input now that the system is operational. During the development phase, the submission and loading of data on events was centralized in the OAA, and the OAA will continue to add information on meetings related to the advisory boards. Calendar representatives have been designated for each of the major offices and divisions throughout the NCI who will be responsible for entering and validating data on nonrecurring meetings in their areas. Web-based forms will be tailored to meet the needs of each group. Calendar administration is a specific task and involves granting authorization for system access and quality control. The Calendar Program Manager is responsible for project planning, oversight, and liaison with the contractor and between the contractor and NCI staff to transmit the needs of the users. In closing, Dr. Hammond briefly noted some of the possibilities for future enhancement of the system based on user needs such as profiles for NCI staff that display only specified meetings or automatic alerts through e-mail when meetings are posted in a specific area.

EXTRAMURAL POLICY UPDATE
Dr. Marvin Kalt

Rebuttal Policy. Dr. Kalt reported that the NIH will soon formally announce the termination of the final step in the grants review process. Currently, applicants who do not

agree with the conclusion of the initial review group can appeal to the appropriate advisory counsel (e.g., the NCAB) and then to the central NIH appeals process. The final step is being discontinued because it was so rarely used and, at most, could only result in a re-review, not necessarily a mandate for funding. Henceforth, the NCAB will be the final adjudicator for resolution of grant applications rebuttals in the NCI. Dr. Kalt emphasized the need to ensure a complete discussion of rebuttals during the closed session so that both applicants and the Board are assured that all relevant issues were considered. In response to a suggestion from Dr. Bishop, Dr. Kalt agreed to hold a special briefing for new members on the procedures for rebuttal and the NCAB role.

Modular Grant Awards. Dr. Kalt called attention to the modular grant program being considered by the NIH. Under the program, R01 applicants for grants in the amounts of $50K to $100K (in $25K increments) will be able to submit R01s with very little detailed budget justification and with just-in-time procedures for providing information that would be needed only in case of funding. Details will be provided to the Board as they are announced.

ADJOURNMENT
Dr. Barbara Rimer

There being no further business, the 103rd meeting of the National Cancer Advisory Board was adjourned at 3:27 p.m. on Thursday, September 25.

Advisory Home
Funding Opportunities

created: 27sep95 Lorrie Smith revised: 28jan00