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NATIONAL CANCER INSTITUTE
NATIONAL CANCER ADVISORY BOARD

Summary of Meeting
May 16-17, 1995

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

Liaison Representatives

Dr. John Currie, American Association for Cancer Education, Inc.
Dr. Edwin A. Mirand, Association of American Cancer Institutes
Ms. Margaret Foti, American Association for Cancer Research,
National Coalition for Cancer Research
Dr. Marc E. Lippman, American Association for Cancer Research
Dr. Robert Martuza, American Association of Neurological Surgeons
Ms. Kerrie B. Wilson, American Cancer Society
Dr. Robert W. Frelick, Association of Community Cancer Centers
Dr. Stanley Zinberg, American College of Obstetricians and Gynecologists
Mr. James Kitterman, Candlelighters Childhood Cancer Foundation
Ms. Linda Johnson, Oncology Nursing Society
Dr. James H. Brown, National Science Foundation
Dr. Tracy Walton, National Medical Association

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I. CALL TO ORDER AND OPENING REMARKS—DR. BARBARA RIMER

Dr. Barbara Rimer called to order the 94th meeting of the National Cancer Advisory Board (NCAB). Dr. Rimer introduced guests representing a number of respected institutions and associations dedicated to cancer education and research, as well as Federal agencies whose activities impact cancer-related issues. She welcomed the members of the public and asked them to express their views on items discussed during the meeting by writing to Dr. Marvin Kalt, Executive Secretary of the Board, within 10 days of the meeting.

Dr. Rimer referred to the confirmed meeting dates set for 1995 and 1996, and the unconfirmed dates for 1997, noting that while 3-day meetings have been scheduled, it is hoped that they will not require more than 2 days each. She asked the Board to notify her of any conflicts with future meeting dates.

Dr. Rimer called for approval of the minutes of the December meeting, which were approved without change. She emphasized the need for those present to attend the full meeting agenda to ensure a quorum of voting members and asked presenters to strictly adhere to the times allotted in order to ensure adequate time for all the presentations and full discussion.

Dr. Rimer asked Board members seeking review of grant applications to inform Dr. Kalt by the end of the morning coffee break. Meetings of the subcommittees on special priorities, basic and environmental sciences, and planning and budget were announced, and Dr. Rimer informed the Board that the closed session would be held the next morning, requesting that all members be present.

Dr. Rimer announced that Dr. Paul Calabresi is being appointed to replace Dr. Henry Pitot on the President's Cancer Panel (PCP). She expressed appreciation to both doctors for their service and thanked Dr. Calabresi for his participation as a member of the NCAB, particularly for his work on the Subcommittee to Evaluate the National Cancer Program (SENCAP) report and the Ad Hoc Intramural Committee, which she characterized as expressions of his leadership and wisdom. She said that the Board will miss him and hopes to see him often in his new role on the PCP. Dr. Calabresi thanked Dr. Rimer and assured her of his continued presence in his new capacity.

Dr. Rimer introduced Dr. Harold Freeman, Chairman of the PCP, to update the Board on the last PCP meeting.

II. REPORT OF THE PRESIDENT'S CANCER PANEL-DR. HAROLD FREEMAN

Dr. Freeman began his presentation by welcoming Dr. Paul Calabresi as a new member of the President's Cancer Panel and thanking Dr. Henry Pitot for his participation during the past 3 years. Dr. Freeman acknowledged the Panel's recently published *Report of the Chairman* for the period January 1992 through January 1994, which fulfills the statutory requirement to report annually to the President and the commitment to the American people under the National Cancer Act to reduce suffering and death due to cancer.

Dr. Freeman noted that recommendations regarding the health and future goals of the National Cancer Program were prepared by a subcommittee of the Board and presented in the document *Cancer at a Crossroads: A Report to the Congress for the Nation*. The conclusions and recommendations of the President's Cancer Panel, he continued, are consistent with this Report and can be outlined as follows. First, a strong basic research network must remain the foundation of the National Cancer Program. Second, translational research, including the National Cancer Institute (NCI) designated cancer centers, the community clinical oncology programs, and the Specialized Programs of Research Excellence (SPOREs), must receive greater support. Third, improved communication must be fostered through government at all levels, including advocates, patients, clinicians, scientists, and industry. Dr. Freeman explained that this effort will include enlargement, standardization, and increased accessibility of existing epidemiological and clinical data; elimination of duplication of effort; and legal protection of discoveries. Fourth, the content of educational programs and incentives for young scientists in cancer research must be reexamined. Fifth, a major research emphasis of the National Cancer Program must shift from diagnosis and treatment to prevention and total management, including biomarkers for prognostic use, evaluation of disease progression, and culturally sensitive prevention strategies that respect human dignity. Sixth, a comprehensive school health education program may make better use of limited funding than programs targeted to specific populations that may have limited enduring impact.

Dr. Freeman emphasized that, above all, efforts of the National Cancer Program must recognize that people with cancer and those at risk are both the beginning and the end point of successful cancer research; people cannot be separated from their surroundings. Socioeconomic, cultural, and ethnic factors deeply influence access to education, preventive health care, treatment, and ability to follow required treatment regimens. Attention must also be paid to quality-of-life issues in clinical research and preventive interventions, cancer detection, treatment, and supportive and palliative care. Dr. Freeman concluded his remarks regarding the recommendations of the Report by noting that psychosocial aspects of cancer must be thoroughly researched and supported, which will require drawing upon such nontraditional disciplines as sociology, ethnography, behavioral psychology, and anthropology in designing research protocols.

To illustrate the value and impact of scientific knowledge in the context of real life, Dr. Freeman detailed assessments and conclusions communicated to President Clinton from the March 28, 1995, Panel meeting, which explored the Human Genome Project and Disease Prediction. First, the proliferation of genetic information and its potential for application must be viewed in the context of preventive and therapeutic options and individual rights to privacy.

Next, elucidation of the human genome in the absence of standardized public policy on information dissemination, education of the public and health care providers, confidentiality of genetic information, and the variability of psychosocial support is an incentive to discrimination based on genetic predisposition. Prevention of genetically based discrimination is complicated and may require legislative or regulatory activities at multiple State and Federal levels, especially with respect to health insurance. In this context, the confidentiality of individual medical records must be reexamined in light of the increasing role of the genetic information they may contain.

Dr. Freeman continued by noting that education of the public and the health care industry is needed to clearly convey the impact of genetic information and disease risks in understandable and consistent terms. A clear concept of actual risk based on age, environment, attitude, health care practices, and other variables must be balanced with the research community's concept of relative risk, which must be understood by the public.

Dr. Freeman emphasized that research and the health insurance industry are fundamentally motivated by financial concerns, since the efficacy of treatment has been the basis for determining the value of research findings and the standards of insurability. Economic incentives for public-private partnerships in basic and applied research must be balanced with the public return on Federal investment in research. The focus of insurance must shift from research and treatment to prevention and management of disease, which will require a comprehensive program of public health education, prevention services, counseling, and palliative care when treatment options are not possible.

People, Dr. Freeman reiterated, are the alpha and omega of research efforts as the nation moves into the 21st century. The Panel urged that the impact of scientific breakthroughs on the public must not be overlooked, such as individual rights to privacy and the potential for new levels of high-tech discrimination based on genetic information, which are inadequately addressed by the health care system or legislative and regulatory policies. The Panel suggested that until these issues are adequately addressed, the use of genetic screening should be restricted to the rigorous review of research protocols, rather than exploited indiscriminately among members the public sector.

Dr. Freeman stated that an informed public is the key to an effective prevention strategy. He reported his attendance on May 3, 1995, at the American Cancer Society-sponsored press release of the National Health Education Standards, which resulted from 3 years of effort by the Joint Committee on National Health Education. The Committee is composed of representatives of the American Cancer Society, the Association for the Advancement of Health Education, the American Public Health Association, the American Schools of Health Association, and the Society of Directors of Health, Physical Education and Recreation. He explained that the Standards recommend a comprehensive school-based approach to health literacy from kindergarten through high school graduation, aimed at developing the ability to identify and assess valid health information and health-promoting products and services, and the practice of health-promoting, risk-reducing behaviors. Dr. Freeman described the document as scholarly and practical, and as an effort to link diverse groups for a common health-related goal. He noted that copies may be obtained from the American Cancer Society.

Dr. Freeman announced that the next meeting of the President's Cancer Panel will be held on June 6, 1995, at the Holiday Inn, Bethesda, and will focus on AIDS and associated neoplasms.

Dr. Rimer thanked Dr. Freeman for his remarks and noted that some of the concerns he raised about genetics and genetic screening would be revisited in the planned discussion of the National Breast Cancer Action Plan. She introduced the next speaker, Dr. Edward Sondik, Acting Director of NCI.

III. REPORT OF THE ACTING DIRECTOR, NATIONAL CANCER INSTITUTE—DR. EDWARD SONDIK

Dr. Sondik reviewed recent NCI staff changes, beginning with the April 1, 1995, retirement of Dr. Samuel Broder as Director of the National Cancer Institute. Dr. Sondik added that Dr. Harold Varmus, National Institutes of Health (NIH) Director, was scheduled to address the Board later and might be able to provide an update on the search for a new Director. Dr. Sondik noted the planned June 1st retirement of Dr. Bruce Chabner, adding that Dr. Robert Wittes is serving as Acting Director of the Division of Cancer Treatment (DCT). Mr. Nicholas Olimpio, Dr. Sondik reported, retired as Division of Cancer Prevention and Control (DCPC) Administrative Officer on December 30th; Mr. Damian Crane, formerly Administrative Officer of the DCT Developmental Therapeutics Program, has been appointed as Administrative Officer for DCPC. Ms. Maxine Richardson, who headed NCI's Equal Employment Opportunity office, also recently retired after 30 years of government service, including 15 years with NCI. Dr. Sondik noted that on June 26th, Dr. Larry Kessler, Chief of the Applied Research Branch of the DCPC Surveillance Program, will join the Food and Drug Administration (FDA) as Director of the Office of Surveillance and Biometrics at the Center for Devices and Radiologic Health.

Dr. Sondik thanked these individuals for having given so much of their lives to service. He thanked Dr. Henry Pitot for his distinguished service on the President's Cancer Panel, noting that his term is ending soon. Dr. Sondik announced Dr. Calabresi's retirement from the Board, remarking that he will still attend meetings as a member of the President's Cancer Panel, in Dr. Pitot's place.

Dr. Sondik noted that he and other NCI staff were eagerly looking forward to hearing the scheduled report of the Bishop-Calabresi committee. He added that the report would be broadcast to all NCI locations and that each Division would hold Laboratory and Branch Chief meetings to discuss the report and its importance for NCI staff and the NCAB as they plan for the future.

On May 11th, Dr. Sondik reported, the Department of Health and Human Services (DHHS) Secretary announced REGO-II, or *Reinventing Government Phase II*. One REGO-II initiative, he said, will focus on the cost-effectiveness of NIH Clinical Center operations. This effort is being headed by Dr. Helen Smits, Deputy Director of the Health Care Financing Administration (HCFA). One aspect of her committee's review of the operations of the Clinical Center, Dr. Sondik explained, will be to examine the role of contracting of services in reducing costs. The NCI, Dr. Sondik observed, uses about 40 percent of the capacity of the Clinical Center and, thus, has a keen interest in its future.

In addition, Dr. Sondik continued, the Department is considering consolidation of 107 health programs into five "performance partnership" programs and 11 consolidated grants administered by State and local governments and private providers. DHHS also plans to consolidate the Office of the Assistant Secretary of Health with the Office of the Secretary of DHHS into a single corporate headquarters. This, Dr. Sondik noted, will result in major changes in the way the Department does business.

Dr. Sondik announced that the Cancer Information Service has begun listing all facilities certified by the FDA as capable of providing high-quality mammograms. To date, he added, nearly 8,700 of the approximately 10,300 facilities have been fully accredited. Dr. Sondik noted that the First Lady has initiated a program urging all women covered by Medicare to take advantage of Medicare-covered mammography; NCI has been cooperating with this effort, as well as a similar effort by the American Association of Retired Persons (AARP).

On March 30th, Dr. Sondik reported, NCI staff participated in House of Representatives hearings that focused on several issues, including breast and prostate cancer detection, the decreased rate of breast cancer mortality among White women, and prostate cancer diagnosis and treatment. There were questions concerning lifestyle recommendations, he said, including dietary modification and the role of foods and vitamins in cancer prevention or treatment. Dr. Sondik noted that he was asked about clinical trials and the National Surgical Adjuvant Breast and Bowel Project (NSABP); he was pleased, he said, to be able to report that the NSABP is back on track and making progress.

On June 18th, Dr. Sondik reported, Dr. Varmus will testify before the Senate Appropriations Committee; while NCI is not scheduled to testify, he added, representatives will be on hand to answer questions. On April 11th, he continued, Dr. Varmus announced the removal of the reasonable pricing requirements for drugs and other products developed in cooperation between government and industry. It was felt, Dr. Sondik explained, that this requirement was driving industry away from such collaborations; he suggested that this change is a positive step for NCI research programs.

Dr. Sondik mentioned that later during this meeting, the NCAB would receive a report on the National Action Plan on Breast Cancer, a unique public-private partnership supported by $10 million earmarked in the NCI Cancer Prevention and Control budget. He described the Plan as a method for identifying important activities that are not happening by themselves and, thus, need a "jump start."

Turning his attention to the NCI budget, Dr. Sondik reminded the Board that the Bypass Budget is considered the Institute's most important strategic planning document. He welcomed the insights of Board members on scientific priorities across mechanisms and invited them to suggest ideas for maintaining and strengthening the biomedical research infrastructure.

Presenting slides on the President's budget for 1996, Dr. Sondik noted that the request for NCI represents an increase of 3.9 percent, including 4 percent for cancer and 3.3 percent for AIDS. A breakout by mechanisms showed increases in research grants and cancer prevention and control, while cancer centers remain the same between 1995 and 1996. Dr. Sondik then compared the President's budget projections through the year 2000 with projections based on 1995 levels inflated according to the Biomedical Research and Development Price Inflator (BRDPI), which is increasing at about 4.3 percent per year. He concluded that the President's budget essentially follows inflation, reaching a point just above $2 billion by the year 2000.

Budget projections from the House of Representatives, Dr. Sondik continued, show a 5 percent reduction from 1995 to 1996 and then show the budget holding steady. He noted that

the President's budget and the House budget would arrive at about the same point in the year 2000, although the NCI would receive more money during this period under the President's budget. The Senate's proposed budget, Dr. Sondik continued, begins with a reduction of about 16 percent from 1995 levels and then holds constant. He pointed out that the reductions proposed by the House and Senate are applicable to the NIH in general, and the amounts that individual Institutes would receive are not specified in these proposals. Dr. Sondik summarized that the 5 percent reductions in the President's budget and the House budget and the 16 percent reduction in the Senate proposal can be translated into reductions of 27 percent and 38 percent, respectively, from a budget that in 1991 had increased in proportion with inflation.

Dr. Sondik stated that the implications of these figures are extraordinary, and will cause the NCI to rethink all of its commitments and priorities. He suggested that 1995 success rates of 20 percent and pay lines of 14 to 15 percent would be difficult, if not impossible, to maintain in the face of such reductions. Dr. Sondik urged Board members to consider the implications of resource constraints for NCI's intramural and extramural research programs (IRP; ERP), as well as for their own institutions. Although there is concern throughout the country about some suggested budget cuts, he noted, the Congress is serious about deficit reduction and all discretionary funding will be affected in some way.

Questions and Answers

Noting that the figures presented by Dr. Sondik are for NIH overall, Dr. Sigal asked whether there has been any discussion of exceptions for cancer funding. Dr. Sondik stated that it will be late summer or early fall before these decisions are made, but suggested that cancer funding will inevitably receive some kind of reduction. Cancer is clearly a priority, he acknowledged, but all areas will be arguing that they are also priorities. He expressed the opinion that across-the-board cuts are not the way to go and suggested that specific mechanisms and cancer-specific programs should be examined. He expressed concern that below a certain funding level, cuts would be made in the research infrastructure that would take decades to repair. The cancer program, he stated, could lose researchers, facilities, teaching hospitals, and other resources. The wisdom of the NCAB and the cancer community in general will be needed, he concluded, to help set priorities under these conditions.

In closing, Dr. Sondik expressed his thanks and that of the Executive Committee to the Bishop-Calabresi committee and to Dr. Marvin Kalt, who served as the principal staff person with the committee.

IV. LEGISLATIVE UPDATE—MS. DOROTHY TISEVICH

Ms. Dorothy Tisevich, legislative liaison for the NCI, presented an overview of Congressional activities since the last Board meeting.

Ms. Tisevich reminded the Board that in her last update package she presented the first few days' activities of the 104th Congress to give an overview of the types of issues under consideration. She explained that this current legislative update would focus specifically on issues related to the National Cancer Program or biomedical research.

Ms. Tisevich described the first 100 days of the 104th Congress—2,098 bills were introduced, nine of which were passed into law. Most of the activity related to the Republican Contract With America, including two of the new laws: the Congressional Accountability Act of 1995, which applies 11 major labor laws to Congress; and the Unfunded Mandates Reform Act of 1995, which requires an estimate of the cost of new regulations and a cost-benefit analysis before they can be implemented. Speaker of the House, Newt Gingrich (R-GA), referred to the rapid passage of the Congressional Accountability Act on January 23, 1995, as "the fastest passage of a peace time domestic bill" since the first New Deal Congress in 1933.

With regard to NIH, Ms. Tisevich said that most Congressional attention has focused on the budget. The House Appropriations Subcommittee on Labor, Health and Human Services, and Education convened a hearing in February to hear the testimony of Nobel laureates on the future of biomedical research. Dr. Michael Bishop of the University of California, San Francisco, testified at the hearing. Dr. Harold Varmus, with whom Dr. Bishop shares a Nobel Prize, also attended the hearing, which focused on prioritizing research and identifying the most promising areas for progress. When asked how best to absorb a reduction in the NIH budget, Ms. Tisevich said that the Nobelists emphasized the need to continue support for basic research. She noted that the tenor of the hearing had changed from past years, with a greater emphasis on reducing the deficit and closer scrutiny of the merit of Institute programs.

Ms. Tisevich referred to Dr. Edward Sondik's presentation on the House and Senate Appropriations Committee hearing and Congressional action with respect to balanced budget proposals. She explained that Representative John Kasich (R-OH) chairs the House Budget Committee, which is responsible for creating the House Congressional budget, identifying targets, and providing guidance on how to reach targets. Representative Kasich introduced a bill, HR 1215, called the Contract With America Tax Relief Act of 1995, that was passed by the Budget Committee and the full House and provides a list of illustrative cuts to reduce the Federal budget by $11 billion in FY 1996. The bill has been referred to the Senate Finance Committee for consideration. Ms. Tisevich noted that several of the bill's proposed cuts would significantly impact NIH and NCI and are part of the debated balanced budget proposal in Dr. Sondik's slides.

Ms. Tisevich said that Representative Kasich and Senate Budget Committee Chairman Pete Domenici (R-NM) revealed their proposals on May 9th and 10th to balance the budget over the next 7 years. The Senate and House plans are based on cuts of $1 trillion and $1.4 trillion, respectively; both would substantially reduce the size of government. According to Ms. Tisevich, the Senate plan would eliminate 283 programs, 14 agencies, and 68 commissions. It would terminate more than 80 job training programs, restructuring them under State block grants; overhaul the welfare system; privatize the General Services Administration; and revamp veteran, student loan, housing, and agriculture programs. Ms. Tisevich stated that the House bill suggests additional cuts to abolish block grants and compress or privatize 372 Federal cabinets, departments, agencies, and programs. The House plan would also cut the Defense Department Procurement work force and cut funding for the Points of Light Foundation by about 50 percent.

Ms. Tisevich highlighted some other features of the Senate plan: changing the base for calculation of cost-of-living adjustments for Federal retirees from high-3 to high-5 years of

earnings; reducing funding for the Agency for Health Care Policy and Research by 75 percent; reducing spending for the Executive Office of the President by 25 percent; reducing construction and acquisition programs; saving funds from the legislative branch appropriation; eliminating the Office of Technology Assessment; freezing salaries for members of Congress until the budget is balanced in 2002; charging parking fees at Federal buildings; repealing the Davis-Bacon Act to reduce Federal construction costs; reducing the number of political appointees from 2,800 to 2,000; and streamlining intragovernmental bookkeeping.

Ms. Tisevich noted that the House plan took similar measures with several additions: increasing user fees on FDA-regulated products; reducing ineffective funding for the National Health Services Corps; reducing NIH funding by 5 percent by encouraging prioritization of NIH-supported research; imposing a 5-year moratorium on construction and a 7-year moratorium on acquisition of new Federal buildings; eliminating the Office of Technology Assessment; reducing funding to the General Accounting Office; reforming the Office of Personnel Management by transferring its functions to other agencies; reducing Federal agency overhead; reducing the number of political appointees; and increasing Federal civilian retirement contributions by 2.5 percent.

Ms. Tisevich reported that the House and Senate hope to reconcile the differences between their plans and issue a conference report by June that would serve as a blueprint for the appropriations process. By July, they hope to achieve reconciliation on the budget and introduction of an appropriations bill, and, by September, they intend to have reconciliation on the appropriations bills through a conference report so that the President may then sign or veto the bills. Ms. Tisevich emphasized that the appropriations subcommittees will be scrutinizing each program under their purview to allocate the spending cuts, which will mean fundamental questioning of NIH research, funding decisions, involvement of the extramural community, and, most importantly, prioritization.

Describing other bills that had been introduced since the last meeting, Ms. Tisevich mentioned HR 1130, the Integrity in Government Act, introduced by Representative Robert Dornan (R-CA) on March 3rd, which would prohibit recipients of awards, grants, or contracts from lobbying for their continuation, as well as repeal authority for the payment of expenses of intervention and attorney's fees related to these issues. The bill has been referred to the House Committee on Government Reform and Oversight, chaired by Representative William Klinger (R-PA), and the Committee on the Judiciary, chaired by Representative Henry Hyde (R-IL), but no hearings have been scheduled nor action taken on the bill.

Ms. Tisevich described HR 1130 as one of the more comprehensive lobbying bills, explaining that other bills on the subject focus on lobbyist disclosure issues. She quoted the language of the bill as it states, "No recipient of an award, grant, or contract from the federal government may engage in or have others engage in lobbying for (1) the continuation of the award, grant, or contract; (2) the program under which the award, grant, or contract was made; or (3) the continued funding of any program within or the department or agency administering such program. Lobbying is defined as lobbying contacts and efforts in support of such contacts, including preparation and planning activities, and research and other background work that is intended at the time it is performed for use in contacts in coordination with the lobbying activities of others."

Ms. Tisevich noted that several bills were introduced addressing preventive services. HR 805 contains a section entitled "Funding Initiative for Programs Providing Health Services" that authorizes additional funds for the Centers for Disease Control and Prevention (CDC) to increase activities in breast and cervical cancer screening, cancer registries, and prostate cancer research and screening. Under the Older Women's Breast Cancer Detection Act of 1995, Medicare Part B would provide funding for annual mammograms for women aged 65 and older.

The Prostate Cancer Diagnosis and Treatment Act, Ms. Tisevich continued, would provide coverage for early detection and drug treatment services under Medicare and the Department of Veterans' Affairs and would expand research and education programs on prostate cancer at NIH. The bill was introduced by Senator Richard Shelby (D-AL), a prostate cancer survivor whose cancer was detected through a prostate-specific antigen (PSA) test, who remarked that breakthroughs in detection and treatment of prostate cancer have occurred despite neglect in funding. The bill would cover a number of procedures under Medicare, including digital rectal exams and PSA transrectal ultrasound as well as authorize additional funds for NCI's prostate cancer research. Ms. Tisevich reminded the Board that at NCI's reauthorization, the Institute was given a mandate and additional funds to expand and intensify research in breast and prostate cancers.

Senator Frank Lautenberg (D-NJ) introduced a bill similar to one he introduced during the 103rd Congress; the Medicare/Medicaid Solvency Act would establish a trust fund to reimburse the government for the health care costs of individuals with diseases attributable to the use of tobacco products. In a similar vein, Representative Pete Stark (D-CA) introduced legislation to increase the excise tax on cigarettes by $1.76 per pack.

Ms. Tisevich concluded her presentation, pointing out other bills of interest in the legislative package she distributed to the Board and offering to assist members in obtaining legislation or information. Dr. Rimer noted that the Senate Appropriations Committee hearings schedule was also included in the legislative package.

Questions and Answers

Dr. Ellen Sigal asked about a piece of legislation dealing with a trust fund set aside for biomedical research. Ms. Tisevich explained that the bill did not pass but has been reintroduced in a similar form.

Dr. Schein expressed his concern that the reinvention of NIH may not account for the critical health priorities of the nation and suggested that the Board issue a statement to the Congressional committees on budget and reform about the importance of allocating resources to NCI programs to wage the war against cancer. Dr. Rimer agreed with his recommendation and asked him to draft a statement that would alert the public to the impact of the imminent budget cutbacks for review by the Board the next morning.

Dr. Rimer thanked Ms. Tisevich for keeping the Board informed and aware of Congressional activities during this troubling time.

V. NEW BUSINESS–SESSION I—DR. BARBARA RIMER

Dr. Rimer opened the floor for introduction of new business, draft resolutions, or items of special public concern. She said that further consideration and final action would take place the following day, during the second new business session, after the grant review. Dr. Sydney Salmon commented on the importance of addressing in Board resolutions those managed care issues that impact health care and research. Dr. Rimer asked the Board to listen to the afternoon report of the Ad Hoc Working Group on the NCI Intramural Programs and consider whether it could be approved in principle or required any language changes. No new business was presented.

VI. EFFECTS OF THIRD PARTY PAYMENT ON CLINICAL RESEARCH—DRS. ROBERT WITTES AND MICHAEL FRIEDMAN

Introduction by Dr. Wittes

Dr. Rimer introduced Dr. Robert Wittes, Acting Director of the Division of Cancer Treatment, to provide an overview of the effects of managed care on cost reimbursement for clinical research.

Dr. Wittes provided the Board a brief historical context for the current issue, explaining that approximately 10 years ago, concern began to increase among physicians and researchers about the "research exclusions" contained in most insurance contracts and their possible effect on the future of clinical research. A dialogue ensued between clinical investigators and insurance companies in an effort to clarify the issues and misperceptions and resolve any legal issues. With the great expense of high-profile technology, concerns about reimbursement have intensified and disputes are often resolved in court. The current emphasis on cost containment and the consequent spread of managed care promises to change the configuration of health care delivery in this country.

Dr. Wittes described the tremendous involvement of NCI in the dialogue on this issue and introduced Dr. Michael Friedman, Associate Director for the Cancer Therapy Evaluation Program, to discuss the progress and status of developments on this subject.

Presentation by Dr. Friedman

Dr. Friedman referred to an editorial in the *New York Times* that reflected a highly critical public opinion towards the academic medical community, quoting from the last paragraph, "The Republicans are right; the teaching hospitals are riddled with waste and turn out the wrong mix of doctors—too many specialists and too few primary care doctors. Many such hospitals in New York and elsewhere ought to shrink, if not close. But these truths do not justify a mindless assault.... We should be careful." He noted that this is a stunning indictment and illustrates the clarity with which these issues must be approached.

Dr. Friedman informed the Board that he would try to provide summary information about the current direction of health care reform and its impact on clinical research, and would presume some familiarity by the Board with the various health care mechanisms to which he

alluded. He mentioned that he would not offer any specific proposals for Board endorsement, but simply provide background on this complex subject, including prior NCI activities, and draw attention to future issues.

NCI's public position is that quality clinical research must continue; the emphasis being on quality. NCI has also stated its position that research and clinical care costs can and should be identified and separated, since Federal funding is not likely to cover clinical care costs. He explained that clinical research involves both the standard costs for patient care (incurred regardless of the treatment offered) as well as costs associated with conducting the research. While these costs are sometimes difficult to separate, this must be accomplished so that the research sponsor can bear the research costs while the clinical care costs are borne by the appropriate party (e.g., a third-party payer). It is also the position of NCI that regardless of health care financing mechanisms established in the future, the clinical care costs for NCI-sponsored research should be covered and reimbursed by third party payers in the interest of the national good. Dr. Friedman qualified the position as only applying to NCI-sponsored research, since the Institute is not responsible for reviewing, monitoring, or evaluating other clinical trials and can offer no assurances about their quality. He noted that while he represents the DCT, NCI's position applies to prevention, epidemiology, or other NCI trials as well.

Dr. Friedman reviewed some institutional background issues to demonstrate the complexity and fragility of the financial support system. He expressed the opinion that there is an intimate and commensal relationship among the clinical activities at a site, which applies to all academic pursuits, and pointed out the fragile web of financial supports upon which all institutions rely (grants, overheads, clinical income from patients, donations, endowments, etc.). He mentioned the need for institutional access to clinical specimens and pointed out that institutions offer ideal training environments. He also recognized that institutions will increasingly include both general and specialized facilities, and stressed that modern research of all types—laboratory, clinical, translational—is increasingly complex and expensive. The current focus on controlling medical care costs affects not only clinical care costs, but the health of the entire institution.

Dr. Friedman pointed out that while it has received very little Congressional or public attention in light of the major problems associated with Medicare and Social Security financing, clinical research is being drastically affected by new health care mechanisms.

There has been a dramatic increase in enrollment in managed care plans since the 1970s, from 10 million to 40 million individuals in 1994. In the early 1990s, about half the patients at medical centers had traditional indemnity insurance in which the insurance company reimbursed physicians and institutions at a certain rate, with no incentives to keep costs down—only about half of patients were enrolled in managed care plans. About two-thirds of patients now are enrolled in managed care, and the trend shows this number is increasing. Current proposals to convert Medicare to managed care would have a dramatic impact with profound repercussions on the conduct of medical research, training, etc.

Dr. Friedman identified problems resulting from the fact that health care reform is now proceeding under the powerful pressures of market forces and health care providers no longer control the health care system. As traditional relationships shift, Dr. Friedman suggested, the fiscal integrity of hospitals, as well as academic institutions, is threatened. Hospitals are being

asked to do more, while they are reimbursed less. He described not only clinical oncology research, but *all* research as being at risk, based on the unpredictable pace and direction of change. He also predicted a high degree of variability in the health care solutions developed in different regions of the country.

Recognizing that few institutions have gained experience in this area, Dr. Friedman stressed the current need for scientific entrepreneurs to manage ideas, form creative alliances with other investigators, and apply the same creativity and ingenuity to fiscal issues as to biologic concerns.

Reviewing past activities, Dr. Friedman mentioned the importance of efforts aimed at establishing an environment of trust and collaboration with insurers. Efforts have been directed to foster dialogue with insurers regarding autologous bone marrow transplantation initiatives for breast cancer patients and developments for patients with ovarian cancer and multiple myeloma, as well as the historical use of taxol for breast and ovarian cancer. Since 1988, Dr. Friedman said that the Cancer Therapy Evaluation Program (CTEP) has been meeting with insurers to discuss these issues, mitigate developing problems, and gain mutual understanding of problems and concerns. Since 1990, NCI representatives have met with a variety of companies and associations to get their perspectives. Meetings with government programs began in 1987, but Dr. Friedman noted that meetings with the Health Care Financing Administration (HCFA) have been disappointing because of extraneous issues confronting that organization.

The Board's attention was called to a handout containing the results of a Congressionally mandated survey the NCI was asked to conduct along with representatives from National Institute of Heart, Lung and Blood Institute (NHLBI) and National Institute of Allergy and Infectious Diseases (NIAID), as well as other NIH Institutes on how insurers manage patients with serious diseases who are involved in clinical research programs. Individuals from several insurance companies and managed care plans were interviewed about how their companies deal with the enrollment of patients in research protocols with AIDS or cancer. He noted the degree of diversity among the organizations' responses and the fact that responses could vary widely from one year to the next, as policies are constantly changing. It has yet to be determined how these results will be used, but there are plans to conduct additional surveys.

Dr. Friedman raised the difficult question of autologous bone marrow transplantation for breast cancer patients, citing the debate over whether such interventions are helpful or simply expensive and toxic. He stressed the need for the NCI to work to answer this type of clinical research question, so that if patients are found to benefit, the procedure can be made available to them, and if it is not helpful, the money can be diverted to more efficient use. Dr. Friedman noted that Blue Cross/Blue Shield has been very cooperative and creative in establishing a demonstration project and that other insurers have acted similarly. He also noted the increased level of cooperation of insurers with investigators today, compared with 5 years previously, to complete clinical trials, and opined that relations between investigators and reimbursers are improving, despite the struggle over these difficult issues.

Excerpts from a resource book on autologous bone marrow transplantation that Dr. Friedman said had been compiled at the request of insurers was also distributed to Board

members. This book defined NCI sponsorship by indicating criteria for institutional certification and reassured insurers of the quality of transplants performed at various institutions. NCI continues to provide insurers with updated lists of approved institutions and current protocols to assure them that definitive answers will be forthcoming and their investments will be worthwhile.

Dr. Friedman described his meetings with advocates, insurers, and investigators, highlighting a recent meeting on breast cancer that helped to identify methods for increasing awareness and enrollment in clinical trials. Similar efforts are under way for ovarian cancer and myeloma to establish randomized Phase III national trials of autologous bone marrow transplantation that will definitively indicate whether or not patients benefit. He noted that current difficulties in starting these trials are not the fault of reimbursers—who are, in fact, interested and supportive—but are resulting from the lack of agreement among investigators who feel vested in their own proposals and pilot studies.

In regard to taxol, Dr. Friedman continued, prior to its FDA approval, the drug was used in the treatment of those with ovarian and breast cancer and was administered to hospitalized patients via 24-hour infusions, which were very expensive. Reimbursers were hesitant to cover this treatment and questioned its efficacy. In response, NCI arranged for investigators to give presentations to reimbursers to convince them of taxol's benefits to patients. As a result, the insurers began to reimburse health care costs for patients on taxol, even before the FDA fully approved the drug.

Though admittedly self-serving, Dr. Friedman stressed the need for the NCI to work with all constituencies to ensure support for NCI-sponsored clinical research. He indicated that NCI's efforts have included reassessment of current clinical trials and reimbursement systems to arrive at novel solutions and advocated maintaining a position of neutrality with respect to the financing and scientific merit of studies, so as to enable the NCI to act as an effective broker.

Dr. Friedman emphasized the complexity of the constituency base and the need to recognize the various perspectives of patients and their advocates; investigators; care providers; reimbursers; the general public, which is concerned about the way its taxes are spent for health care; employers and businesses that pay for health insurance; and research sponsors, like NCI, universities, hospitals, and medical schools. He also mentioned the unusual realignments of relationships between providers, institutions, and payers, which create challenges for researchers. As examples, he cited insurers, such as Blue Cross/Blue Shield and other managed care organizations, who are starting their own hospital and medical facilities.

Dr. Friedman remarked that, in the past, people blamed insurers for not paying. With the change to different managed care systems, he predicted that hospitals will become the gatekeepers responsible for deciding whether a patient can enter a clinical trial. The reimburser will provide a set amount of money to an institution to spend as it sees fit; consequently, it will be the hospital that may decide to forgo participation in clinical research because it cannot afford to do so.

Dr. Friedman described the complex responsibilities clinical investigators will face in the future to provide quality care (meeting the expectations of patients and referral sources)

despite pressures to see more patients at less expense. He questioned how investigators would conduct high-caliber clinical trials with higher overhead costs and less funding. He pointed out the problem that research institutions will face in identifying, tracking, and controlling the costs of routine care, diagnosis, and prevention, whether or not they are linked to research. He also stressed the need for the future to formulate economic as well as biological hypotheses for conducting clinical trials.

Turning to the role of the research sponsor, Dr. Friedman suggested encouraging all involved parties to reduce unnecessary expense by critically selecting which clinical trials to support and streamlining trials to eliminate unnecessary tests. He emphasized the need for better pilot studies with more specific biologic correlates that lead to larger definitive trials in a more orderly way. He noted the difficulty investigators face in choosing from among the multitude of important and interesting hypotheses for clinical study. There is need, Dr. Friedman continued, for fewer, larger, and better-designed Phase III trials to answer questions more rapidly and with greater precision. Large, simple trials present an opportunity for treatment that has not been fully explored. He also cited a need to encourage and support economic outcome analyses, such as cost effectiveness or outcome studies, as part of clinical trials, where appropriate, in order to provide reimbursers a vested interest in seeing the clinical trial completed, since it will answer questions critical to them.

Dr. Friedman warned against counterproductive attitudes and approaches, including arrogance and refusal to accept criticism on the part of investigators; demonization or scapegoating of a certain group for creating a health care crisis; and a lack of flexibility in the manner of conduct, i.e., doing it this way because it has always been done this way. He also cautioned against unrealistic expectations, stressing that there will be no painless solutions and no return to the health care system of the past. He opined that a focus on pure science will not be perceived as valuable by the public unless it has practical application, and expressed doubt that cancer issues will be given priority over other diseases nor that research will be separable from the entire institutional financial integrity.

To summarize, Dr. Friedman recognized a need for highly specific regional solutions, not only on a geographic level, but for individual institutions and companies. He proposed developing strategies for dealing with competing issues and reiterated the responsibility of the NCI to foster cooperation and collegial dialogue among the different constituencies. He assured the Board that the CTEP will remain active in pursuing these issues and welcomed suggestions, but cautioned that the breadth of the issues is beyond CTEP's ability to handle alone.

Dr. Friedman concluded by acknowledging Drs. Mary McCabe and Robert Wittes for their insights, noting that their collective thoughts were being presented.

Questions and Answers

Dr. Rimer asked whether Dr. Friedman has been involved in the discussions regarding designating cancer projects as a special area of managed care. Dr. Friedman said that he has talked generally with cancer centers and reimbursers about this issue, but distinguished these talks as being purely private, rather than involving government or public policy. Dr. McCabe

added that several cancer centers have been engaged in dialogue with insurance companies and managed care groups to build an innovative solution.

Dr. Rimer informed the Board that Dr. McCabe has been working with the National Action Plan on Breast Cancer and a working group seeking to increase women's access to participation in clinical trials. Dr. McCabe explained her role as that of an advisor to some of the major insurers and companies in devising an action plan.

Dr. Robert Day asked if any data were available on the number of patients involved in clinical trials and the marginal cost for the research component of such trials. Dr. Friedman estimated that 35,000 to 50,000 new patients are enrolled each year in NCI-sponsored studies. He added that individual cancer centers carry on activities for which he has no figures, but said he does not believe these numbers are substantial. He mentioned that there are about 1.25 million new cancer patients yearly, and fewer than 5 percent are believed to participate in clinical trials. Financially, this 5 percent does not represent a substantial burden to insurance companies, so it has not received much attention. The patients who are treated off-study with traditional care represent the vast majority of cancer patients.

Dr. Debbie Mayer asked for Dr. Friedman's impression of what the managed care groups perceive as their role and responsibility in conducting clinical research. Dr. Friedman explained that there is a wide variety of views. While the reimbursers are sensitive to developing knowledge and providing the best treatment for their patients, they must be concerned about remaining fiscally viable companies. He pointed to the example of Kaiser hospitals in northern California, which have traditionally been seen as well managed and cost-effective, but are currently being financially threatened by other managed care groups. Such previously secure organizations are now threatened and, hence, hesitant to pay for many activities, such as bone marrow transplantation for breast cancer, when there is no national policy assessing their utility.

Dr. Charles Wilson emphasized Dr. Friedman's point that market forces prevent insurance companies from being persuaded to act simply for the public good. He suggested that cost-effectiveness analyses showing inefficiency in *current* treatment practices could be used to convince insurers and health maintenance organizations (HMOs) that providing financial support for clinical trials of new treatment techniques is ultimately in their best fiscal interest. Dr. Friedman agreed that reimbursers are much more likely to cooperate when potentially useful cost or outcome evaluations are built into the trials and added that efforts to identify individuals in the research community who can assist in determining economic outcomes are currently under way.

Dr. Salmon expressed his concern about the material presented by Drs. Friedman and Sondik. He noted the intense competition among managed care organizations to undercut each other and capture the market, while dealing with declining health care reimbursements from the government and other sources. Dr. Salmon proposed that national legislation may be needed to create solutions. He pointed out that managed care is most common in urban areas which are also where most clinical research is performed; as a result, 80 to 90 percent of clinical research will be impacted by managed care. Dr. Salmon suggested that nationally important priorities in cancer research may need to be funded in the same way prevention activities are funded rather than through traditional reimbursement. He stressed the importance of informing the public

and Congress about the long-term impact of an aggressively cost-conscious policy and the danger that financial pressure will extinguish groups that support clinical research.

Dr. Sondik asked whether NCI is coordinating its activities in this area with other Institutes at NIH. Dr. Friedman agreed that a coordinated approach would be beneficial, but it has not yet been fully organized. He mentioned that he and Dr. McCabe plan to meet with the person responsible for the general clinical research centers, Dr. Judith Vaitukaitis, who will, at Dr. Varmus' request, oversee a survey to gather information about clinical research and reimbursement. Dr. Shulman, Dr. Varmus' ombudsman for clinical activities, will advise him on this topic, and there are a few efforts under way to coordinate activities with NIAID and NHLBI.

Dr. Freeman offered his perspective that it is not health care reform but, rather, cost-of-care reform that is going on uncontrolled. He mentioned that the training of scientists and oncologists is at risk and that researchers themselves, as well as support for research, is threatened. He suggested that the NCI advocate the training of scientists as part of the public debate. Dr. Friedman agreed and, referring to the *New York Times* editorial, expressed concern over the existence of the next generation of teachers and researchers. Dr. Freeman commented that current formulas by which Medicare reimburses hospitals take into account the money needed for residency programs. With cuts in Medicare, this support for teaching could be eliminated, which would deeply influence the training of scientists not only in the cancer arena, but in all other areas as well. Dr. Freeman urged the Board to create some type of strategy by the end of the day to deal with these problems.

Dr. Becker complimented Dr. Friedman on his presentation and suggested that it be distributed as a working document. He shared his experiences with insurers as a doctor at a teaching hospital, describing them as "vendors" of medical care who express no interest in academia, research, or clinical care, but are concerned with obtaining basic standard care at the lowest possible price. He expressed deep concern about the impact of this business strategy on training, quality of care, and prevention research.

Dr. Becker noted that the only money available for prevention research has come under capitation plans and stressed the need for prevention research funds for ultimate success in preventing cancer. He suggested that regulation is needed, but that the managed care movement has become widespread so suddenly that none yet exists. He predicted that patients will eventually be forced to accept the cheapest care available until abuses become so rampant that the legislature is forced to act. He offered the example of patients being forced to undergo radical mastectomy because managed care plans determined they were cheaper than lumpectomy and radiotherapy. He warned against the naive notion that reimbursers will support clinical research in any way.

Dr. Sigal asked Dr. Friedman what specific actions and changes NCI should implement to ameliorate the situation. She referred to his suggestions to streamline clinical trials, look at outcome research, do cost benefit analyses, and broaden education. She said she does not think it likely that legislation will pass to cover NCI-sponsored research, so she would like to focus on tangible changes NCI can make to maximize its control.

Dr. Friedman described his mixed experiences with insurers and managed care organizations, noting that just 1 year ago, many of them refused to reimburse for NCI-sponsored trials whereas, currently, many of them have changed that policy. He indicated that NCI is scrutinizing its trials in efforts to increase efficiency and effectiveness, and has sponsored a working seminar on integrating cost-effectiveness and outcomes research into cooperative group clinical trials, which will be published as a monograph in the *Journal of the National Cancer Institute*. The level of interest in the seminar has been so high that a follow-up meeting is being planned. Dr. Friedman stressed the importance of pursuing all these ideas, since no single strategy will necessarily be effective, especially in light of the constant changes in the system. He pointed out that while answers to national questions are needed, investigators often wish to pursue their own ideas. Compromise is needed within the investigative community in recognizing the validity of both approaches and the need to work collaboratively on some issues while others are pursued individually.

Dr. Vaitkevicius inquired about the waste involved in "pseudo trials" and how insurers can be alerted to clinical research for which they should not pay, to distinguish it from bona fide trials that deserve support. Dr. Friedman agreed that this has been a thorny problem with which the NCI has wrestled. Since it is neither possible nor appropriate for the NCI to survey and assure all clinical trials in existence, the Institute offers assurances for only those trials it sponsors, as they are known to be of high caliber and are constantly being improved. Dr. Friedman noted that national debate would be required to resolve the tension between the public's desire to control health care costs and support quality research versus the view of individual patients (or their families or advocates) that they are entitled to whatever treatment they want, regardless of cost or likelihood of benefit.

Dr. Schein expressed the view that clinical trials can be a means of restricting access to therapies in that protocols are defined with restricted entry criteria and limited testing. While trials are conducted, this form of therapy is not available to the general public. The managed care organizations are currently able to support clinical trials because access to expensive therapies like bone marrow transplantation is effectively limited by the participation restrictions built into the trial. In the past, he said, if an approach seemed to obtain positive results in a few studies, it was adopted into practice without the same constraints of rigid proof.

Dr. Rimer thanked Dr. Friedman for his presentation and asked the Board to contemplate appropriate follow-up for discussion the next day. She referred to Dr. Becker's point that these health care system changes affect not only clinical research, but prevention trials, screening, and virtually all of NCI's other activities as well. She asked the representatives of other affected institutions to consider possible joint efforts with NCI to protect the integrity of the medical research establishment.

Dr. Rimer announced a short break to be followed by a presentation on cancer centers. She stated that the cancer centers are challenged by the environmental pressures of managed care and the cost of clinical research. She suggested that these centers will need to change from the models of the 1970s to survive in the next century, and the NCAB will bear responsibility to aid in envisioning the cancer centers of the future, in order to nurture them and prevent them from being buffeted by the changes of managed care and health care reform. She informed the Board that three directors of major cancer centers would present their perspectives on nurturing

clinical, prevention, and translational research, and invited Dr. Rabson to introduce the speakers.

VII. CANCER CENTERS: EVOLUTION INTO THE 21ST CENTURY—DRS. BRIAN KIMES, ROBERT YOUNG, MAX WICHA, MARTIN ABELOFF

Overview of Cancer Centers—Dr. Kimes

Dr. Kimes began his presentation by acknowledging Dr. Rimer's emphasis on cancer centers, which he characterized as microcosms that must begin to face real-world problems. He expressed the hope that a glimpse of the Center's program would foster development of truly efficient and effective research infrastructures.

In remarking on resource problems described by Drs. Sondik and Friedman, Dr. Kimes mentioned some milestones over the past 24 years since the passage of the National Cancer Act in 1971, and pointed out that every cancer center is unique, with unique leadership, and unique fragility relative to economic forces. Dr. Kimes briefly reviewed some historical sign posts, starting with the freestanding centers established prior to 1971, on which the whole cancer center program was based. The National Cancer Act of 1971 defined the importance and expectations of a national network of cancer centers and in 1973-74, initial guidelines were designed to help academic centers reach the level of significance that had been achieved by the freestanding centers.

Dr. Kimes explained that the first guidelines for cancer center support grants featured four essential characteristics; this underlying paradigm, he observed, was developed in a world quite different from today, but is clearly still in use at this time. In 1977 and 1978, a one-time review of 21 institutions was conducted by the NCAB, which resulted in these institutions being awarded comprehensive status. From 1989 to 1992, a comprehensive peer-review system was developed to evaluate every competing renewal application. In 1990, a regular dialogue was initiated between the cancer centers and the American Association for Cancer Institutes, which includes annual meetings with the center directors and participation in the administrator's forum. These mechanisms help the NCI deal with major issues likely to be faced in the future.

Dr. Kimes pointed out that major revisions of the guidelines in 1992 strengthened the peer review system and better separated quality control among the cancer centers. He reminded the Board that these guidelines were based on the original paradigm of 1973-74. In 1992, under Dr. Broder's leadership, a planning grant initiative was designed to increase the geographic diversity of cancer centers, as mandated by Congress.

Since 1992, two major problems have surfaced within the Cancer Centers Program. Dr. Kimes suggested that the opportunities presented by the basic research enterprise are realizable in terms of the translation of research moved into a patient or population research setting and back into the laboratory. He reminded the Board of the effect of managed care and free-enterprise economic forces, and reiterated that the whole centers program is founded on 20-year-old paradigms. He remarked that many of the original assumptions and expectations of the centers may no longer hold, just as current strategic assumptions on how to use the NCI

budget are in question. He recommended revisiting a number of issues and expressed the hope that the NCAB would play a significant role in this undertaking.

Dr. Kimes presented a slide illustrating that the NCI budget rose between 1984 and 1992, and then remained stable to 1995. During this past 11 years, there has been a stable number of cancer centers, fluctuating between 54 and 56, which reflects a progressive, competitive program.

Dr. Kimes then described the different organizational models for cancer centers. Freestanding centers were the original organizational model, and Dr. Kimes remarked that many people think that the NCI clinical center is one of the original freestanding centers. Matrix centers reside in academic institutions, such as the departmental matrix at the Johns Hopkins Center, which Dr. Kimes said would be described by Dr. Martin Abeloff, and the pure matrix, to be described by Dr. Max Wicha of the University of Michigan Center.

Dr. Kimes continued by pointing out that in a freestanding center, the center director is responsible for all business and research activities; the matrix center, however, is a component of a larger, more complicated academic enterprise that reports to a higher level of management. Institutional support and the authority of the center director are particularly important for an academic cancer center.

Dr. Kimes explained that there are 26 comprehensive centers, 17 clinical centers, and 12 basic laboratory centers, that are primarily in freestanding institutions. One consortium center probably will not be continued. Including the 17 planning centers, approximately 80 institutions in the entire country can be called legitimate cancer centers based on the depth and breadth of their research bases. Dr. Kimes noted that the NCI is now dealing with 73 such centers and has been successful in ensuring the excellence of its funded institutions.

Dr. Kimes reminded the Board that this national program is unprecedented in its size and the expectations placed upon it in terms of integrating research. He presented a slide showing the location of planning grant initiatives, noting that if even a small proportion of these are successful, the geographic diversity of the centers will be increased. Dr. Kimes explained that 56 active cancer centers represent 50 percent of the NCI's research support. He suggested that cancer centers can be major players as NCI moves into new strategic assumptions regarding how to do the best possible research with limited resources.

In regard to the qualities of a strong cancer center, Dr. Kimes stressed, first and foremost, excellence in research. Second is excellence in leadership. Dr. Kimes remarked that the cancer centers are headed by some of the most distinguished scientists and leaders in the cancer research community. The third quality is strong institutional support, the expectations for which, in the future, will need to be redesigned and rethought. The economic forces that allow institutions to support cancer centers will be different in the future. The extensive scientific interactions that Dr. Kimes said represent the heart and purpose of cancer centers must be maintained even under the constraints of limited resources. Determining how best to accomplish this will be an important question for the future.

Dr. Kimes suggested that cancer centers provide access to resources, technology, expertise, and services that make them more cost-effective. They are responsive to

opportunities and have the capability of developing and funding pilot and feasibility studies, and bringing people and resources together rapidly to explore and achieve new scientific leads. The centers help the NCI respond to national imperatives as a partner. The strong linkages of cancer center research programs to research-care programs may be threatened. Dr. Kimes pointed out that the NCI has always expected comprehensive cancer centers to maintain strong linkages to their communities and regions, which could also be threatened by current economic forces.

In terms of the concepts of cancer centers, Dr. Kimes explained that they are, first of all, institutional—they are designed to bring all of the research resources and potential of the institution together. They are multidisciplinary and inclusive in membership. Center directors and senior leaders should have the authority to bring scientists together horizontally within the typical vertical structures of organizations. Dr. Kimes stressed that the same opportunities are provided to scientists in all disciplines, not just cancer scientists. He further described the centers as flexible, innovative, and opportunistic; he suggested that such a stance must be maintained to pursue important leads quickly. He explained that the centers are responsible for relating research to actual cancer incidence and mortality in their communities, and pointed out that local differences will be found in cancer incidence and mortality.

Dr. Kimes stated that, clearly, centralized services and technology-based resources are fundamental to providing scientists the most cost-effective research opportunities. The centers are very proactive, with leadership that is responsible for motivating, encouraging, and persuading scientists to interact by collaboratively pursuing new opportunities that they might not pursue alone. He described the final concept of cancer centers as leverage in attracting institutional, public, and philanthropic resources. Even as institutional resources become less accessible, the centers remain successful in attracting public and philanthropic funding.

Dr. Kimes mentioned barriers to translational research, which he said typify the problems faced by cancer centers nationwide. He cited dwindling resources and an erosion of the basic science foundation, without which, opportunities will be unavailable for translational research and the development of new therapies and prevention strategies.

In a brief discussion of impediments and threats to clinical research, Dr. Kimes mentioned the increase in regulations affecting clinical research. He cited concern among many individuals in clinical research that such regulations may become so oppressive that no one will want to pursue a career in clinical research. Dr. Kimes suggested that it is important that the nation consider where regulations are and are not needed. Second, he mentioned the lack of investigator-initiated opportunities and the fact that the NIH initial review study sections still are not in place. He expressed his belief that investigator-initiated opportunities are the way to the most innovative research and that clinical research does not have the same opportunities as basic research. He raised the specter of managed care and referred to Dr. Sondik's statement that the expectation of increasing Federal resources is probably a dream, and that managed care will reduce institutional resources for clinical research. Dr. Kimes noted that the profit margin that generated clinical income, which was responsible for some of the more innovative institutional trials, has been invested in basic departments, building prevention and control programs, and other priorities. Managed care will now be responsible for a reduction in access to patients.

Dr. Kimes noted the difficulty of building a strong prevention and control research base and the need to train more people. He further mentioned the need to establish equity for prevention and control research as a legitimate cancer research activity, with opportunities for researchers to achieve tenure and other benefits equal to clinical and basic researchers. He concluded by reiterating the lack of investigator-initiated research opportunities.

Dr. Kimes introduced the next three speakers as distinguished center directors who would describe "real-world" problems in greater detail. He described Dr. Robert Young's distinguished career in cancer research and mentioned his former position at NCI and current presidency of the Fox Chase Cancer Center, one of the oldest, most successful cancer centers in the nation. He characterized Dr. Max Wicha as another prestigious scientist and leader of one of the newest comprehensive cancer centers, a pure matrix center at the University of Michigan. He alluded to Dr. Wicha's chairmanship of the Cancer Center Support Grant Review Group and his major role in conceptualizing and developing the review system. Dr. Kimes characterized Dr. Martin Abeloff of the Johns Hopkins Cancer (Oncology) Center as extremely influential and successful in pursuing translational research.

Freestanding Cancer Centers—Dr. Robert Young

Dr. Young explained that he would talk about freestanding cancer centers, using Fox Chase as an example and covering its structure and functions, as well as the clinic's impact of and response to managed care.

Dr. Young began by pointing out that this is the 33rd year of a support grant to Fox Chase from the NCI. He remarked that peer review support represents an investment in the institution both in its support and infrastructure of cancer research. Dr. Young displayed a slide of Fox Chase Cancer Center and emphasized that the Center existed prior to NCI's first investment. Over the past 30 years, the 850,000 square foot complex, valued at over $150 million, Fox Chase has embodied the importance of a cancer-research-focused institution.

Dr. Young cited facts and figures about Fox Chase, an amalgamation of the oldest continuously operating cancer hospital, the American Oncologic Hospital, founded in downtown Philadelphia in 1904 and the Institute for Cancer Research, founded in 1925. The institutions were unrelated until creation of the national cancer plan, when the cancer center program stimulated basic scientists and oncologists to work together constructively. This freestanding cancer center has 127 members, with 366 M.D.s, M.D./Ph.Ds., or Ph.D.s. linked to full-time research investigators. The staff totals 1,800, with total grant support of slightly over $40 million. Philanthropy raises about $7 million, $6 million represents the total support of the core grant, and approximately $8 million per year is invested in institutional funds in support of the center and its activities. All of the profits from the hospital and health services are invested into support for cancer research in its various forms.

According to Dr. Young, the Center's singular mission is to reduce the burden of cancer, with a focus on interdisciplinary research. The Center is organized to encourage the mission, which summarizes the purpose of the institution and facilities: to support cancer research in one form or another. The Center features the spectrum of research activities characteristic of a comprehensive cancer center. That the central purpose and only function of the entire enterprise is cancer research and treatment is a great advantage.

Dr. Young remarked that all staff of the institution are aware of the purpose and mission of the institution, an advantage in focusing attention on cancer research and being creative and enterprising in addressing challenges and new directions. Another advantage of a freestanding center is that science and business are constructively melded. Fox Chase's science is divided into three major divisions: medical, population, and basic science. Stimulating an environment where cancer prevention and control research can be done is a challenge. Another advantage is the ability to structure the free standing cancer center independent of traditional academic lines and to recognize the importance of population science research in cancer prevention and control, which, at Fox Chase, has weight and peer review funding equal to the other two divisions.

Dr. Young discussed the Center's core grant funding over time and explained that, although core grant support has declined six percent overall since 1989, the Center has been able to leverage the presence of this institutional investment, along with recognition of Fox Chase. Peer review funding has risen about 45 percent and philanthropic support has increased about 113 percent, providing an example of the leverage effect of the cancer center core grant mechanism on an institution. Fox Chase's core grant, the largest in the United States, represents less than 5 percent of its support.

This grant, Dr. Young pointed out, supports a number of important endeavors, such as the animal facility, library, and the glass-washing facility that are not likely to be supported by a donor. Fox Chase boasts a Nobel laureate in medicine, seven members of the National Academy of Sciences, two GM prizes in the last 7 years, and two gold medals from the American Cancer Society. Dr. Young stressed the importance of the nurturing aspect of these grants to the science within the institution.

Freestanding centers, which are influenced by the attitudes and challenges also faced by the NCI, are stimulated to increase translational, or interactive, research. Dr. Young cited, as an example, the number of Fox Chase investigator publications that cross two or three divergent scientific disciplines working together on translational cancer research. He mentioned a series of studies done at Fox Chase on a drug that was long believed to act partially as an estrogen and partially as an alkylating agent. He referred to Dr. Ken Teu of the Drug and Radiation Resistance Program, who decided on the basis of a series of pharmacologic studies that the drug's mechanism of action was neither as an alkylating agent nor an estrogen but, rather, that it functioned to inhibit microtubular-associated proteins. Dr. Teu and Dr. Jenny Glusker, a crystallographer with the Biomolecular Structure and Function Program, performed three-dimensional structuring of the molecule and discovered that the alkylating moieties were so hidden that they could not function as an alkylating agent. Based on a new mechanism of action postulate, they approached the Prostate Cancer Group and questioned whether the drug could be combined with another, such as vinblastine. When their clinical trial showed promise, it was moved to the Fox Chase Network of community hospitals, where two-thirds of patients on the trials are seen through the Fox Chase Network. The trial represents one of the most active regimens in hormone-resistant prostate cancer yet published.

Dr. Young turned to Fox Chase's longtime interest in hepatitis B by noting that large-scale epidemiology and prevention and vaccination programs in China and Senegal have been made possible by P01 funding. Much of the research that antedated the discovery of the hepatitis virus by Fox Chase's Nobel Prize winner, Dr. Barry Blumberg, was supported by the

NCI, as was the core grant. Dr. Young suggested that the resultant vaccine development, in collaboration with Merck, will reduce health care costs in this country to an extent greater than every dollar invested in past and future research at Fox Chase.

In terms of future directions at Fox Chase, Dr. Young emphasized the opportunity for a multidisciplinary program centered around the science of cancer prevention. He noted the impact of the genetic aspects of risk, and the science of cancer prevention pharmacology. One behavioral research component of the center addresses some of the issues of the impact on patients genetically defined as high risk; plans for expansion will enhance the ability to define populations at risk through genetic epidemiology; plans are underway to construct a 125,000-square-foot facility devoted to this interdisciplinary approach to cancer prevention. Dr. Young mentioned the need to expand critical masses of researchers in basic and medical science and to further integrate interdisciplinary and translational research at Fox Chase.

Turning to developments in managed care, Dr. Young echoed Dr. Friedman's statement that we are moving from a provider-driven system to a payer-driven system; we are leaving fee-for-service and entering managed care. Talk of quality and service has turned to talk of quality and cost, the latter being the subject of some debate. Dr. Young expressed that we are clearly moving from an inpatient focus to an integrated delivery system and an outpatient focus. Physicians are moving from being customers to economic partners, from being specialty driven to primary care driven, which carries risk. Whereas the payer used to be solely at risk, capitated care structures cause the provider to assume risk.

Dr. Young noted some interesting paradigm shifts by stating, "It used to be that a full bed was a good bed. Now an empty bed is a good bed. A full office used to be a good office and now an empty office is a good office. We used to talk about market share or . . . the number of patients . . . and now the lexicon is covered lives. Dollars or cents per person per month in a capitated health-care system."

Dr. Young reiterated that the increasing focus on outpatients, primary care, diagnosis, and prevention reveals no evidence that anyone is prepared to pay. He suggested that we are moving from a clinical-technology focus to an enormous investment in information systems necessary to monitor large, complex medical care systems. He observed that there is no evidence to suggest any endpoint in sight for the increase in Health Maintenance Organizations (HMOs). He remarked that HMO mergers have led to more patients covered, rather than to an actual increase in HMOs. Dr. Young cited some major threats to oncology posed by the HMO increases. For example, there is little evidence of guaranteed access to centers of excellence. Many HMOs focus exclusively on an in-system reimbursement structure. While some systems pay for often prohibitive point-of-service outside costs, sometimes such payment is disallowed. Dr. Young observed that the Federal Employees' Health Benefits Program—highly touted as an example of a perfect system does not guarantee Federal employees access to clinical trials, with the exception of bone marrow transplantation. He suggested that the NCAB address this issue. Dr. Young mentioned the similar risk to academic centers, as well as the fact that no one is willing to pay for either education or innovation in the present or emerging systems. Access to oncology and to clinical trials is not guaranteed. He noted that while some clinical trials do result in cost reduction, clinical trials research is not cost-effective as currently practiced, because many of the regimens tested turn out to be ineffective.

As an example, Dr. Young mentioned the Philadelphia region, and cautioned that viewing one health-care environment is just that—one environment. He noted the large and growing HMO coverage, and the substantial Medicare population—supported by the Federal Government—which will pose a challenge for the HMOs to capture. He cited the large, though shrinking, fee-for-service structure through Blue Cross and the small number of self-pay or commercial-coverage patients. Dr. Young noted the sensitivity of hospital and health service programs in the current cost-shifting environment and the question on people's minds regarding how hospitals can charge so much. In responding, he stressed that what is charged is not what is received from various payers. Citing his own Center as an example, he noted that 11 percent of inpatients carry commercial coverage and provide 19 percent of overall income; 13 percent of outpatients have such coverage, which provides 20 percent of overall income. Inpatient revenue from Medicaid accounts for 4 percent, with 1 percent in outpatient revenue. Thirty-seven percent of outpatient charges come from Medicare, representing 28 percent of reimbursements. HMOs in the region have focused primarily on inpatients, representing 21 percent of charges but only 18 percent of revenue. The discrepancy has been offset in the last couple of years because of the focus on reducing charges. Reimbursement is likely to shrink 10 to 20 percent based solely on these shifting proportions.

Turning to what Fox Chase has done in light of the above realities, Dr. Young described the network of 17 community hospitals in eastern Pennsylvania and mid- and southern New Jersey established primarily for clinical trial research, cost-effectiveness management, and support for the development of oncology programs and radiation therapy. In 1994, the network enrolled 527 patients in clinical trials. This successful research effort has formed the nucleus to create regional networks that can contract for managed care cancer carve-outs in the Delaware Valley. To qualify for entry into the network, community hospitals were required to have oncology leadership and focus, experience with clinical trials, an institutional review board, and a genuine interest in developing an oncology program. The benefits to the community hospitals have included marketing advantage, increased market share, development of oncology services that they might not have developed in other settings, and a very successful reciprocal referral relationship with Fox Chase.

Dr. Young acknowledged collaboration among many in the audience in developing a National Comprehensive Cancer Network (NCCN), a national alliance of cancer care providers promoting the development of standards and patient care guidelines across comprehensive cancer centers. Outcomes and cost-effectiveness research will also be conducted through this collaborative group. Noting that Network hospitals perform 2,800 bone marrow transplants per year—the volume of which increases the capacity to dissect cost-effectiveness issues—he underscored the need to focus on cost containment while ensuring quality.

Dr. Young noted his belief that such a group can create a body of force sufficient to negotiate directly with payers. He noted a recent meeting with Blue Cross and another scheduled in the near future with General Electric. He explained that a menu of services is being developed that so far includes pediatrics, bone marrow transplantation, radiation therapy, and other cancer carve-out mechanisms. He noted plans to examine patient and payer satisfaction survey structures, as well as the focus on prevention and early diagnosis and screening. He stressed that such adaptation to the managed care world will enable cancer centers to secure access to sufficient patient populations to perform the central mission. He reiterated that cost control and effectiveness will have to be addressed realistically and directly.

Dr. Rimer introduced Dr. Max Wicha, head of the Cancer Center at the University of Michigan.

Matrix Cancers—Dr. Max Wicha

Dr. Wicha began by thanking Dr. Rimer and the Board for the opportunity to speak from the perspective of a matrix cancer center and as chair of the Cancer Center Review Group. He mentioned his travel and review of more than half of the nation's cancer centers during the last 3 years. He noted the uniqueness of each center and suggested that matrix cancer centers face some issues and problems that differ from those faced by freestanding centers such as Fox Chase.

The University of Michigan Cancer Center was established 7 years ago and has developed rapidly. Situated within an academic institution and medical center, the Center draws upon the strengths of multiple departments and schools within the system, such as the medical school and the schools of public health and nursing.

Referring to opportunities in managed care, Dr. Wicha explained that, as part of an academic health center, the University of Michigan Center is part of a larger health-delivery system, or network, that deals with all aspects of patient care, not only with cancer. Therefore, discussions with insurance carriers focus on broad issues of managed care and patient care, as well as more specialized, or niche, markets in cancer. Among the challenges that matrix centers face from being in an institution with other structures in place are the issues of the authority and resources of the cancer center director and the need for the director to be a politician able to work with multiple department chairs and deans of multiple schools. He acknowledged that while the challenges are formidable, they offer some unique opportunities to reexamine practices. This has led to fundamental changes and restructuring at the University of Michigan Center that have proven fortuitous and helpful in the development and success of both the cancer center program and health care in general.

While Dr. Wicha acknowledged the problems of limited access for clinical research and funding, and the potentially destructive results of competition for patients among cancer centers, he noted the importance of working together as cooperative institutions. For example, because the managed penetration in the health care market is very low at 5 to 10 percent, the University of Michigan has had an unusual window of opportunity. Dr. Wicha noted that, surprisingly, the auto industries and unions have prevented managed care rather than facilitating or fostering it because members desire to choose their health care providers. He acknowledged this as a temporary situation and again noted the importance of fundamental changes in business practices.

Dr. Wicha reported that the University of Michigan Medical Center has undergone a major restructuring in the last 6 months, which resulted in a clinical-delivery system. The new structure is of key importance to matrix cancer centers previously centered upon departmental lines, where each department could perform fee-for-service, bill as much as it wanted, and build fiefdoms for department chairs. He acknowledged that while such a structure might have been good for individual departments, it was very bad for interdisciplinary and collaborative research. He noted the importance in a managed-care environment of interdisciplinary coordination of care in increasing the efficiency of clinical care and the marketing advantages.

He characterized the shift from a departmental to a programmatic focus as critically important, in that cancer represents a big share of business for almost every hospital and becomes a product or program line. This change has led to willingness of hospital directors, including his own, to invest large sums of money in clinical programs. Dr. Wicha noted that such alignment of programs supports the academic mission of the center, including support of clinical research, which is difficult in these times.

Dr. Wicha explained that the national effort has seen the establishment of a regional health care delivery system. In a matrix center and in academic institutions, managed care requires a regional network with a large primary care base able to supply the tertiary care needs of the academic institutions. He noted the opportunities for niche markets and the NCCN, cited earlier by Dr. Young.

Dr. Wicha posed the question, "What can NCI do to help support some of this?" He explained that while supporting patient access to designated clinical trials and convincing insurers that there is waste in ineffectual therapies outside the NCI's scope, the NCI must also emphasize the need for linkages in research and patient-care service activities. These can no longer be separated in the new environment.

Turning to facilitation of translational research at the University of Michigan Cancer Center, Dr. Wicha noted that the matrix-style organization has established multidisciplinary programs, such as disease-oriented programs for different kinds of cancer. Multiple specialists from many disciplines operate multidisciplinary clinics for patient management, as well as for research. Such a disease-oriented research program becomes the intersection of basic research, molecular oncology, immunology, pharmacology, and drug development. Research grants have been funded to facilitate work between laboratory and clinical investigators. During the last 2 years, research programs in cancer prevention and control have fit into the matrix organization. Investigations of tumor types range from basic biology to prevention and treatment issues. One of the cancer center's most important missions is to provide shared core resources that facilitate translational research.

Dr. Wicha provided some examples of the direction of his Center in developing more innovative translational research requiring NCI support through core grant mechanisms. Ten clinical trials in gene therapy required establishment of expensive shared core facilities to move basic research in gene function into clinical trials. One core produces vectors for basic researchers and animal models. A larger human applications laboratory, funded by the Medical Center, cost almost $2 million to take vectors from the laboratory and manufacture them for clinical trials under Good Manufacturing Practices. Dr. Wicha briefly mentioned the obstacles of immunologic-suicide and tumor-suppressor genes in development of gene therapies as examples of how cancer center core grants can provide facilities that could not be provided any other way.

Turning to molecular diagnosis core grants, Dr. Wicha suggested that to facilitate interactions between epidemiologists and molecular biologists, shared cores could be promoted by the NCI; he praised current efforts in that direction. Noting the liberalization of core grant guidelines in development of cores, Dr. Wicha noted Dr. Kimes' work with the Branch on changing guidelines to permit development of technologies within cores; he urged pushing the envelope of such technologies through collaboration among multiple institutes. As examples,

he cited the work of general clinical research centers in establishing his center's gene therapy program and the collaboration between the vector core and the clinical research center in the human applications laboratory.

Dr. Wicha turned to the critical need for training of physician scientists, around whom the nucleus of a strong translational research program can be formed in which discoveries in the laboratory can move into the clinic. He characterized such physician scientists as a "vanishing breed" and cited the increasing difficulty of training and support. He pledged his support for a clinical study section for translational and clinical science and noted that the NIH peer review system falls short in this area.

Stressing the critical need to move forward in prevention and control research, an area least developed in most cancer centers, Dr. Wicha noted his center's decision to create a division of cancer control and prevention equal to the divisions of clinical and basic research. Again illustrating the need for shared core facilities, Dr. Wicha acknowledged the need to increase training in molecular epidemiology, nutrition, chemoprevention, behavioral research, and community outreach. He reiterated the need for a molecular diagnosis core to do genetic testing on populations. He reported development at his center of a health communications laboratory for the new director of cancer prevention and control research that will produce interactive videos and educational materials.

Dr. Wicha reiterated his recommendation that the NCI encourage translation of research into the community, as well as to the bedside, and fund epidemiologic and behavioral research. He suggested tapping the resources of and working cooperatively on cancer control initiatives with State departments of public health, which he characterized as acting autonomously, independent of cancer centers or the NCI.

Dr. Wicha showed a map of State and regional networks in his area composed of 25 groups who collaborate on research and managed care contracts and alliances. The networks are connected by computer linkages and visits by cancer center personnel. The member groups share joint management of patient care. In the future, some patients managed locally will utilize the cancer centers for second opinions and clinical protocols that will be administered in their local communities and followed up in the cancer centers, where they will also receive specialized care unavailable in local communities. He suggested such a model as the way of the future and reiterated the need for the NCI to support linkages between service and research. He further suggested that unless research goes out into communities, there will be little incentive for communities to participate in research. He cited the example of investigational, or Class C, drugs, which, distributed through cancer centers, would represent a tangible contribution to network affiliates, as well as support of outcomes and prevention research.

Dr. Wicha concluded his presentation by showing a slide of the cancer center building under construction at the University of Michigan that will house the new hospital, outpatient clinics, and research laboratories. The building supports the Center's mission of linking clinical and basic sciences.

Dr. Rimer thanked Dr. Wicha and praised the tremendous accomplishments of his center in just 7 years. She introduced Dr. Martin Abeloff, head of the cancer center at the Johns

Hopkins University Oncology Center, and announced that he would focus on translational research.

Translational Research and Cancer Centers—Dr. Martin Abeloff

Dr. Abeloff began his presentation by thanking Dr. Rimer for the opportunity to talk about translational research at Johns Hopkins. He noted having grown up with such research in the years before the term was coined.

In presenting examples of types of translational research under way at Johns Hopkins, Dr. Abeloff expressed that the interactions fostering such research provide potential approaches and solutions faced in the managed care arena. He presented an overview of his presentation: the history and evolution of the cancer center at Johns Hopkins, the current organizational structure, a summary of major translational research programs, a discussion of some helpful ingredients for fostering such research, and managed care.

Dr. Abeloff showed a slide of the current Oncology Center. He pointed out the well-known Hopkins dome and noted that the building was planned by prior director Al Owens and colleagues in an L-shaped format to locate basic scientists next to clinical investigators to create enhanced opportunities for collaboration. He pointed out that the Oncology Center assumes responsibility for cancer research in the whole institution. In the 1970s, the Center was authorized by the trustees of the universities and hospital as an academic department and functional unit. Designation as a comprehensive center also occurred in the 1970s, with award of the first core grant about 34 years ago. The cancer center support grant and a wide variety of other funding mechanisms, including the SPORE grants, have been essential in recent years. The transition from a department-based to a broader multidepartmental center has promoted involvement throughout the University, particularly of the Schools of Medicine, Hygiene and Public Health, and Nursing. Cancer center membership has increased by approximately 35 percent in recent years and represents 20 departments throughout the University, not only the Department of Oncology.

Turning to organizational structure, Dr. Abeloff explained that the cancer center director reports directly to the dean and the hospital president and performs with the full authorities of an academic department and functional unit head in the Johns Hopkins medical institutions. At the time of his recruitment, Dr. Abeloff was given additional responsibilities for overseeing cancer care and research in other areas of the institution. This illustrates the Center's evolution as a hybrid of a department and a matrix center. The Center houses six research programs involving investigators from throughout the institution, including cancer biology, hematologic malignancies, solid tumor research, cancer prevention and control (in conjunction with the School of Public Health), GI cancer, and urologic oncology.

Dr. Abeloff turned to a report of some of the efforts under way in the research arena. The prostate SPORE, headed by Dr. Donald Coffey, involves major commitments of more than 20 investigators from the Departments of Urology, Oncology, and Pathology. Dietary and chemoprevention studies aimed at reversing the methylation changes in glutathione S transferase involve extraordinary collaboration of investigators from multiple departments. Genetic linkage studies identify candidate genes as the hereditary prostate cancer gene. A variety of mechanistic-based therapy studies are under way. The Center interacts with the

Baltimore Longitudinal Study of Aging housed at the Bayview campus on studies of Prostate Specific Antigen (PSA) and predictors of cancer risk, as well as with orthopedic investigators on the physiology of bone metastases. The GI cancer SPORE is headed by pathologist Dr. Stanley Hamilton.

Dr. Abeloff pointed out that when the original Department of Oncology was established, it was largely composed of medical, radiation, and pediatric oncologists, with a core of basic science investigators concentrating on human cancer. Now, there is extensive involvement of the pathology department. He cited the work of Dr. Bert Vogelstein and colleagues on the molecular genetics of colorectal cancer that has spun off a variety of research and clinical programs throughout the institution.

The lung cancer SPORE, a collaborative effort of multiple departments headed by Stephen Baylin focuses on defining the molecular steps of the early stages of lung cancer. The current focus of the lung SPORE is on molecular epidemiologic approaches to new screening strategies, changes in DNA methylation patterns, and other areas depicted on Dr. Abeloff's slide.

Dr. Abeloff mentioned the leverage throughout the institution and the collaboration of an increasing number of investigators as powerful aspects of the SPORE grant mechanism as well as the Cancer Center Support Grant (CCSG). He noted the paradoxical effect of some of the threats of managed care upon decreasing departmental boundaries and enhancing multidisciplinary collaboration.

Dr. Abeloff noted the national and international impact of the model set up by Dr. Bert Vogelstein for examining stages in evolution, particularly of colorectal cancer, as well as the impact within the institution. He mentioned development of interventions in risk assessment, early detection, and treatment. Dr. David Sidrensky, a protégé of Dr. Vogelstein, has been applying some of these principles to head and neck malignancies, which has led to exciting developments in staging and potential therapeutic interventions. Dr. Abeloff also noted major interest in the mechanisms of the action of the *p53* gene and the implications on categorizing tumors for various therapeutic approaches based on the gene's effect on cell cycle mechanisms and programmed cell death, or apoptosis. He noted Mike Kasten's major role in working on these concepts with radiation therapists, surgical and medical oncologists, and investigators throughout the institution.

Dr. Abeloff finally noted the example of an immunotherapeutic gene therapy approach led by Drew Pardoll. While an active study in rodent models progresses, a human program is well under way in renal and prostate cancer to examine gene therapy approaches to immune therapy.

Dr. Abeloff asked, "What are the ingredients for successful translational research?" He proposed that many of these ingredients are applicable to the challenges of managed care. At an individual level, he suggested the need for talented, committed investigators to navigate the ups and downs of working between the laboratory and the clinic. At an institutional level, resources and space are needed, but equally important are a breadth and depth of expertise, collegiality, and collaboration among investigators, scientists, and physicians throughout the institution. External support is essential from the NIH, foundations, philanthropy, and industry. The latter

three will become increasingly important, as will flexibility of scientists, investigators, and funding agencies, so that the best ideas may be pursued in a nonbureaucratic way.

Dr. Abeloff then asked, "How does one facilitate translational research within an institution?" He noted that Dr. Vogelstein's work began as part of a loosely affiliated bowel tumor working group of investigators, initially funded by the Baker Clayton Foundation. Such working groups continue to be fostered throughout the cancer center. Developmental funds for pilot projects and faculty recruitment for new investigators in the CCSG are critical for developing such working groups. Training grants testing a variety of approaches have been equally important. A training grant in molecular medicine from a private foundation enables graduate students coming to clinical departments through basic scientific activities to learn the fundamentals of clinical and basic research. Enhancing interdepartmental and interdisciplinary interactions is critical.

Dr. Abeloff next posed the question, "What is the impact of managed care on translational research?" Acknowledging an incomplete list and examples cited by other presenters, he first noted the major threat to patient referrals for clinical trials and the current inability to subsidize research from clinical revenue. Referring to the increasing difficulty in supporting patient care costs of clinical trials, he concurred with Dr. Becker's experience in dealing with third-party carriers, who ultimately talk about price, or cost. He noted that while in a separate setting they may acknowledge some interest in research, the overall experience has not been pleasant.

Dr. Abeloff referred to Dr. Wicha's discussion of the paradoxical enhancement of opportunities to interact across departments and disciplines; he concurred that the threat from managed care has caused components of the institution to come together in a variety of ways, facilitated by his predecessor and mentors who had fostered such a cooperative environment. He noted increasing collaboration across departments in developing unified approaches to both research and patient care.

In describing Maryland data as striking, Dr. Abeloff noted that Maryland was sixth in HMO penetration in 1992 and third in 1993, in the range of 35 percent and rising. This translates in the payer mix to a marked decrease in the self-pay group, with increasing volume and charges accompanied by decreasing collections. The separating curves constitute a major impact on subsidies of research or educational programs. He further noted the increase in the number of HMOs in Maryland, as well as the active, changing environment.

Dr. Abeloff reported that Hopkins' translational research experience is based on past experience and lessons about working together across the institution, which has led to an extensive reengineering process. He pointed to development of a regional network, participation in the NCCN, and alliances throughout the region.

Dr. Abeloff posed a final question, "What can the NCI do in terms of enhancing translational research [while] helping [centers] deal with threats from managed care organizations?" He mentioned his earlier emphasis on flexibility and the need for a broad range of available funding mechanisms, such as the CCSG, R01s, and SPOREs. He proposed an even better dialogue with the NCI in discussing patient access to NCI cancer centers. He raised the issue of how to enhance the value of the NCI cancer center designation and noted that in the

current marketplace, every institution is a cancer center, evidenced by Sunday supplement fold-outs. Readers cannot differentiate reality from advertising. He cautioned against bureaucratizing clinical research in this time of more exciting opportunities for translational research. He suggested that restrictive approaches to clinical translational research will prove devastating to a field faced with so many problems from the external world.

Dr. Abeloff concluded that he has never seen a more exciting time scientifically, with more collaboration, collegiality, and productivity on focused research areas throughout the institution, nor a more threatening time requiring increasing partnership with the NCI. He concluded his presentation by reiterating that lessons learned from building translational research efforts can be applied to approaches to the managed care arena.

Discussion of Cancer Centers

Dr. Rimer opened the discussion by mentioning that this meeting represented only the beginning of thinking about how the paradigm of the cancer center might need to change to address challenges not only to the health care system but to changing medicine and basic science. She noted similarities and differences among the presentations of Drs. Kimes, Young, and Abeloff, and requested that Dr. Day's subcommittee consider some of their suggestions.

Dr. Alfred Goldson suggested the need to think tough and referred to the managed care/translational research approach. He cited Dr. Friedman's figure that the NCI has 38,000 covered lives and noted that the 50 percent of the NCI budget earmarked for cancer centers represents an existing commitment. He suggested that the networks can probably perform some of the translational research at lower cost than the cancer centers. He referred to hearing that the centers are sending patients to their networks and that some patients are coming back into the centers. He characterized this as a loop, or framework, from which to deal with managed care, which is about cost. He suggested including the primary care physician because what controls primary care physicians, HMOs, and managed care will also control dollars.

Dr. Goldson further suggested that more primary care physicians should be trained and designated as scientists in early prevention, such as the tamoxifen studies. Such physicians should be brought into the network to feed the centers. He noted that including medical oncologists as part of the team puts patients in a financial bind. He suggested that the NCI, to survive and support its designated cancer centers, will need to have volume in the centers and networks to maintain the viability of those facilities. He noted that undesignated centers may not survive. He further noted that managed care people might say that if lung, esophagus, and prostate cancer are incurable at this time, patients should be on pain killers and awarded $1,000 each. The response might be, "Now there is money for biopsies, x-rays, workups, surgery, radiation, and medical oncology, so a dollar figure should be found that could enable translational research under a matrix of charges." If SPOREs do work in lung and esophageal cancer, dollars might be found to undercut or compete with managed care systems, perhaps through networks with lower overhead and fewer training programs.

Dr. Salmon responded to Dr. Goldson by noting, first, that the SPOREs and cancer center core grants have very little money, if any, for patient costs. Funds cannot be readily converted to patient costs. Second, the costs of clinical research are two to three times greater than the costs of delivering standard care. Third, primary care physicians cannot afford to

spend the time necessary to see a research patient who requires three to four times as much time as a standard care patient.

Dr. Salmon asked the speakers to comment on whether, if trends continue, there will be a need for some kind of national clinical cancer research emergency bill to assist in maintaining current abilities and instruct insurers, or vendors, about the 1 percent of the patient population and infrastructure necessary for the maintenance of future health care.

Dr. Wicha responded by wondering if the best vehicle would be legislation or another possibility. He agreed with Dr. Salmon that clinical research costs money and concurred that a way to pay for it must be found, such as through the private sector and insurance vehicles that specifically support clinical research. He cited limited examples of riders on insurance policies that cover, at modest costs, clinical research costs in clinical trials. He explained that the rest is spread in a population so that the actual amount added on top of the standard of care is not that much. He posed the question of whether to develop such vehicles so that patients could choose to have money designated to an insurance vehicle to support clinical care.

Dr. Young agreed that cancers centers' three missions include providing care, training, and innovation. He suggested that while centers can become more efficient, as long as three missions are maintained, a commensurately efficient institution with only one of these missions will ultimately always be more cost-effective. He suggested the need to deal with or abandon the training and innovation missions. He expressed that while these missions are not likely to be abandoned, maintaining them will make it difficult to compete on the basis of patient care costs alone.

Dr. Abeloff agreed and acknowledged that while all of the institutions represented on the panel are becoming increasingly efficient and cost conscious, a mechanism must be found to support clinical research. He referred to a *New York Times* editorial and a *Wall Street Journal* article of the previous day on HMOs and negotiations of individual States that suggested that the centers of excellence concept is falling off in a number of States. He agreed with Dr. Day that centers of excellence cannot be maintained simply on enhanced efficiencies.

Raising the issue of core grants and their rules and regulations, Dr. Day asked panel members to cite their top two or three priorities for a core grant. Dr. Wicha replied that, as a grant recipient and reviewer, the best funds are the most flexible and the least restricted. Developmental funds provide opportunities to do new things, bring in new investigators, set up new cores, and fund pilot projects—all valuable. He acknowledged that while it is important to establish a track record, the most flexible funds are still the most valuable.

Dr. Young agreed, citing the need to preserve flexibility and the ability of a center director to pick from a matrix of available mechanisms the most critical for his or her particular cancer center. Rather than shrink the model, it should be as broad based as possible to enable the individual cancer center to prioritize and select from a menu.

Dr. Abeloff stressed developmental funds and shared resources. He agreed with Drs. Young and Wicha on the importance of flexibility. Demonstration of an extraordinarily high level of productivity should be demanded of cancer centers while enabling directors and centers flexibility on how to deploy funds. Dr. Wicha added that cancer centers should be places where

risks are taken in new, innovative areas. That such ventures do not often pan out should not matter. He noted that to earn an R01, the research has to be half completed. A high-risk R01 with little preliminary data does not have a chance in today's environment. Yet, high-risk, innovative ventures are where centers should shine and directors should be allowed the most flexibility.

Dr. Sigal raised the issue of carve-outs for cancer and the consortium, and expressed worry that freestanding, and perhaps all, cancer centers are becoming an endangered species. She observed that insurance purchasers' criteria for centers of excellence do not mention cancer but, rather, specific procedures, such as bone marrow transplants. She asked the speakers to comment on whether purchasers will look at specific cancer or procedures rather than cancer centers.

Dr. Young replied that it is unknown, but perhaps there is more heterogeneity in the system than imagined. Corporations with national bases have expressed a wide spectrum from disinterest to intense interest. A number of analyses suggest that parts of medicine do lend themselves to the capacity for carve-outs, such as asthma, pediatrics, diabetes, cancer, and mental health. While acknowledging that there is no guarantee, he suspected that new things will be tried and many will fail. Corporations and insurers are interested in locking up costs while securing quality by one cost-effective mechanism or another. He cited the example of capitated radiation therapy contracts that solve insurance companies' problems. He observed that there are mechanisms to allow cancer carve-outs to emerge from the changing system.

Dr. Abeloff cited technology-driven examples, such as bone marrow transplants, as opportunities for cancer carve-outs. He suggested that there will be a temporary phase in which no one will know exactly where it all is going, because it is totally unmanaged. He further suggested that cancer, specialty, or disease carve-outs, given the current direction, will be a temporary phase until the issues of covered lives and primary care networks as gatekeepers are addressed. He pledged to compete vigorously in the temporary phase in an attempt to determine what the future will hold.

Dr. Wicha agreed with Dr. Abeloff that carve-outs are here today, but will be gone tomorrow. The future for centers is to establish regional networks and linkages with community hospitals and other institutions. The challenge will be how to preserve the research and teaching missions when dealing not only with an academic institution, which can be controlled, but with communities whose goals and aspirations differ from those of the center.

Dr. Abeloff noted attempts to take a more active regional role. Suggesting that what goes on in States and communities served will be critically important, he noted that Maryland has a health care cost commission, which regulates hospital costs.

Dr. Freeman noted that the speakers had painted the picture and problems beautifully. He noted a crisis, as centers of excellence require refunding beyond what will be funded in the environment of concurrent reform, managed care, and government cuts. He suggested that innovative changes will need to be undertaken and noted the presenters' understanding that, unless the private sector is tapped initially, monies will be cut down in two major ways, at great risk to the academic centers represented. He questioned, if national health care reform emerges in some fashion after the catastrophe is over, whether that would be the way to go,

provided that health care reform required special support of the centers. He solicited direction in informing the President of the problems raised by the panel.

Dr. Wicha concurred with the key problems raised by Dr. Freeman and noted that the President has his own set of problems in trying to sell health care to the public. He stressed that constituents with frightening, life-threatening diseases represent the most effective advocates, and acknowledged representatives of patient advocacy groups in attendance. He suggested that their voices must be heard, since people who have cancer and their advocates will be hurt most by cuts and limited access to major centers. While the message must be carried by professionals, it may seem self-serving. Messages carried by patients and patient advocates ring truer.

Dr. Freeman agreed with Dr. Wicha, and asked again what he should tell the President about this problem. Dr. Wicha replied that among the reasons that health care reform failed were people's conclusions that it would cost money and limit access. He suggested that any future attempt take into account people's wishes for access to the best care, which includes the centers of excellence and the cancer centers.

Dr. Young added that the previous health care reform proposal contained mixed blessings. While there was a commitment to support training and academic health centers, the price tag was high, which influences how many people get trained, where they get trained, what they go into, and how training is done. He suggested searching for a decentralized mechanism to support the centers' training, education, and innovation missions.

Dr. Abeloff added that despite the complexities of the prior health care plan, it provided a focal point that could be addressed; now, there are a multitude of disguised moving targets. He stressed access to centers of excellence as foremost, especially for serious diseases such as cancer. He reiterated decentralization as essential. Of the major issues, he cited access as the most important.

Dr. Salmon recommended to Dr. Freeman that continuation of clinical research should be advocated through the President's Cancer Panel, as should the serious threat to the future viability of all clinical research, not just cancer research. He suggested that affordability and inability of insurers to deny coverage for prior illness are universally accepted, and emphasized that the kind of bureaucratic nightmare seen last time need not be the result. He agreed with the importance of clinical research and academic training. He noted that his network of 12 or 13 years still functions well in the prevention program, but colleagues report that managed care organizations frown upon such networks, which poses a threat to ongoing access.

Dr. Rimer solicited comments on ways in which cancer centers might need to change. For example, she wondered whether cores should become more regional or national resources, such as to the health communications laboratory, and whether cancer centers duplicate core resources.

Dr. Wicha expressed concern that health care reform will push cancer centers apart rather than together. Citing exceptions, such as the networks being formed by his center, he acknowledged that they are in business ventures. He suggested that the cancer center networks, by design, are not competing with each other. He posed the question of how to handle cancer

centers down the road with the same patient population and suggested vehicles that promote interaction, especially regional cooperation. While few such regional cores exist, some have been successful, such as the tissue cores and the recent RFA for a vector core. Cores that are duplicative do not have to be at each institution, though many do need to be located within individual institutions.

Dr. Young noted the likely emergence of regional cooperative group structures and the potential for massive change in clinical trial research. He suggested that centers are merging into regional systems of medical care and that clinical trial research could be organized around the same regional structures to provide care and utilize comprehensive cancer centers in the same regions as collaborative participants in the regional clinical trial research base.

Dr. Abeloff suggested that shared resources could be utilized in limited ways across institutions. He expressed that regional and national networks may avoid duplication and provide a coherent approach for patient access to centers located near patients' homes. The current unfettered competition poses a danger for cancer centers. He noted that while the national coalition and other opportunities exist, competing in one's own back yard will not be a constructive approach in the long run.

Dr. Schein noted that cancer centers are being neglected by the failure of medicinal science to obtain control of the agenda and priorities. He expressed that cancer centers are in danger of becoming an anachronism. He noted that the lexicons created for health care reform and managed care have slipped up regarding where the future lies—in research and training. He suggested that we are dealing with the status quo and making it cheaper. In reality, the message must be carried that the status quo is inadequate. Statistics tell the tale, and the American public will neither be satisfied with current technology nor mortgaging the future with the current approach. Continued investment will be required on every level, and cancer centers are a major part of the picture. He suggested that the American public's expectations will not be filled with the shortsightedness of the Administration and Congress to date. The message must be carried by the cancer centers through their constituencies and the NCI. Further erosion will result from cancer center directors having to negotiate with insurance carriers. He stressed the need for more long-range approaches.

VIII. UPDATE ON THE NATIONAL ACTION PLAN ON BREAST CANCER—MS. FRANCES VISCO AND DR. SUSAN BLUMENTHAL

Presentation by Ms. Visco

Ms. Visco introduced herself as the co-chair of the National Action Plan on Breast Cancer (the "Plan"), the President of the National Breast Cancer Coalition, and a member of the President's Cancer Panel. She reminded meeting participants that during the prior NCAB meeting she had provided background information on the Plan's conception and formation, including the involvement of the National Breast Cancer Coalition; the signature campaign, which compiled 2.6 million signatures; and the conference sponsored by the Secretary of Health and Human Services in regard to the Plan. Ms. Visco commented that she would focus on detailing some of the developments since the last meeting and describing the innovative ideas and strong public/private partnership that has evolved. She remarked that she hopes that the atmosphere on Capitol Hill and NIH's present budget situation do not negate the possibility

of further discussions of the Plan. As an aside, Ms. Visco indicated that the National Breast Cancer Coalition has issued a full alert opposing reductions in NIH funding and supporting the NCI Bypass Budget. She projected that this effort will probably represent the group's strongest movement on Capitol Hill.

Ms. Visco then began a discussion of the steps that the working groups formed around the six priorities of the Plan have been taking toward achieving its goals. She stated that the working groups have presented many of their strategies and initiatives to the steering group and that several have been approved. The first working group, which is chaired by Dr. Susan Sieber of the NCI and Ms. Nancy Evans, President of Breast Cancer Action, focuses on breast cancer etiology. The primary goal is to expand the scope of biomedical, epidemiological, and behavioral research activities related to the etiology of breast cancer. Within the group, subcommittees have been established to represent priority areas of radiation and electromagnetic fields, chemicals, hormones, lifestyle factors, viruses and genes, and environmental interactions.

Ms. Visco indicated that the group has presented several initiatives to the steering committee that have been approved. The first is to hold a workshop to review the state-of-the-art knowledge in terms of the role of chemicals and hormones in breast cancer, identify research gaps, and make recommendations for research priorities. The meeting is envisioned to be a small, technical workshop that will be held at the Environmental Health Center at Tulane on October 12th and 13th, 1995. Participants will work to create a research agenda that not only identifies knowledge gaps and recommends how to fill them, but also establishes priorities for research needs. Dr. John McLachlan, Director of the Environmental Health Center at Tulane, will chair the workshop.

This working group also recommended that a working session be held to initiate the development of a core questionnaire related to breast cancer etiology. The forum will convene individuals with diverse perspectives and be structured to identify various opinions as to what data are necessary to allow the comparison of breast cancer etiology studies conducted across different times and locations. Teams of recognized experts in each topic area will be organized into working groups to review draft core modules and reach consensus on the final content and format of the questionnaire.

Ms. Visco discussed another working group's efforts to establish a National Biological Resource Bank to ensure the availability of biological materials for the various areas of breast cancer research. This working group has also presented several initiatives to the steering committee that have been approved, the first of which is to create a referral database for specimen and data resources. To develop this database, the working group plans to survey all public and private sources of tissues, cell lines, and other biological materials, and to determine their accessibility. A prototype database of these resources that will be accessible through Internet will then be created. Ms. Visco explained that the working group will then evaluate the level of use of the database and its listed resources, as well as whether these resources are sufficient to meet the needs of the breast cancer research community. The steering committee also approved the working group's proposal to conduct a survey of researchers, particularly individuals who are new or unfunded, to assess their needs for biological resources. Ms. Visco reported that the third initiative involves an examination of the ethical and legal issues associated with biological resource banks, including questions such as, "What are a patient's

rights to his/her tissues?", "When is consent or reconsent appropriate?", and "Who owns the tissue?" Ms. Visco stated that a report presenting the recommendations resulting from the examination will be generated and, it is hoped, will guide national policy. She reiterated that the group's long-term goal is to establish a national mechanism and standard for obtaining and storing biological tissues, and added that the group is chaired by Drs. Susan Love and Alan Rabson.

Ms. Visco summarized the purview of the working group on hereditary susceptibility as focusing on the health needs of individuals carrying breast cancer susceptibility genes, as well as the ethical, legal, and policy issues surrounding their condition. The group will recommend and support pilot interventions that target health care providers, at-risk patient groups, and consumers, with the eventual goal of creating a comprehensive plan for all these groups. Ms. Visco added that the group is co-chaired by Dr. Francis Collins and Ms. Mary Jo Kahn, who works with the Virginia Breast Cancer Foundation and is a breast cancer survivor herself.

Ms. Visco indicated that the working group plans to hold a forum, during which the highest priorities in breast cancer susceptibility research will be identified; however, the initiative has not yet been discussed by the steering committee. Topics proposed for inclusion in the forum include the feasibility of retrospective genotyping of participants from previous large clinical studies to identify those individuals carrying BRCA-1 mutations; protective factors that may explain the absence of disease in some individuals who carry susceptibility genes; and the actual efficacy of current screening and therapeutic options, particularly serial mammography and prophylactic surgery. Members of the working group envision a 2-day forum that will convene approximately 70 participants, with a number of RFAs being issued in 1996 as an end product.

Ms. Visco reported that the steering committee has approved a forum for July 1995 that will gather individuals with diverse perspectives on insurance discrimination legislation. The forum will examine proposed and existing legislation on both a State and Federal level, as well as both proposed and implemented approaches. The group hopes that the forum, which will involve all communities interested in this issue, not just the breast cancer community, will achieve a consensus on what types of legislation need to be passed and what approaches should be taken. Ms. Visco stated that the steering committee has also approved a forum to create an educational message regarding genetic testing and a mechanism for disseminating this information to primary health care providers. Forum participants would design an understandable message for patients, as well as begin to foretell possible long-term complications that may arise from providing this information to both health care providers and patients. Participants will include genetic testing experts, members of various professional organizations and involved government agencies, individuals involved in health care provider education, and representatives from consumer groups.

Ms. Visco moved to a discussion of the information dissemination working group, whose charge it is to develop innovative mechanisms and strategies not only to disseminate information, but also to facilitate communication among researchers, consumers, and health care providers regarding breast cancer, breast care, and breast cancer clinical trials. The group is led by Dr. Anna Chacko of the Brooke Army Medical Center and Ms. Arlyne Draper, President of the Women's Cancer Task Force, Y-Me, San Diego Chapter, and a breast cancer

survivor. Members of this group are currently creating an inventory of available information regarding breast cancer, particularly through Internet and other resources that are part of the "information superhighway," as well as establishing methods to assess the quality of these data and determining who will access the information. One of the working group's primary goals is to link consumer groups and other community service associations to the information superhighway. Ms. Visco pointed out that the Department of Commerce has already begun to establish this connection and, therefore, the working group will work closely with them.

Another group is working to reduce barriers to participation in clinical trials so that they become more accessible to women with breast cancer and those at risk. The working group, led by Drs. Kay Dickersin and Leslie Ford, has proposed a number of action steps to achieve this end. The first is to assemble representatives from the insurance industry, government, and consumer groups, as well as health care providers, to design a policy that would allow costs associated with clinical trial participation to be reimbursed. A strategy to induce cooperation among all affected institutions would also be created. Ms. Visco commented that such a groundbreaking policy could act as a model for reimbursement of costs for trials associated with many other cancers, and added that this is one of the National Breast Cancer Coalition's top priorities.

The clinical trials working group is also working to revise the informed consent process. The group has proposed that, in combination with the Office for Protection From Research Risks (OPRR), research be conducted to evaluate the process and establish new standards to make it more concise and less complicated, without undermining its ethical considerations. Ms. Visco remarked that the group has also proposed that marketing strategies be utilized to solicit participation in clinical trials. In addition, members of the working group will present information regarding the importance and benefits of participating in clinical trials at professional meetings for health care providers. Ms. Visco indicated that the group has also suggested that a fund be designated to reimburse participants for hidden costs, such as transportation, work loss, and baby sitting. Finally, the working group has proposed various strategies to simplify the design of clinical trials, and has recommended that a clearinghouse be established to provide information about existing clinical trials that are open for enrollment.

Ms. Visco announced that the final working group is concerned with ensuring consumer group involvement in the creation and implementation of policies and services designed to reduce breast cancer incidence, and participation of advocacy groups and women with breast cancer in establishing research agendas and developing patient education materials. The working group is chaired by Ms. Jan Hedetniemi from NIH and Ms. Jane Reese-Coulbourne, a breast cancer survivor and head of the Washington, DC, chapter of the National Breast Cancer Coalition. Ms. Visco explained that the group has proposed creating advocacy guidelines for researchers, practitioners, consumers, and government workers. A database listing consumers who are willing to help will be created, and areas will be identified that are without consumer representatives. An outreach nomination process will also be established to ensure continual expansion and diversification of participating individuals. The working group will also create a videotape as a tool to increase awareness of the issues related to consumer involvement in health care provision decisions.

Ms. Visco highlighted the National Breast Cancer Coalition's Project LEAD, which has organized a diverse and talented team of researchers who are training breast cancer activists

in the language and concepts of science at four different sites in Washington, DC. This project is a primary example of a private-sector effort to achieve the goals outlined in the Plan. Ms. Visco emphasized that many of the priorities she mentioned are associated with access issues, and added that four of the six working groups are focusing on areas that impact access. She suggested that in the past access has been limited to a focus on mammography; however, a broader definition of access that includes clinical trials, consumer involvement, information dissemination, and hereditary susceptibility is being developed by participants in the Plan.

Ms. Visco concluded by commenting that individuals involved with the Plan are not molding these ideas to consume a $10 million budget, but are simply focusing on developing outstanding and innovative strategies that will be funded because they genuinely work toward achieving the goals of the Plan.

Presentation by Dr. Blumenthal

Chairperson Rimer introduced Dr. Susan Blumenthal, who is the Deputy Assistant Secretary for Health and the Assistant Surgeon General, and thanked her for coming. Dr. Blumenthal commented that she is honored to co-chair the Plan with Ms. Visco and expressed both her own and the Department's appreciation for Ms. Visco's vision, leadership, and energy in the fight against breast cancer. Dr. Blumenthal also thanked Dr. Edward Sondik and the NCI staff for their work in support of the National Action Plan on Breast Cancer activities. She indicated that she is extremely proud to serve as the nation's first Deputy Assistant Secretary for Women's Health, a new position created to resolve inequities in the performance of research and access to health care services that have negatively impacted American women's health. Dr. Blumenthal assured members that breast cancer has the highest priority within her office. She added that the Secretary of Health and Human Services, Donna Shalala, asked her office to coordinate implementation of the Plan.

Dr. Blumenthal indicated that she would highlight some of the funding mechanisms that have been created to support the initiatives introduced by Ms. Visco. She emphasized that the Plan has initiated an unprecedented partnership between private- and public-sector groups to foster innovative and novel approaches to fight breast cancer. Dr. Blumenthal reminded participants about the topics Ms. Visco had discussed, including the six priority areas that have been targeted for immediate action and the strategies and priorities that the working groups assigned to each area. Dr. Blumenthal reported that six different funding mechanisms, which were announced in April, 1995, have been developed for FY95 to support projects that are initiated through the Plan. She explained that emphasis will be placed upon funding new and innovative approaches to both research and outreach activities related to breast cancer, as well as new investigators, so that a wider array of researchers will be attracted to the study of breast cancer. Applicants were requested to respond to one of the six priority areas, and Dr. Blumenthal stated that special consideration will be given to projects that would involve public/private partnerships and test creative approaches.

Dr. Blumenthal discussed specific funding mechanisms to support the Plan, indicating that there is a total allotment of $10 million for this fiscal year. The working groups have targeted areas that require immediate action, and contracts to address these areas will be awarded. A small grants program has also been announced, with to $3 million in funding available this fiscal year, allotting each project with $50,000 per year for either 1 or 2 years. Up

to an additional $4 million will be allocated to supplement existing Federal and Public Health Service grants that involve either intra- or extramural projects. Dr. Blumenthal emphasized that the parent grants do not have to focus directly on breast cancer; however, the supplement must clearly address one of the six priority areas with a breast cancer focus. Dr. Blumenthal stated that up to $1.5 million would be budgeted to supplement funding for those grants that were approved, but for which money was not available to meet the pay line.

Dr. Blumenthal indicated that all applications would be judged based on technical merit. The small grant program will be reviewed at NCI by ad hoc committees composed of representatives from both public and private sectors. Dr. Blumenthal commented that mechanisms would be instituted to ensure that working group members would sit in on the review sessions. The other supplemental funding mechanisms will be reviewed by four ad hoc review committees. She explained that the ad hoc reviews will be convened under the Plan's auspices and administered by the Public Health Service's Office on Women's Health (OWH). Federal grant managers will participate in the review, as well as private-sector representatives and former members of the working groups. After all of the applications are reviewed by the ad hoc committees, the working groups will be convened to rank the approved grants and assess their relevance to the Plan priorities. The steering committee will then meet to review the six working group rankings and make recommendations. Based on these recommendations, final funding decisions will be made. Dr. Blumenthal remarked that the Plan will expand its focus to other priority areas in the future. A long-term implementation plan will be developed, whereby an evaluation component will be added to determine progress toward meeting the goals of the Plan.

Dr. Blumenthal discussed a new project initiated by the Administration in conjunction with the Health Care Financing Administration, the Public Health Service's Office on Women's Health, and NCI to address the lack of use of Medicare benefits for mammography screening among older women. Only one-third of these Medicare-eligible women are using this benefit, and most are employing it for diagnosis rather than screening purposes. Dr. Blumenthal described the project as a two-pronged strategy that will educate consumers, their friends, and family members, as well as health care providers, about the availability of this lifesaving benefit. Dr. Blumenthal added that the FDA has announced that a consumer hotline is being started through the 1-800-4-CANCER number. The First Lady has been holding testimony sessions across the country with older women and launched the educational campaign on Mothers' Day. The President and First Lady have made a public service announcement concerning the use of mammography, "A Picture That Can Save Your Life!", in which the President discusses his mother's breast cancer.

Dr. Blumenthal praised the work that has been accomplished to date under the Plan's guidance and reiterated that it is a true public/private sector partnership. In addition, she underscored that this is the first project that has assembled representatives from all Federal agencies to address breast cancer, and highlighted Ms. Visco's role as liaison to the Federal coordinating groups. She added that steps to foster broader collaboration among government agencies are being considered and that she has already seen several productive partnerships arise from work done to achieve the goals of the Plan.

Dr. Blumenthal concluded by thanking the NCAB for inviting her to speak about the Plan and for its support of related activities. She also reiterated her thanks to Dr. Sondik and

NCI staff members who have expended a great deal of energy supporting the Plan, and cited the following individuals for their contributions: Dr. Suzanne Haynes, Dr. Paulette Gray, Dr. Debbie Sazlo, Dr. Cheryl Marks, Ms. Kathy Crosson, Ms. Anne Middleswarth, Dr. Susan Siebert, Ms. Maria Klebanoff, and Dr. Diane Wagner.

Questions and Answers

Dr. Sigal asked whether the Plan's ability to support unfunded meritorious grants is a result of its public/private nature or whether these grants are typically available for other institutions to fund. Dr. Blumenthal responded that sometimes funding for grants that have been approved but were not funded becomes available at the end of the year or through other mechanisms. Dr. Sigal clarified her question by asking whether other institutions can fund grants that do not receive funding because their priority scoring placed them just over the pay line. Dr. Marvin Kalt commented that because information regarding unfunded grants is privileged, outside organizations must first request copies of the grant or summary statement directly from the proposing organization or principal investigator and make awards based on this information. As an example, the Juvenile Diabetes Foundation sometimes awards grants to those applicants who are declined by the Diabetes Institute. Ms. Visco emphasized that a formal process must be adhered to before an organization can examine information regarding unfunded grants.

IX. REPORT AND DISCUSSION OF THE NCAB AD HOC WORKING GROUP ON THE NCI INTRAMURAL PROGRAMS—DRS. VARMUS, BISHOP, AND CALABRESI

Dr. Rimer presented background information regarding the NCAB Ad Hoc Working Group responsible for reviewing NCI's intramural program. She explained that for the past 6 months this group of dedicated and talented investigators has been working to understand the structure of NCI's intramural program. She commended the efforts put forth by Drs. Paul Calabresi and Michael Bishop, and Dr. Marvin Kalt and his staff, and indicated that their leadership allowed the group to complete the large task in a very limited timeframe. Dr. Rimer attested to the detailed focus and care that was given to each point and the candid input that was provided by all participants.

Dr. Rimer then established some guidelines regarding the presentation, stating that participation in the discussion would be limited to NCAB and NCI Executive Committee members to ensure that these individuals would have sufficient time to discuss the report. She announced that the report would be available to NCI staff within a few days and that a press briefing would occur at the end of the day. She then introduced Dr. Harold Varmus, the Director of NIH.

Presentation by Dr. Varmus

Dr. Varmus began his presentation by thanking Drs. Bishop, Calabresi, and Kalt, as well as the numerous NCAB members who have worked hard to complete the review of NCI's intramural program in a very limited timeframe. He stressed that the Office of the Director will aid the NCAB and NCI Director in implementing the final recommendations. Dr. Varmus then commented on the selection of NCI's new Director, relating that an

announcement of the appointment was not yet possible, but that he would like to update NCAB members on the process. He also thanked Dr. Paul Marks, chairman of the search committee that identified the applicants for the position. Telephone interviews were conducted with 10 or 12 applicants, five of whose names were submitted to Secretary Shalala; approximately 6 weeks ago, after the finalists were interviewed by Secretary Shalala, Dr. Phil Lee, and Dr. Varmus, the Secretary submitted her recommendation to the White House. Dr. Varmus stated that a final decision from the White House should soon be received, and that the new Director is anticipated to begin work on August 1st. Dr. Varmus commended the individuals who assumed the task of interim governance, including Drs. Edward Sondik, Robert Wittes, Jerry Rice, Peter Greenwald, and Alan Rabson.

Dr. Varmus then moved to a discussion of factors that will impact clinical research, an issue that is particularly relevant to the NCI. He announced that the Secretary of Health, as part of Reinventing Government, Part II, requested that the feasibility of contracting out certain services within the Clinical Center be evaluated. The Secretary appointed Dr. Helen Smits, the Deputy Administrator of HCFA, to chair a committee of extramural and intramural individuals to study potential ways to make the Clinical Center more cost-effective and to increase performance through new, creative mechanisms. Dr. Varmus also announced that Dr. John Gallin, Director of the Clinical Center, recently launched a training program involving an outstanding core curriculum in clinical research, that is being presented to 25 clinical associates. The curriculum covers diverse topics relevant to clinical research, including epidemiology, ethical and regulatory issues, monitoring of patient-oriented research, and methods for designing and attaining funding for clinical research studies. Dr. Varmus recommended that in view of the NCI's large-scale support of the Clinical Center, that NCAB members learn more about this training program.

Dr. Varmus continued his discussion of issues impacting clinical research, indicating that he has assembled a panel of individuals representing a wide array of interests, including clinical investigators, leaders in the biomedical research community, and representatives of academic health centers, to address some broad concerns regarding clinical research that have arisen during the past year and a half. The panel will hold its first meeting in July and will report to Dr. Varmus' advisory committee. Members will be charged with discussing prominent issues related to clinical research, including the manner in which this type of research will be financed during years of limited funding; future roles for both NIH's Clinical Center, and the general clinical research centers administered by the National Center for Research Resources (NCRR); methods for attracting and training clinical researchers; procedures for ensuring appropriate levels of monitoring safeguards, informed consent, indemnity, and other related topics; and the peer review process for clinical research. Dr. Varmus suggested that the NCAB may want to have a member, preferably the chairperson, of the clinical research panel present an update of the panel's activities later this year.

Dr. Varmus indicated that he has also formed a panel, which will be co-chaired by Drs. Stewart Orkin from Harvard and Arno Motulsky from the University of Washington, to review NIH's investment in research related to gene therapy, particularly in light of current activity in the field. The group will review NIH's research portfolio and make suggestions regarding opportunities and concerns that will be used to guide the development of future NIH budgets as early as 1997.

Dr. Varmus also discussed a report that will be released soon regarding the Division of Research Grants (DRG). Since long-time DRG Director, Dr. Jerry Green recently resigned, a search for a replacement will soon be launched; however, in the interim, Dr. Varmus felt it would be useful to examine the structure and function of the DRG. A committee chaired by Dr. Marvin Cassman, Acting Director of the National Institute of General Medical Sciences (NIGMS), performed the review and made several recommendations to improve the Division. Dr. Varmus reported that the committee's primary recommendation called for the creation of a peer review oversight group that will work to enhance collaboration among review groups within institutions and those that operate within the DRG. He added that a future discussion of the issues encountered by the oversight group may be valuable to the NCAB.

A review is also being conducted by the Office of AIDS Research (OAR) to examine the range of AIDS-related efforts during the past 10 years. The group conducting the review is composed of an association of smaller review groups and is chaired by Dr. Arnold Levine from Princeton University and coordinated by Dr. Bill Paul, Director of OAR. Dr. Varmus pointed out that the NCT investment in this area is large and that special focus will be targeted to NCI activities associated with the AIDS program.

Dr. Varmus briefly discussed concerns regarding the 1996 budget and assured NCAB members that a great deal of effort is being expended to improve economic conditions. He announced that a press event organized by advocacy groups would be held on Thursday at 10:00 a.m. in Dirksen Room 430 and would be an assemblage of bipartisan senators, representatives from academic health centers, basic researchers, young researchers, and patient advocates to support restoration of funding for NIH.

Questions and Answers

Ms. Visco asked whether any consideration has been given to including a consumer advocate on the clinical research panel. Dr. Varmus responded by stating that representatives from these groups would be asked to speak to the panel. Dr. Dickersin asked whether any epidemiologists will be included on the clinical research panel. Dr. Varmus answered that it was decided to structure this panel as a core group, so that when questions relevant to epidemiology are handled by the panel, previously identified individuals in the field will be summoned to participate in discussions. Dr. Dickersin commented that the importance of including individuals with doctorates, particularly in public health, needs to be emphasized, as most attention focuses on individuals with M.D. degrees. She added that public health experts need to be more involved in setting clinical research agendas and should be included in these visible and important committees to lend credence to their role. Dr. Varmus agreed with Dr. Dickersin's comment.

Presentation by Dr. Bishop

Dr. Bishop expressed his affection and respect for the NCI and its intramural program, stating that in his view the NCI "represents our nation's best hope, perhaps its only hope, for conquering cancer." Dr. Bishop clarified this statement by adding that the NCI undoubtedly requires help from all interested citizens to achieve this incredible goal; however, the Institute is at present unmatched in its sense of national purpose, variety of tools, and magnitude of resources that can be mobilized to meet the challenge of cancer. He asserted that those who

participated in the Ad Hoc Working Group were driven to complete the colossal task by their admiration and hope for the Institute. Dr. Bishop indicated that Working Group members began to realize the far-reaching consequences of diminishing Federal funding when a well-respected NCI intramural science veteran resigned late last year because, as he stated, "It has simply become too difficult to do quality science in the Federal Government." The Working Group devoted the next 6 months to exploring the foundations of this comment and found consequences far beyond even what this speaker expressed.

Dr. Bishop explained that the presentation that Dr. Calabresi and he would deliver is a distilled version of the Working Group's final report. He warned that their wording would be explicit and sometimes sound "harsh"; however, the intent was that the information be constructive. Dr. Bishop informed members that the document they received contains a complete listing of the recommendations that will be included in the Working Group's final report, which will be finished by the end of May. Extensive research and discussion were conducted to write the report, and the recommendations contained within are not final or binding, but simply suggestions for the NCAB to consider and act upon.

Background

Dr. Bishop outlined the structure of the presentation, indicating that background information developed by the Working Group would first be discussed, which would make the strengths and weaknesses in the program apparent and lead to a discussion of the Working Group's suggestions for ameliorating these problems. Dr. Bishop provided a history of Federal funding of cancer research that eventually led to the establishment of the NCI. In 1927, the first Federal allocation for cancer research was made at $30,000 for field investigations. In 1937, the NCI was formally established by President Roosevelt. Then, in 1947, the Institute was restructured to create the division between the intramural program, which would be housed in Bethesda, and the extramural program, which would award grants to researchers at other institutions. NCI admitted its first patient in 1953, when NIH opened the Clinical Center. Bureau status was granted to the NCI by the National Cancer Act, which was enacted by President Nixon. This Act forms the statutory foundation for most of the research currently conducted by the Institute.

Dr. Bishop explained that the structure of the NCI evolved over many years and it has become the largest and most complex Institute at NIH. He stressed two unique features of the Institute's organization as vital to understanding the remainder of the presentation: the unified leadership that guides both the extramural and intramural research; and the compartmentalization of both the intramural and extramural research programs into four Divisions, with each Division being responsible for both intra- and extramural research. Within each Division there are three to five major programs, whose leaders report directly to the Division Director. Each program is then split again, into Laboratories and Branches, which are divided even further into Sections. Dr. Bishop reported that a recent inventory showed that NCI's intramural program contained 57 Laboratories and Branches, nine of which had no leader. The variation in the number of Sections within each Laboratory or Branch ranged from 2 to 20. The intramural program is composed of 2,100 full-time equivalents (FTEs), of whom approximately 1,250 are doctoral-level researchers who are either permanent employees or research fellows. Fewer than 400 of these individuals have received tenure. Dr. Bishop pointed

out that these researchers are viewed as the functional equivalents of principal investigators in the extramural program, in that they can independently manage research groups and budgets.

Two additional primary programs support intramural activity as well. The first is composed of what is often referred to as in-house activities, which are formerly part of the extramural program. The contracts awarded to the Frederick Cancer Research and Development Center (FCRDC), particularly to the Advanced BioSciences Laboratory (ABL) at Frederick, which is a government-owned, contractor-operated facility, are primary examples of in-house activities. The second program involves the awarding of contracts to provide logistical support or research outreach for the intramural program.

Dr. Bishop informed NCAB members that the Institute receives an annual allocation of more than $2 billion. The 18 percent apportionment of government funding to intramural research at the NCI is larger in both absolute and relative terms than that at any other NIH Institute. The average allocation for intramural research among the Institutes is approximately 11.3 percent. The Working Group found that an additional 7 percent of the total funds are used to administer research and development contracts, which although listed separately in the budget, actually support intramural research as well. Dr. Bishop asserted that, therefore, a more accurate portrayal of the allocation for intramural research is approximately 25 percent of the total budget for the NCI. NCI's expenditure of the largest proportion of funds of any Institute to operate the Clinical Center has been used to justify the magnitude of the allocation for intramural research. Dr. Bishop commented that as the NCI, as well as the other NIH Institutes, faces staff downsizing and potential allocation reductions unprecedented in its history, it must reevaluate the mission, structure, and future of the Institute.

Commenting that the Institute has often been the target of reviews, Dr. Bishop explained that Presidential panel examined the full NIH program in 1976, and in 1988, a committee of the Institute of Medicine (IOM) reviewed NIH's intramural program. NIH's intramural program was revisited in 1992 by an intramural effort that produced what is referred to as the Klausner-Paul report. A tremendous amount of scrutiny occurred in 1994. The NCAB's SENCAP report reevaluated the National Cancer Program and projected the resources necessary to meet both short- and long-term goals. The prospect of largely diminishing funds for the NCI caused the Institute to examine its own structure, which resulted in a report entitled *Hard Times at the NCI* that contained numerous suggestions to increase the efficiency and quality of operations at the Institute. In addition, a Congressionally mandated study of NIH's intramural program was conducted in 1994 by an ad hoc external advisory committee that presented its findings to the Director and his advisory committee and issued a document known as the Marks-Cassell Report.

Dr. Bishop remarked that some individuals may judge that this history reveals an excess of scrutiny; however, he suggested that it may instead reflect "a continuing concern about performance and perhaps even a lack of response to criticisms and recommendations." The Marks-Cassell Report recommended that Institutes be reviewed separately to discern issues distinctive to each. The Report also called for evaluation of the response to the recommendations from the external advisory committee. The effort to adhere to the Marks-Cassell Report recommendations has been largely aided by the implementation plan created by Dr. Michael Gottesman, Deputy Director of Intramural Research for all of NIH, which addresses each of the points made by the committee. Dr. Bishop indicated that this report also

guided the efforts of their Working Group. He stated that the NCI was the first target of scrutiny by the external advisory committee because the Institute contained the largest intramural program and presented an opportune situation for revision and renewal at the highest level due to the leadership change. In response, Drs. Varmus and Broder organized a working group composed of respected basic and clinical investigators from the extramural community to conduct the review. The group received advice from several members of the NCAB as well.

Dr. Bishop commended the outstanding and energetic work of not only the Working Group members, but of the NCI staff as well. He cited Drs. Kalt and Vincent Oliverio in particular, who provided the group with full access to data and impartial advice, as well as Dr. Kathy Hanna, who acted as a consultant to help with the preparation of the report. Dr. Bishop also expressed his admiration for Dr. Calabresi, whose strong nature was of great value to the effort, and thanked the numerous NCI staff members who patiently waited to appear before the Working Group. Dr. Bishop informed members that the data collection procedures will be described in detail in the report; however, nearly 100 of the 400 doctoral-level staff at the NCI intramural program responded to his solicitation for their views. He characterized those letters as the most revealing and useful data that the Working Group received.

Dr. Bishop stated that the Working Group was charged with its task in October of last year and requested to complete it by this meeting. The 11 primary components of the charge were to: 1) examine the NCI within the context of the points raised by the external advisory committee; 2) identify and evaluate those issues that may be unique to NCI; 3) assess how well the intramural program performed quality control procedures, as well as how well its researchers had performed in recent years (Dr. Bishop pointed out that the Working Group immediately determined that assessing the research performance was beyond its capabilities, as well as unrealistic in view of the limited timeframe for the project. He stated that the Group made an effort to gain a rudimentary perception of the intramural program's performance in the biomedical research arena and also focused on quality assurance); 4) study the attitudes of researchers regarding their work and each other; 5) assess whether the organizational structure—particular whether the intra- and extramural programs existence under the same leadership—is still appropriate for achieving its mission; 6) assess the quality of NCI's strategic planning to determine for example, whether it is realistic and farsighted; 7) assess the strength of clinical research within the intramural program and determine whether the large investment in this research is appropriate or another instrument should be created to serve the same purpose; 8) review the NCI's present level of activity in drug discovery and development and assess its appropriateness and efficiency; 9) assess the level of AIDS research being conducted to determine whether the Institute's level of involvement is appropriate, whether funds are being well used, and the extent of the coordination between NCI's AIDS-related intramural program and the AIDS effort at NIH as a whole; 10) assess the necessity and performance of the FCRDC and to explore additional ways in which it may work with the NCI and NIH; and 11) discuss innovative methods for NCI to cope with the potentially unprecedented funding cuts.

Dr. Bishop summarized all of the charges as addressing one fundamental question: "How well do the activities of the intramural program fulfill its mission?" The first step in answering this question involved developing an explicit definition of NCI's mission—a sizable endeavor in itself. Based on previous written statements, staff memories, and Working Group

perceptions, six tenets were devised to compose a formal statement of the Institute's mission. Dr. Bishop presented these components to the Board. First, the intramural program should act as a "flagship" for NCI-related efforts and as a visible symbol of the National Cancer Program for both the government and the public. Second, the program's proximity to Capitol Hill deems it a convenient source of advice for the Federal Government. Third, the relative stability of funding for the program provides the chance for its researchers to take "intellectual risks" and stretch the limits of experimentation. Fourth, the intramural program should conform to the highest standards for conducting basic as well as clinical research, to act as a model for the entire community of cancer investigators. Fifth, the intramural program should perform groundbreaking translational research to bridge the gap between basic research and clinical applications. Sixth, NCI should "provide strike forces to meet newly emerging challenges in the fight against cancer."

Dr. Bishop commented that some of these tenets represent "double-edged swords." The visibility of the intramural program in Bethesda can cause legislators and the public to misperceive this facility as the entirety of the NCI and the National Cancer Program, which can lead to legislative difficulties. Being visible also makes the intramural program a primary target for funding diversions through legislative and executive mandates. Dr. Bishop asserted that while it is necessary for the intramural program to be conservative in its findings, it is often faulted for being unnecessarily repetitive, which is a discussion that cannot be won. He pointed out that stability of funding, while intended to promote risk-taking, can produce "complacency, inbreeding, intellectual isolation, and lack of vision." These difficulties impacted the course of all Working Group discussions. Dr. Bishop explained that the presentation was organized around the broad issues that were defined by the Working Group in response to their charge. For each area, background information would be provided, which would include the area's strengths, then the problems that were unearthed would be detailed, along with subsequent recommendations to ameliorate these problems.

Strategic Planning

Dr. Bishop began with NCI's process for strategic planning. He remarked that wise and effective planning is imperative, particularly for an institution of the NCI's size, and that the Institute faces several unique challenges to accomplishing this task. A large proportion of NCI's funding is already committed for several years and, therefore, is not available to support new projects. In addition, new mandates often place unexpected demands on the budget.

These factors necessitate that the NCI be led by resourceful and knowledgeable individuals and have clear mechanisms for strategic and tactical planning. The NCI is primarily governed by the Executive Committee, whose membership includes a wide array of managers, but few full-time researchers. The primary source for scientific advice is said to be the Board of Scientific Counselors (BSC) of each Division whose members are appointed by the extramural community and report to the scientific directors of each Division, not NCI's Director or the Executive Committee.

Dr. Bishop stated that NCI's strategic planning has substantial strengths. A formal process has been articulated and the Executive Committee is both active and highly prone to debate. The annual development of a Bypass Budget offers an opportunity for yearly review of

the Institute's mission, tactics, strategy, and funding requirements. Strategic planning has also involved self-scrutiny, as exemplified by the recent *Hard Times at the NCI* report.

Dr. Bishop informed members that despite its strengths, the strategic planning process could be improved. First, the Working Group found that the planning process has become more reactive than proactive, which he admitted is partly a result of the continuing funding difficulties and recurring unexpected mandates. Regardless of the cause, however, the consequence is the same—decisions become less visionary. The group also determined that consultants, particularly scientific experts, have not been adequately involved in the planning process; members of the BSCs testified that they are not being consulted consistently or effectively in regard to planning. Dr. Bishop commented that while the intention to involve the BSCs exists, it is often not followed up. The Working Group also discovered several programs that are not well coordinated, either within themselves or across NCI's entire intramural program. Finally, the Working Group was concerned about the highly disproportionate investment in the intramural program, as compared to the resources available to the rest of the National Cancer Program. Dr. Bishop remarked that the target of 11.3 percent funding for intramural research established by the external advisory committee is simply the current average at NIH and, therefore, is arbitrary; there were no articulated strategic plans to explain how the NCI reached its relatively disproportionate focus on its intramural program. The Group's concerns regarding the size of the intramural budget do not stem from any belief that the program is wasteful or being favored but, rather, that it is receiving disproportionate funds relative to the rest of the National Cancer Program. He added that to apportion one quarter of the entire Federal investment in cancer research to a single site is expecting too much from that community.

Dr. Bishop stressed that the Working members Group believe that responsibility for strategic planning lies so explicitly with the Director of the NCI that they are disinclined to offer many recommendations; however, two areas of concern have been addressed by the Group. They recommend, first, that consultants be more consistently utilized, particularly scientists from a wide variety of backgrounds. Two mechanisms were suggested to achieve this end, the first being to establish a standing committee comprised of the leading basic and clinical researchers from the intramural program. The Director would be expected to frequently and systematically consult with this group to formulate the Institute's long-range plans, and members of the committee should participate in all planning retreats and have a representative on the Executive Committee. In the second mechanism, the NCI Director would regularly consult with a standing committee of leading extramural basic and clinical researchers, including the chairs of the BSCs. In addition, it would be wise for these two groups to meet with the appropriate subcommittees of the NCAB at least annually in order to establish a firm communication link between these new advisory groups and the NCAB. Dr. Bishop added that the Working Group also suggested that each advisory group submit a brief annual report of its recommendations each year. These documents would provide tools for evaluating the effectiveness of these groups and NCI's response.

Dr. Bishop indicated that the second and somewhat controversial recommendation is to review the current investment in NCI's intramural research program to determine its appropriateness and adjust the level to be more proportional to the other segments of the National Cancer Program. He emphasized that no target figure has been suggested, but that the Working Group expects that a reduction will be found to be necessary. While this readjustment may seem to be a natural outcome of the mandated downsizing and the recommendations to

reorganize and consolidate the structure of the intramural program, it is also true that the NCI has been extremely creative in its strategies to resist downsizing. One such method was to increase term-limited appointments, such as postdoctoral fellows and other nontenured scientists that do not require FTEs. This strategy has provided greater flexibility in structuring staff and has attracted a larger number of energetic young researchers to the intramural program; however, it has also crystallized the need to carefully plan modifications to the level of funding NCI devotes to its intramural program, since change is not likely to occur under the current circumstances. Dr. Bishop stated that to ensure that efforts to adjust the intramural allocation are made, this issue should become part of the formal agenda for NCAB's annual program review. At this review, the NCI should present its projections for the allocation of funds between the intramural program and the rest of the National Cancer Plan, as well as their justification for the distribution. Dr. Bishop also urged the NCI to designate expenses associated with research and development contracts, which support intramural contracts, as intramural expenditures. He added that while the current practice of excluding these costs as part of the intramural budget is understandable, it can appear to be a deliberate deception. Dr. Bishop then invited Dr. Calabresi to deliver a presentation regarding the organization of the intramural program.

Presentation by Dr. Calabresi

Dr. Calabresi began by thanking NCI's staff, particularly Drs. Kalt, Oliverio, and Hanna for their outstanding contributions to the group's efforts. He credited their efforts with enabling the group to complete their task in the allotted timeframe. Dr. Calabresi also expressed his admiration for the members of the Working Group, who he said were not only knowledgeable and insightful, but dedicated to helping to improve what is already an exemplary institution. Dr. Calabresi offered that the highlight of his experience has been the chance to work closely with Dr. Bishop, who he characterized as unique, endlessly energetic, and a visionary with deep concern for his fellow researchers, particularly those just beginning their careers.

NCI Organization

Dr. Calabresi indicated that he would follow Dr. Bishop's outline for presenting findings, beginning with an area's strengths, then its problems, followed by recommendations for remedying these issues. He began by discussing the organization of the intramural research program remarking that the process for strategic planning is largely influenced by the program's complex structure. He reported that the Working Group reviewed two unique features of NCI's structure related to the IRP: the grouping of the intramural and extramural programs under the same leadership, and the delineation of four scientific Divisions within the IRP, instead of one, as at other NIH Institutes. Dr. Calabresi recognized the strengths of the present organization, which accommodates the large size of the NCI and its IRP and also fosters collaboration between the intramural and extramural programs. The structure is both "thematically comprehensive" and responsive to legislative and executive mandates.

Dr. Calabresi commented that despite the strengths of the current organizational structure, the method by which it evolved was not a planned process and, therefore, it is not surprising to learn that the structure has caused problems as well. Among the research programs within each of the four Divisions, there are excessive thematic repetitiveness and

wasteful administrative redundancies as well. In addition, separating the laboratories into several nearly independent units has fostered intellectual fractionation within the IRP, which the Director of the NCI has not been able to overcome, despite efforts to do so. Dr. Calabresi also pointed out that there is a marked disparity in size among the intramural units; for example, the Division of Cancer Prevention and Control is responsible for only a very limited proportion of the effort within the intramural program. While this may not be deleterious in terms of intellectual considerations, it creates administrative issues, particularly when the intramural projects of a Division are viewed as an isolated unit. NCI's structure has inhibited remedying of administrative and regulatory impediments to research and technology transfer, which is a common criticism among intramural researchers. By dividing the administration among four Divisions, remedies to the fractionation become nearly impossible. In addition, the substructure within each Division has been influenced as much by personnel considerations as by strategic decision making. Dr. Calabresi explained that it has become the practice to designate successful researchers as Section, Laboratory, or Branch Chiefs, even if a new unit must be developed to do so.

The working group determined that the fusion of IRP and ERP leadership is more disadvantageous than helpful. The current structure allows the IRP to more readily voice its needs and concerns than the ERP, and also distracts attention from the former. Dr. Calabresi commented that numerous individuals have suggested that this may have contributed to the problems associated with the National Surgical Adjuvant Breast and Bowel Project. To address these issues would require substantial restructuring and a serious dedication to the task, and the Working Group has outlined several fundamental modifications to NCI's organization for the next NCI Director. Dr. Calabresi noted that such alterations may be facilitated by the changes in leadership; however, they have not been designed to exploit the situation. The Working Group recommends that the IRP and ERP become completely separate units.

Dr. Calabresi informed members that the group determined that efforts to implement this and the following recommendations require that there be a single leader, who would be designated as a Deputy Director to report directly to the Director of the NCI. The Working Group firmly believes that the IRP's scientific efforts should have a single director, who should be a renowned researcher who would provide intellectual oversight for the program, as well as be ultimately responsible for impartial peer review of research programs, doctoral-level recruitment, and promotions. The recommended structure is very similar to that of the intramural program of NIH in its entirety, which Dr. Calabresi credited with fostering NIH-wide reforms consistent with recommendations of the Marks-Cassell Report. The Working Group determined that the IRP should be consolidated into two scientific Divisions, which would also foster the elimination of thematically redundant units, and urged that this modification be implemented immediately. Dr. Calabresi added that the consolidation would be consistent with the intent of reinventing government. He also reported that while the ERP is not within the purview of the Working Group, they suggest that the ERP be split into four Divisions that encompass larger magnitudes of activity. The final recommendation promotes the establishment of an administrative policy board composed of intramural researchers to address criticisms of management and regulatory policies. Dr. Calabresi commented that a similar entity has been established for the entire NIH. The policy advisory board would solicit comments from IRP staff and then advise NCI's Director about the impact of managerial and regulatory policies. In addition, the board would be responsible for identifying methods to reduce the negative effects of such decisions.

Dr. Calabresi detailed the Working Group's plan for reorganizing the IRP. Of the two Divisions, one would focus on the etiology and biology of cancer, while the other would target prevention, diagnosis, and treatment. The first would include primarily basic research, while the other would involve clinical and related laboratory research. Each would have a Director, and an Associate Director would head the activities at FCDRC. Dr. Calabresi explained that the Working Group intends for the two intramural Division Directors and the Deputy Director of the IRP to be members of the NIH Board of Scientific Directors and the Executive Committee of the NCI, of which the Associate Director for Frederick would also be a part. The Group also suggests that the ERP have four Divisions, including cancer etiology and biology, cancer prevention and control, cancer diagnosis and treatment, and cancer centers and training. Within the proposed structure, a Deputy Director of the ERP would report directly to the Director of the NCI.

Clinical Research

Dr. Calabresi then moved to a discussion of clinical research. He asserted that the NCI's IRP should be the leader in clinical research, blazing the pathway for innovative tools for the prevention, detection, and treatment of cancer. The IRP's mission should be to expand the limits of research, particularly within the arena of translational research. The IRP has the foundational requirements necessary to achieve its mission, including a celebrated track record; a national patient base to whom it can offer free transportation and care; none of the problems associated with managed care; relatively stable funding allowing researchers to conduct long-term studies; a structural layout that optimizes collaboration between clinical and basic laboratories; and proximity to the Naval National Medical Center and its clinical resources. The IRP has the tools necessary to respond to challenges that develop in the National Cancer Program. Because of the scope of the cancer challenge, NCI provides the primary support for the Clinical Center, meeting approximately 40 percent of its funding needs—support, therefore, that is vital to the Center's economic welfare.

Dr. Calabresi informed the Board that despite all these advantages, concerns that the IRP's clinical research is not achieving its potential abound. Several factors support this concern, including reduced patient enrollment, the diminishing excellence of its training program, and a reduction in its prestige among members of the research community. He asserted that an excessive amount of the IRP's clinical research program is repetitive of work being conducted by extramural researchers. In addition, not enough translational research is being completed and the procedures for reviewing protocol research must be improved. Dr. Calabresi indicated that the Working Group could not distill a precise statement of the standards for scientific quality for the review of clinical protocols. He also pointed out that the quality and availability of subspecialty care through the Clinical Center has been criticized as being poor. He qualified this statement by adding that this care does not involve service provision by the Cancer Institute, but by the consultants who treat patients who develop other problems while in the Clinical Center. In addition, the facility itself is deteriorating and will need renovation.

Dr. Calabresi presented the Working Group's proposed solutions to the above issues. They suggest that all intramural clinical research be gathered within one Division, which would facilitate coordination and collaboration among researchers from various disciplines, as well as foster improved strategic planning. The Working Group recommends that the IRP create a

protocol review and monitoring committee, which could be modeled after those used by the extramural cancer centers. The committee would establish priorities for clinical trials and ensure more stringent and consistent review of proposed trials. Translational research targeting prevention, diagnosis, and treatment of cancer should be the foremost concern of the IRP's clinical researchers, and its importance should influence the selection of the next Division Director.

Dr. Calabresi also indicated that the Working Group believes that the NCI could be equally served by reducing the size of the Clinical Center and expanding its outpatient facilities. To offset the Clinical Center's reduction, increased collaboration with the Naval Medical Center would allow more inpatient care. This collaboration would solve several problems currently facing the Clinical Center, such as lack of in-house staff, inadequate availability of specialty and subspecialty providers, and insufficient introduction to standard oncologic practice among the medical oncology fellows. Among the oncologic fellows, about half go into practice and half pursue academic careers; the fellows consistently complained that they were not privileged to see the "bread and butter oncology" that they had been promised. Dr. Calabresi suggested that avenues for communication to foster collaboration between the NCI and the Naval Medical Center's training programs in pediatrics, radiation, and surgery be established. He said the Working Group also proposed that the clinical and laboratory research of Frederick's Biological Response Modifiers Program (BRMP) be relocated to the Clinical Center, while the production facility should remain at Frederick. Dr. Calabresi explained that this move would benefit the entire IRP clinical research program and emphasized that this relocation is not an effort to penalize the BRMP, but to capitalize on its outstanding practices and allow it to act as a model for the rest of the clinical program.

Dr. Calabresi recommended that intramural research staff become more familiar with NCI-sponsored activities among the extramural community and commented that travel to attain this end should be supported, not frowned upon. He also proposed that clinical investigators being peer reviewed for a promotion be subjected to the same process as laboratory researchers. He noted that the tenure review committee should acknowledge appropriate variations in methodology and the frequent necessity for team research that results in multiple authors for a single paper and different venues for publications. He also stated that training for clinical care and research needs to be improved and that increased collaboration with the Naval Medical Center, as well as the new training program for clinical researchers that Dr. Varmus described, will work to this end. The relocation of the BRMP would also be a significant benefit for the training program.

Drug Development

Dr. Calabresi next discussed drug development at the NCI. He acknowledged that the development of effective therapeutic agents is among the top priorities in cancer research. NCI's IRP has a long-standing and distinguished record regarding new drug development and testing, with most of the work conducted within the Division of Cancer Treatment under the Developmental Therapeutics Program (DTP). The facilities and programs of the DCT have become an international resource for academic and commercial researchers. Examples of this include their development of a unique screen for cancer therapeutics, their facility for extracting and storing natural materials, and performance of groundbreaking work on therapeutic agents for AIDS.

Dr. Calabresi asserted that despite these outstanding achievements, the Working Group was introduced to several criticisms of the drug development program, some of which they witnessed themselves during their own investigation, which included a site visit to the DTP at both the Frederick and Bethesda campuses. He commented that the Program's resources have not been optimally utilized by the extramural community. In addition, the Program does not appear to have the strict controls it should have. Dr. Calabresi also reported that the Program's efforts are intellectually isolated because of its primary location at Frederick and also because its researchers are not accessing the larger community of investigators. He added that the Program has displayed limited flexibility in its strategic planning, which may be a result of its isolation. It also has insufficient medicinal chemistry support and its extramural contracts appear to be subjected to minimal review for quality and cost-effectiveness.

Dr. Calabresi stressed that the Working Group firmly believes that NCI's DTP should continue, but that major changes in the Program are necessary. The Working Group suggested that consideration be given to establishing the DTP as a core facility for the NIH, which would be available to develop drugs for various diseases other than cancer and be funded accordingly. Dr. Calabresi stated that this move would be consistent with the precedent established by DTP's efforts regarding AIDS, which have been entirely funded by the NCI and require nearly 50 percent of the DTP's funding. He expressed the Working Group's support for peer review of DTP investigators' research and budget, as is the standard practice in other areas of NCI's IRP. DTP researchers should also be subject to the same tenure review as investigators in the rest of the IRP. Dr. Calabresi added that the Working Group concluded that there is no foundation for the belief that the new tenure system would penalize investigators working in drug development.

Dr. Calabresi also addressed review of DTP's extramural contracts, which should receive full and standard consideration. Review of the contracts should attempt to expedite and improve drug development, as well as reevaluate resource allocation. The reviews should be completed by academic and industrial investigators. Dr. Calabresi also asserted that the entire mission and program of the DTP should receive detailed review every 3 years by its BSC in collaboration with appropriate consultants. He completed the recommendations regarding the NCI's drug development program by emphasizing that communication and collaboration with other IRP investigators and the extramural community must be greatly improved.

Frederick Cancer Research and Development Center

Dr. Calabresi then began a discussion of the FCRDC. He explained that the Center can trace its origins to two mandates sponsored by President Nixon, the first of which involved the President's executive order abolishing Federal research on reagents for biological warfare, which left a large laboratory facility at Fort Dietrich in Frederick, Maryland vacant. In addition, President Nixon's support of the National Cancer Act provided the funding resources and mandate necessary for NCI to use the vacant facility.

The NCI invests approximately $140 million annually in the Frederick Center's activities. Three primary components exist in the Center's budget, including a support contract costing $95 million, a direct budget for the Advanced BioScience Laboratories of $15 million, and approximately $20 million for the intramural research program. This funding supports a staff larger than 2,000 individuals, of which some 350 are part of NCI's intramural program.

Dr. Calabresi reiterated that the Working Group was charged with making recommendations regarding the current and future use of the Frederick Center in the context of a flat or decreased budget.

Dr. Calabresi described Frederick's facility as substantial and complex. He indicated that some of its components are highly meritorious and cited the basic and translational research programs as examples. Developmental research has been fostered by the facility's ample research space, effective use of contracts, and low-cost environment. Dr. Calabresi remarked that the Working Group views Frederick as having great potential to be a core facility for all of NIH. He stated that the components of the facility do not add up to a coherent whole, however, in that they are not integrated amongst themselves or with other areas of the IRP. For example, while the ABL as an autonomous research unit is very productive and highly regarded, the Working Group could find little evidence of its impact on NCI's IRP. Dr. Calabresi also commented that several intramural laboratories are located at Frederick for no strategic purpose other than the fact that more space is available there; as a result, the investigators become intellectually isolated from the remainder of the IRP. The independent Biological Response Modifiers Program (BRMP) unit located at Frederick appears to be content where it is located; however, its distant location deprives the rest of the IRP from witnessing and following its exemplary practices in clinical and translational research. Dr. Calabresi pointed out, for example, that when a unique myeloma transplantation research project was conducted recently at Frederick, fellows from the IRP were not given the opportunity to witness this event. The Working Group concluded that the BRMP does not contribute to clinical training within the IRP—one of the most vital components of the program.

Dr. Calabresi characterized the Frederick satellite facility as large and costly, and noted that in order to complete its own activities, its facilities necessarily duplicate those on the Bethesda campus. He stated that the Working Group could not locate any evidence of recent inquiry into the cost-effectiveness of the Frederick facility. The Working Group's effort to evaluate the effectiveness of the facility were complicated by its complex organization, which includes an intricate mixture of contracted and intramural operations, and by the considerable amount of new construction being supported primarily by royalty funds generated from the AIDS patent, which imply a long-term commitment to the site.

Dr. Calabresi then presented the Group's recommendations regarding the Frederick Center, which propose that it become a cost-effective core facility for the entire NIH. He pointed out that the supercomputer center, drug screening and development program, natural product facility, and animal facilities serve NIH-wide needs, not just those of the NCI. The role of these programs could be expanded and other programs and facilities moved to Frederick. Dr. Calabresi announced that the Working Group also recommended that three components of the Frederick facility be relocated to the Bethesda campus, and presented these in order of priority. First, the laboratory and clinical activities of the BRMP should be moved at the earliest possible time, taking into consideration available space and facilities. This recommendation is repeated in the report in two different sections to emphasize that the same conclusion was reached from two distinct perspectives. Second, those intramural researchers still remaining at the Frederick location should be relocated to the Bethesda campus. Dr. Calabresi remarked that the Working Group believes that this move will improve the quality of the researchers' work by ending their isolation. Third, the ABL program should be relocated to the Bethesda campus. Dr. Calabresi recognized that this recommendation is accompanied by some misgivings

because of the outstanding quality of the ABL. He emphasized that it is their excellent quality that drives the Working Group to recommend that the ABL be amidst the rest of the IRP. He also acknowledged that having a major contract facility located within the IRP is unprecedented, but asserted that the possibility of using government-owned, contractor-operated (GOCO) facilities to the advantage of the IRP has been raised before. Dr. Calabresi concluded by adding that if the relocation is made, then the salary and other resource inequities between contract facilities and the IRP will have to be resolved. He then invited Dr. Bishop to conclude their presentation.

Conclusion by Dr. Bishop

AIDS Research

Dr. Bishop indicated that he would start his presentation with a focus on AIDS research. He described NCI's history in conducting AIDS research as worthy of praise, noting that when AIDS first emerged as a challenge, NCI was a leader in the field. He pointed out that as the national effort to combat AIDS has grown, focus has shifted from the NCI; for example, NCI's extramural program is restricted to investigate only AIDS-related neoplasms. Dr. Bishop explained that in the context of a shifting emphasis from the NCI, AIDS research within the intramural program has continued to expand in a manner that causes concern. He reported that the total intramural budget apportioned for AIDS research has increased to nearly 35 percent, while the funds designated for cancer are decreasing. Dr. Bishop characterized this funding disparity as a sign that the NCI has been distracted from its principal mission. He suggested that the large expenditure on AIDS-related research also obscures the decrease in cancer funding within the intramural program.

Dr. Bishop stated that the increase in AIDS funding within the intramural program is partially a result of the increasingly relaxed definition of AIDS-related issues. This statement is based upon a survey of AIDS-related activities within the intramural program, which evidenced some very loose definitions of AIDS-related research. Dr. Bishop said that this has been compounded by the lack of strategic planning that has accompanied the NCI's AIDS-related effort. He concluded that this is not the fault of any individual, but a result of evolution of the structure of the AIDS program. He also commented that not only has the intramural program not planned within its own entity, it has also not coordinated with OAR.

Dr. Bishop indicated that the Working Group recommends that special attention be devoted to AIDS-related intramural research. He added that under the Working Group's proposed reorganization, the Deputy Directors of intra- and extramural research should be responsible for coordinating all AIDS research supported by the NCI. This would provide the collaborative efforts the authority and mandate they currently lack. Dr. Bishop suggested that the Deputy Directors should seek the aid of OAR to perform a review of the Institute's AIDS research in terms of its quality, appropriateness, repetitiveness, use of contracts, and NCI's future in the event that AIDS research funding decreases. The final consideration should also be of concern to NCI's strategic planning. The Working Group believes that a dedicated effort to redirect funding in a gradual and logical manner should be undertaken, while ensuring that meritorious AIDS research remains under NCI auspices and more emphasis is placed on cancer.

Quality Control

In regard to quality control within the intramural program, Dr. Bishop stated that this issue was specifically targeted by the external advisory committee in terms of NIH as a whole and that quality control became a primary issue for the Working Group as well. He reported that the Working Group agrees with all of the external advisory committee's recommendations and suggests that they be implemented. In addition, the implementation plan that was recently released was deemed to be an effective response to the committee's report. Dr. Bishop explained that while the Working Group's task could have been expedited by simply recommending full implementation of the report's recommendation, while conducting their research among NCI staff working group members discovered a great deal of opposition to the recommendations and the implementation plan. Therefore, the Group decided to reconsider quality assurance issues within the NCI.

Dr. Bishop qualified that a discussion of quality control within the intramural program must take into consideration its unique mission, charging it to "push the envelope" of feasible experimentation and to commit to retrospective rather than prospective review. This mission, which is clearly distinct from that of the extramural community, was reemphasized by both the Director of NIH and NCI. Dr. Bishop explained that this unique mission results in some special features among NCI researchers, including that they have secure funding, whereby few individuals in the intramural program lose grants; they must remain responsive to legislative or executive mandates; and they must employ team efforts for certain domains of research.

Dr. Bishop reported that NCI's current process for quality assurance within the IRP accommodates these considerations and establishes a formal procedure for review of all intramural activities. In addition, efforts have been made within the past few years to evaluate and improve this process, which could be further enhanced by the suggestions in the implementation plan. Dr. Bishop also pointed out that an appealing tenure system was recommended by the implementation plan. Finally, the process calls for ongoing oversight by the NCAB.

Dr. Bishop indicated that considerable concerns regarding quality assurance exist despite the strengths of NCI's current plan. He asserted that review of programmatic performance has not been sufficiently impartial or strident. This opinion was voiced by individuals from diverse perspectives, including IRP staff. Many BSC members and chairs expressed the opinion that the Boards are ineffective; have amorphous charges; are often underutilized, depending upon the Division; and characteristically involve rushed, superficial, reactive discussions. Dr. Bishop reported that the same criticisms were offered regarding the site visits to evaluate individual IRP investigators and programs. He stated that site visitor selection is often abused, allowing cronyism to affect judgments.

The review process has also not devoted sufficient attention to the budgets of research programs and individual researchers, which has partially been a result of a lack of data and also an inadequate mandate to do so. Dr. Bishop remarked that the funding requirements for certain laboratories have clearly expanded beyond reasonable and effective levels, yet have not been investigated. At least 55 individual researchers from NCI's intramural program have line budgets exceeding $1 million and an additional 12 are very close. Dr. Bishop recognized that inflation has necessitated increases in funding and that purchasing power between the intra- and

extramural programs has not been compared, as it is extremely difficult to do this type of comparison. He pointed out that these figures would induce surveillance within the extramural community, however, and should cause similar actions within the intramural program. Dr. Bishop also reported that no formal process of appeal exists for those investigators who are negatively reviewed. He concluded his comments by stating that the Working Group found completely unacceptable the continuing discovery of individuals who are independently conducting their research with absolutely minimal peer review.

To improve these conditions, the Working Group made numerous recommendations. Quality assurance should be the purview of the proposed Deputy Director for Intramural Research, who would work closely with the Deputy Director for Intramural Research for the entire NIH. The proposed organization also calls for a BSC that would oversee the activities of just the intramural division, which would allow members of the Board to focus their efforts more efficiently. The Board would monitor research, budgets, strategic planning, leadership, and recruitment, and would be formally charged with this mission through a detailed written document that would be uniform throughout the IRP. Members of the BSC would be nominated by the Chair and appointed by NCI's Director in conjunction with the Deputy Director for Intramural Research. Dr. Bishop added that while Division Directors could be consulted for their opinions regarding BSC member selection, they should not be involved in the final process. Chairs for the BSCs should be chosen from among current or past members by NCI's Director and, again, in conjunction with the Deputy Director for Intramural Research.

The Working Group also recommends that site visits be abolished as the standard mechanism for review of individual scientists. Dr. Bishop acknowledged that this would be an experimental action within the NIH community, as the implementation plan does not call for it. He asserted that this suggestion evolved from considerable evidence that the site visit has been ineffective and may have too many inherent disadvantages. The Working Group proposes that, instead, a system of written review by extramural scientists, who would report to the BSCs, be implemented. Dr. Bishop emphasized that the reviews should be singularly retrospective and consider the mission of the intramural program. Budgets for individual researchers and programs should receive detailed review, which should be based on full disclosure of budget-related data that present the exact cost of each project and its component parts. They also suggested that NCI's Director establish for all individual investigators a budget figure, which, if exceeded, results in automatic review. Research that is not currently subject to consistent and rigorous review should be identified and brought under the same review as all other intramural research. Finally, the Deputy Director for Intramural Research, which is a proposed position, should develop a formal process whereby investigators receiving negative recommendations from the BSCs could appeal. Dr. Bishop stressed that this should be an impartial process.

Dr. Bishop then detailed the proposed system for written review, which would be administered by the Deputy Director in conjunction with the Chairs of the BSCs. He pointed out that the Working Group anticipates that the Deputy Director will work very closely with the BSCs, and, in particular, their Chairs. The process mandates that all tenure track and tenured researchers be reviewed at intervals no longer than 4 years. Individual investigators would be responsible for submitting written reports to extramural scientists for review. The reports would include publications, details of published and unpublished results, explanations for any impediments to progress, and itemization of and justification for the operating budget. The reviewers would have written, standardized instructions for the review process,

emphasizing the review's retrospective nature and the need to scrutinize budgets. Based on their evaluation, the reviewers would then submit written reports to the appropriate BSC. The BSC would discuss the findings of the report and make a final recommendation regarding continuation and level of support. The vote would be conducted by secret ballot, which has not been the practice thus far. Dr. Bishop pointed out that this system resembles the one employed by the National Science Foundation for their review of grant applications. He added that written reviews could be supplemented by a site visit, if the BSC deemed it necessary.

Talent

Dr. Bishop then presented the Working Group's findings regarding the final area, which he commented was reserved for the end to emphasize its importance. This area involves maintaining and reinvigorating talent at the NCI. He remarked that quality research requires more than consistent review—it also needs individual talent. To achieve this end, strategies to foster creativity, autonomy, and well-being of NCI staff must be implemented and active recruitment carried out to fill employment vacancies. There are many strengths within the intramural program that suggest its ability to fulfill these requirements. Appointment to the tenure track in the intramural program presents an appealing promise of steady resources for young investigators. Dr. Bishop emphasized that his experience with young researchers leads him to conclude that they want to work at the NCI, which stands in contrast to the opinion he has heard voiced on the campus asserting that scientists do not want to work at the NCI. He stressed that the benefits of working for NCI's intramural program can be utilized to attract new doctoral-level staff.

Dr. Bishop also reported that the Working Group found that the leadership of the intramural program has been monitored in terms of their administration of talent and resources. Recent praiseworthy measures to encourage doctoral-level careers for women and underrepresented minorities are another strength of NCI's intramural program.

Dr. Bishop asserted that despite these strengths, the Working Group uncovered inadequacies in the recruitment and retention of scientists in NCI's IRP. He remarked that among the most disturbing concerns found was the broad-based dissatisfaction with the atmosphere within the intramural program. He explained that the adherence to a hierarchical approach to research can produce intimidation of individual researchers, as well as autocratic control over funding. These types of negative behaviors were found among Section, Laboratory, and Branch Chiefs, and while not a universal problem, it was certainly prevalent. Consequently, individual investigators have their autonomy squelched, and generating creative approaches to science becomes secondary to meeting programmatic needs of superiors. Dr. Bishop acknowledged that while IRP's mission necessitates teamwork, there is no replacement for the innovative work of individual investigators. He added that this principle needs to be rediscovered among members of several portions of the intramural program.

The IRP's recruitment practices were found to match the same poor standards as those identified by the external advisory committee among the entire NIH. Fulfillment of vacancies is typically achieved with resident staff, rather than through vigorous recruitment or solicitation of the extramural community, which leads to inbreeding of ideas and attitudes and prevents utilization of the full talents available to the NCI. Dr. Bishop stated that attempts to recruit from the external community are often guided by the programmatic needs of a unit, as opposed to an

individual's ability. The Working Group examined some recent advertisements for available positions and determined that they targeted individuals with specific skills, not broad credentials. Dr. Bishop's final criticism of the intramural program involved NCI's track record regarding reducing the barriers faced by women and underrepresented minorities in pursuing research careers within the IRP. He concluded by stating that, in combination, these factors may serve as the greatest obstacle to excellence that the intramural program faces.

Dr. Bishop detailed the Working Group's recommendations to resolve these concerns regarding the recruitment and retention of quality staff at the NCI. First, the duties of Laboratory and Branch Chiefs should be more explicitly defined. These individuals, who are comparable to departmental chairs in academic settings, are responsible for promoting the professional development of the investigators that work under them. They are responsible not only for their own behavior, but for that of the leaders working beneath them. Another recommendation asserts that Division Directors, Laboratory Chiefs, and Branch Chiefs should receive 5-year appointments, and when this time period has nearly reached completion their administration should be reviewed by site visit. Dr. Bishop indicated that a site visit is vital to perform this task well, and should involve extramural scientists under the direction of the Deputy Director for Intramural Research and the BSC. Areas of review should involve their performance as mentors, success in recruitment and sustenance of staff, appropriateness in apportionment of funds, rigor in the administration of research, and other qualities important to leadership. He added that research performance reviews should be completely separate from the stewardship reviews, and that in the conduct of the latter, the views of all individuals performing under the researcher being reviewed should be sought. Dr. Bishop urged that these reviews be completed with more energy than in the past. If a stewardship review finds sufficient inadequacies, then re-review should be scheduled for 1 year, and two poor reviews should result in termination from the position.

The Working Group also emphasized that the IRP should fully adhere to the tenure system that was developed by NIH's Deputy Director for Intramural Research in response to external advisory committee review. Dr. Bishop expressed his strong belief that if the system is properly implemented, no adverse effects will be experienced among those scientists pursuing a career in clinical research or areas requiring team efforts. While numerous criticisms of the new tenure system cited this concern, the Working Group has found that it is unfounded and possibly an excuse to maintain the status quo. The Group also suggests that doctoral-level vacancies be filled through rigorous recruitment among scientists in both intra- and extramural communities. Consideration of an individual's talent should be given priority over a unit's programmatic needs, although the Working Group does acknowledge that a balance between the two factors is necessary.

Dr. Bishop shared the next suggestion that all tenure track and tenured scientists receive fully itemized budgets prior to each year, and then be held accountable for those budgets throughout the following year, with any alterations in funding allocations reflecting fair and impartial judgment. He asserted that this procedure is not currently followed. The Working Group also recommends that the intramural program have a mechanism that provides opportunities for outstanding young investigators to establish themselves, but that these researchers should move to other institutions after a 3- to 5-year period. Dr. Bishop noted that the decline in FTEs reflects a shift consistent with this recommendation and urged that this initiative be designed to target the finest investigators. To this end, the Working Group suggests that a distinguished fellows program be instituted that would annually fund up to 10

new investigators, who should already have established research groups consisting of three to five individuals. This program would be directed by the Deputy Director for Intramural Research. Fellows would be solicited through a broad-based advertisement of a national competition that would result in a 5-year appointment. Harvard University and Whiting Institute both have model programs of this sort. Dr. Bishop indicated that in this manner the NCI's resources could be used to attract the highest caliber of young investigators.

The Working Group also recommends that the BRMP establish a competitive grants program, which could be used to supplement funding for its participating investigators. This mechanism could be utilized to promote the development of innovative approaches to research questions, particularly among junior researchers. Dr. Bishop reported that the Working Group also suggests that efforts to advance the careers of women and underrepresented minority group members should be made. Initiatives may include special efforts related to recruitment and promotion, and appropriate salary and resource adjustments for existing staff. All of these efforts should be implemented as soon as possible. Dr. Bishop noted that the Working Group is aware of several recent praiseworthy efforts to study the advancement of women and minority members throughout NIH and within NCI. Recommendations that were formulated based on these examinations could be readily implemented through stewardship reviews.

Dr. Bishop expressed the Working Group's belief that an ombudsperson should be appointed by the Deputy Director for Intramural Research to handle issues related to career advancement, as well as other concerns voiced by women and minority members. The ombudsperson would also function to address any administrative impediments to research and as a confidant for all staff. This individual should be in direct contact with the administrative policy board suggested by the Working Group, as well as the Deputy Director for Intramural Research. The Working Group also suggests that NCI initiate a competitive grants program for its research staff, which is an idea being considered by several NIH Institutes. The program, which would be administered by the Deputy Director for Intramural Research, would be open to all tenure track and tenured researchers; however, the emphasis would be on younger researchers. The grants would be funded from an annual set-aside of $3 million, which Dr. Bishop asserted is not a relatively large amount of money. He further explained that individual awards should not exceed $100,000 per year and should not last longer than 3 years. No programmatic specifications would be offered and, therefore, research ideas would be conceived by the investigators themselves. A committee of NIH-wide intramural scientists would determine which grants to fund. He emphasized that these grants would be considered supplemental and, therefore, would not act as a reason to reduce the base budget of an investigator. Dr. Bishop further suggested that if the program is found to be effective, the NCI should consider expanding it to include all NIH intramural investigators working in areas relevant to cancer.

Dr. Bishop announced that the Working Group recommends that the NCI submit a written implementation plan regarding the Board's final suggestions to the NCAB during its May 1996 meeting. The Working Group further recommends that annual review of NCI's progress toward meeting the goals of the implementation plan be conducted by the NCAB. He concluded by commenting that the final report contains some 60 direct recommendations, as well as several implied suggestions. Some of the initiatives are previous recommendations that have not been followed; however, many of the recommendations are precedent-setting, innovative ideas. He indicated that the recommendations are offered with both hope and urgency, as the NCI is a vital resource that must be adapted to current economic conditions to

thrive. Dr. Bishop related that several months ago he informed members of a Congressional committee that he believed that human beings are finally in a position to eventually conquer cancer in all forms. This statement was met with a certain degree of disbelief; however, of more concern was the automatic assumption of many of those present that conquering cancer meant finding a cure. Dr. Bishop emphasized that the goal should be eradication of cancer, not a cure once disease has occurred. He charged that the conquest of cancer will necessarily be led by the NCI and, therefore, the Institute must be made the best it can be. Dr. Bishop then solicited questions and discussion from the NCAB.

Discussion

Chairperson Rimer reconvened the meeting after a short break and expressed her desire to hold an open discussion of the Working Group's recommendations, particularly while Dr. Varmus was still present. Dr. Bishop informed those present that the report has already been presented to NCI's Executive Committee and that their response has been extremely positive. He indicated that the Working Group is pleased and appreciative of their reaction. Dr. Day asked whether the Board approves of the plan and what the timeframe for implementing the plan will be. Chairperson Rimer indicated that the question of the procedure for approval of the report has already been the topic of some discussion and requested that NCAB members provide input on the issue. She announced that at this point the procedure should probably allow Board members to ask questions, have time to fully read the report, and then mail a ballot regarding approval of the report. Dr. Rimer clarified that approval of the report will not have to indicate agreement with each and every recommendation, but with the spirit of the recommendations. Dr. Bishop assured members that the report issued to NCAB members contains all of the final recommendations that will appear in the final formal report, which will probably be completed by the end of May. He added that the final report will also include the background information that was presented to members.

Dr. Rimer stressed the importance that the Board's reaction to the report, as well as the report itself, be part of the material that greets the new Director and helps to form a blueprint for reorganizing the Institute; therefore, reactions to the report must be quick. Dr. Becker stated that because of the report's size and scale, discussion of its individual points would not be possible at the moment; however, he moved that the spirit and content of the report be approved with the provision that once consideration is given to its details, further comment will be made. Dr. Mayer seconded Dr. Becker's motion to approve the spirit and content of the report. Regarding the process of approval, Dr. Salmon asked whether it would be proper to have a period during which NCI staff, the public, and extramural investigators could comment on the report, before the final form is approved. Dr. Salmon added that he believes that the report is outstanding and, therefore, his comments reflect consideration of process, not opposition to its content. Dr. Schein supported Dr. Salmon's suggestion that NCI staff be allowed to thoroughly consider the report and be provided with a mechanism for input, particularly in light of the substantial nature of the reorganization recommended within the report. Dr. Sondik also agreed with the suggestions made thus far by recommending that staff be given sufficient time to consider the final draft of the report that will be issued at the end of the month. He suggested that either the Board could collect related comments and then hold a final discussion during its September meeting, or that the committee could collect and integrate the comments. Dr. Sondik emphasized that the important component of the approval process is that input be allowed. He also expressed his appreciation of the report's thoroughness,

foresight, and construction, and pointed out its timely release in that the National Cancer Program was initiated more than 20 years ago.

Dr. Mayer also offered her support for the report, characterizing it as exciting and "on target," and added that the process of approval should therefore move forward. She did recognize the need for a formal comment period, but emphasized the importance of having the report approved, with any necessary amendments, by the time the new Director takes over. Dr. Calabresi indicated that the report is for the NCAB, who can then amend it as they deem necessary.

Dr. Becker assured members that his motion was not intended to reduce discussion of the report, but simply to offer the Board's approval of the nature of the plan. Dr. Rimer announced that since all of the recommendations that would be included in the final plan had been presented and no new suggestions would be added, a vote regarding approval of the plan's spirit was appropriate to allow Board members to express their opinions. She added that the implementation process and period could be discussed after the vote. Dr. Becker's motion to approve the spirit of the report was unanimously approved. Dr. Rimer announced that the spirit of the plan had been approved and thanked Drs. Bishop and Calabresi for the report and Dr. Becker for expediting the process of approval. She indicated that a discussion of the feedback process and implementation of the plan could now begin.

Dr. Greenwald also commended the plan and asked whether its designers have considered the funding effects of increasing the focus on extramural research, which will require increased administrative costs. Dr. Calabresi addressed Dr. Greenwald's concern by stating that it was not within the charge of the Working Group to review the extramural program. The recommendation that four Divisions be instituted in the extramural program was made by the Working Group, knowing that it was not their responsibility to do so. He recognized that the new Director of the NCAB may wish to change the recommendations regarding the extramural community. Dr. Bishop supported this response and reiterated that reorganizing the extramural program would be the responsibility of the new Director.

Dr. Day asked how coordination between intra- and extramural activities is currently achieved and how the plan designers envision collaboration occurring within the reorganized Institute. Dr. Bishop responded by stating that the Working Group recommended that the extramural program be separated from the intramural program because of the scope of its activities and the lack of formal processes for collaboration. He explained that it would be extremely difficult to gain a coherent view of the Institute's processes for collaboration, as each Division accomplishes it differently. Supposedly, it occurs at the lower levels under the guidance of strategic planning and the advice of the BSCs. He offered that the Working Group believed that efforts to improve coordination would be easier to design, monitor, evaluate, and change if the extramural program were separate. In theory, having the two programs combined seems to create an intimacy that would foster extensive collaboration; however this has not been the case.

Ms. Visco asked what the process will be for input and further consideration of the plan. Dr. Bishop suggested that one possibility would be to simply allow the NCI to develop an implementation plan based on the NCAB's approval of the spirit of the report. Discussion of the merits of the individual points, particularly in terms of which suggestions the Institute

chose to address and why, could then ensue once the plan was released, which would allow a lengthy amount of time for thought. Dr. Calabresi reminded members that it will not be possible to implement some of the recommendations for 5 or 10 years, or perhaps longer. For example, moving some of the laboratories from Frederick to the Bethesda campus would require new space. Ms. Visco clarified her question as asking whether the Board really has a role in approving the recommendations contained within the report, or whether they are simply passing the report along to the Director for implementation based on his discretion. Dr. Rimer stated that she believes that approval of the plan's specific recommendations will be a collaborative process between the NCAB and the new Director and also welcomed input from any other individuals.

Dr. Varmus addressed Ms. Visco's point by providing some history about the formation of the Ad Hoc Working Group. The process responsible for forming the Working Group deliberately paralleled the plan that established the external advisory committee and produced the Marks-Cassell Report. External advisory committee members reported to Dr. Varmus' advisory committee, who listened to the report, commented on its findings and suggestions, then submitted written remarks to him, as well as a tremendous amount of verbal feedback. After this process, an implementation plan was developed and presented to the Board. Dr. Varmus stated that based on the process followed by the Marks-Cassell Report, the intention was that the NCAB would hear the recommendations, advise the new leadership about appropriate implementation, then ask to receive an implementation plan upon which the Board could comment.

Dr. Sigal emphasized that statutory laws prohibit the NCI from shifting the budget line without Congressional approval and commented that determining an expedited process for approval of recommendations for reorganizing the NCI is extremely important; otherwise, it could take years before any changes are made. She pointed out that the 1997 Bypass Budget is already being developed and suggested that when the Budget and Planning Committee members meet, they should discuss what can be done immediately.

Dr. Ghosh, the Department of Defense's (DOD) ex officio representative, expressed his Department's desire to enter into collaborative efforts with the NCI, stressing that DOD handles more than 1,000 cancer patients every year and that his patients constitute a very controlled population who would make excellent clinical trial participants. He added that his Department has a strong background in diverse areas of oncology, including surgical, medical, pediatric, and radiation oncology. Dr. Calabresi commented that the Clinical Center needs the support of an established hospital, and suggested that the Naval Hospital would be ideal for this situation.

Dr. Rimer suggested that the Board launch a discussion of specific points about the recommendations. Dr. Salmon reiterated his positive assessment of the report and shared his view that many individuals would agree that downsizing the intramural program is necessary. He added that the report's effort to restore NCAB's advisory capacity is also commendable. He suggested that the job description for the Deputy Director for Extramural Affairs should not be included until it is decided whether the individual should be primarily an active researcher or an outstanding grants manager. He also expressed his concern regarding the reduced role of the BSCs, particularly in limiting their focus to the intramural program only, and urged some integration of the oversight for the intra- and extramural programs. Based on

his service on several BSCs, he asserted that members of the extramural community would like to have a formal structure developed that examines whether their programs are appropriately addressing national needs. Dr. Calabresi responded by saying that the Deputy Director's job description was not offered because the Working Group's charge did not involve the extramural program. He added that the report also includes a comment that a mechanism similar to the BSCs should be established within the extramural program; however, again, because of the Working Group's charge, specific recommendations were not laid out. Dr. Bishop remarked that the charge for the BSCs has not changed at all, except to focus solely on the IRP. They are still responsible for strategic planning and the performance of oversight regarding research programs, budget, leadership decisions, and recruitment. He added that their more limited focus should allow the Boards to become more effective and the provision for independent extramural review of individual research programs will greatly increase their efficacy as well.

Dr. Dickersin asked who would design the Requests for Applications (RFAs) if the BSCs focus only on the intramural program. Dr. Bishop responded that the intention is that the development of RFAs will be the domain of the extramural program's functional equivalent of the BSCs. Dr. Freeman supported the decision to give intramural researchers more oversight, but cautioned that too much responsibility for oversight could detract from their ability to conduct research, which is a common complaint among extramural researchers. Dr. Bishop stressed that members of the BSCs are not being required to assume any additional tasks under the new plan. The plan simply suggests a new format for their review process—a progress report that may potentially be only a few pages in length—as opposed to a site review. Dr. Freeman also asked whether the plan allows for special treatment of a gifted researcher. Dr. Bishop replied that the intramural program allows more flexibility in individual hiring or appointment than the extramural program. He added that the distinguished fellows program is specifically designed to support outstanding researchers and that he believes the plan for reorganization will not undermine the Institute's ability to recruit or retain outstanding researchers. Dr. Varmus suggested that researchers may waste more time resolving procurement and hiring-related issues than preparing for reviews.

Dr. Day asked whether the group has any specific recommendations regarding limitations on the size of laboratory budgets or whether that issue will be the domain of subsequent peer review. Dr. Bishop replied that no specific recommendations were offered as the working group is aware of the need for flexibility in this area. He explained that the working group's concerns are related to the lack of oversight regarding the budgets, not the specific figures.

Dr. Chan asked what the different roles for the Deputy Director for Intramural versus Extramural Research will be. Dr. Calabresi indicated that the duties of the Deputy Director for Intramural Research are clearly outlined in the recommendations and that those of the Extramural Deputy Director were not addressed. Dr. Bishop reiterated that these are both new positions that do not correspond to any existing job. He clarified that the differences in their responsibilities will derive from the variations in the two programs' activities. Dr. Bishop added that the new Director could choose not to have a Deputy Director for Extramural Research. He also related that the Deputy Director for Intramural Research will have duties similar to those of Dr. Gottesman for NIH overall. Dr. Kalt clarified Dr. Chan's question as asking the difference between the Deputy Director of the Division of Extramural Activities and for the entire extramural program. Dr. Kalt explained that his functions fall within the realm of

extramural activities, such as grant and contract review, misconduct, and policy issues affecting extramural programs. In contrast, the extramural Branch and Division leaders would report to the Deputy Director of the Extramural Program, who, acting as the chief extramural programs officer, would report directly to NCI's Director. He commented that this Division is supported by NIH's history of separating responsibilities for programs and review.

Dr. Chan asked whether the existing structure will be phased out over a period of time. Dr. Bishop replied that the Working Group has not addressed specifics related to the process, but that he envisions that it will be a more rapid transition, in which it will first be designed on paper and then implemented. He acknowledged that once the transition begins, certain aspects will proceed more slowly, such as the consolidation of laboratories. Dr. Bishop reiterated that members of the Working Group did not give consideration to the specific details of implementation. Dr. Dickersin asked where nonresearch programs, such as the Physicians Data Query (PDQ) and educational programs, are located. Dr. Kalt responded by stating that they are administered directly through the Office of the Director. Dr. Calabresi remarked that the Working Group originally had planned to present a very complex diagram of the new structure, but decided that it would detract from the other major recommendations.

Dr. Schein asked Dr. Varmus about the impact of the reorganization on patient care. He commented that transferring responsibility for AIDS research, which constitutes 35 percent of NCI's budget, to other Institutes will require a slow and careful approach, as well as redirection for all investigators currently involved in this type of research, or a tremendous negative effect on the NCI will be experienced.

Dr. Varmus agreed with Dr. Schein's concerns and expressed his reluctance to usurp the role of decision maker regarding the reworking of the AIDS program at the NCI. According to the report, Dr. Varmus stated, the primary area of initial concern will target those research projects that are denoted as AIDS related but are in actuality very loosely connected to the disease. He reiterated that they are not currently discussing actions for programs that are clearly mainstream and productive AIDS-related work. He emphasized that a very gradual transition to other Institutes will occur to ensure that no investigators or their work are injured by the process. Dr. Sondik supported Dr. Varmus' comments, adding that in conjunction with Mr. William Paul, Director of OAR, it was decided that meritorious research will not be interrupted but, instead, the possibility of achieving more AIDS funding for the extramural program is being examined. Difficulties associated with the manner in which grants are triaged are impeding this effort. Dr. Varmus remarked that changes in the leadership at OAR will affect the NCI and several other Institutes, and reported that he, Dr. Sondik, and a number of Directors from other Institutes met with Dr. Paul to discuss the transfer of AIDS-related research in an agreeable manner, which will help to ensure that no one is injured during the transition. Dr. Schein reiterated his concern that the contribution to the NCI for AIDS-related research is substantial and disrupting that funding level would have a severely negative impact on the Institute. Dr. Sondik supported Dr. Schein's concern about maintaining the funding level for the NCI. Dr. Bishop added that the Working Group did not recommend that the funding for AIDS-related research be reduced. He emphasized that the Working Group had NCI's welfare in mind at all times.

Dr. Sondik indicated that the ethos issue is among the most troubling in the report. He asked whether there is something unique to NCI's organization that exacerbates the situation in

the Institute and caused the Working Group to address this problem more vehemently than the Marks-Cassell Report. He queried whether this problem is a result of the combination of the intra- and extramural programs under the same leadership. Dr. Bishop stated that he does not believe that the NCI's structure intensified the problem in comparison with other Institutes. He suggested that the problem may, instead, be a function of the hierarchical structure of NIH's decision-making and funding deployment. Dr. Bishop explained that the Working Group believes that to resolve the problem, the process of deploying funds needs to become more visible, so that individuals can be held accountable. Dr. Calabresi supported Dr. Bishop's comments and added that the problems are not NCI-wide, but are isolated within certain Laboratories and Branches. Dr. Calabresi reiterated that the Marks-Cassell report indicated that the problem was common throughout the NIH. Dr. Bishop observed that the committee spoke with very few doctoral-level staff who did not eventually identify this issue as a problem.

Dr. Rimer announced that she and Dr. Kalt have drawn up a draft timeline for the report, noting that on approximately June 15th the full report will be disseminated to the NCAB and NCI staff, as well as other appropriate NIH staff; feedback will be solicited through the Internet, mail, fax, or any other mechanism of choice, and it is hoped that the Cancer Letter will publish a summary and request comments; a meeting of all subcommittee co-chairs will be convened during the summer to discuss the report further; comments will be due to Drs. Rimer, Calabresi, or Bishop by August 1st; a meeting with the new Director will be scheduled for approximately August 15th, during which the report and reactions to it will be discussed; the September NCAB meeting will provide a forum for further discussion of the report with the new Director; an implementation plan will be developed during the fall of 1995 by NCI's Director and staff; and a review of the implementation plan will occur in May of 1996.

Dr. Mayer asked whether the new Director will have to wait until the plan is adopted in May of 1996 to begin implementing recommendations. Dr. Rimer indicated that the new Director will not be impeded from implementing any suggestions. Dr. Sigal pointed out that the Bypass Budget is due on September 5th, and that efforts to incorporate any of the recommendations into this document will have to be made immediately. Dr. Rimer replied that subcommittees will have to become involved in the process of implementation as soon as possible. She concluded the meeting by thanking Drs. Calabresi, Bishop, and Kalt; Dr. Kalt's staff; Dr. Varmus; and Dr. Kirschstein for attending the meeting and initiating the entire process.

X. CLOSED SESSION

The morning session of the second day of the meeting was closed to the public because it was devoted to a meeting of the Special Actions Subcommittee. A total of 1,090 applications were received, requesting support in the amount of $250,438,722. Of those, 1,090 were recommended as being eligible for funding at a total cost of $226,879,213.

XI. SUBCOMMITTEE REPORTS

Dr. Rimer described the agenda for this session: subcommittee reports; new business discussion; and two presentations the Board requested at the last meeting—an update on breast cancer trends and a discussion of the implications of the COMMIT Program for tobacco

control. She drew attention to an article about Dr. Sigal crusading for environmentally safer buildings and a picture of Ms. Zora Brown on the cover of Health Magazine with her support group, and she commended these Board members for campaigning for admirable causes.

Cancer Centers

Dr. Day presented the report of the Cancer Centers Subcommittee. The Subcommittee addressed two issues: the comprehensive guidelines requirement that comprehensive cancer centers participate in NCI-designated, high-priority clinical trials research, and cancer center support grants.

Regarding the requirement to participate in high-priority clinical trials, some of the cancer centers have questioned whether this constitutes an appropriate use of their time and resources. Many cancer centers are more concerned with innovative pilot studies, some of which may become high-priority clinical trials. As a result, Dr. Day reported that the Subcommittee will recommend, rather than require, high-priority clinical trials as an element of the guidelines. The cancer centers program group will decide on the appropriate wording of the recommendation. Dr. Day indicated that the Subcommittee made its decision after reviewing letters from Dr. Vincent DeVita; Dr. Charles Coltman, who heads the Cancer Center of San Antonio and chairs the Southwest Oncology Group (SWOG); Dr. Richard Schilsky, who directs the Cancer Center at the University of Chicago; and the Acting Director of Duke.

Another item the Subcommittee discussed was cancer center support grants. The center directors met in March to discuss 10 directives circulated by Dr. Kimes. According to Dr. Day, the directors sought clarification of the guidelines, which will be sent to the Subcommittee for review, circulated back to the various affected groups, presented again to the Subcommittee for any additional changes, and, finally, presented to the full Board for approval. He predicted that both of the items he described would be presented at one of the next two NCAB meetings for the Board's approval.

Dr. Kimes asked that high-priority trials be eliminated as a required element from the comprehensive guidelines immediately, as there are a number of cancer centers trying to satisfy that element under the current deadline. He suggested that they be relieved of that responsibility, since the Subcommittee and the full Board have already agreed that it should be eliminated as a requirement. Dr. Day proposed advising the centers to include participation in high-priority clinical trials as part of their overall clinical research activities, but deleting it as a requirement. Dr. Salmon clarified that the peer review groups will consider it in their evaluation of the cancer center's clinical trials, but not treat it as a required element. Dr. Day made a motion to that effect, which passed with Dr. Salmon's abstention because of his pending application. A motion was made to approve the minutes of the subcommittee meeting, which also passed.

Information and Cancer Control

Ms. Marlene Malek reported to the Board that the Subcommittee met to monitor the nation's progress towards meeting the goals of Healthy People 2000 and discuss future directions for NCI tobacco research as applicable to the goals. The Subcommittee sought to

advise NCI on a 5- to 10-year research agenda with priorities that will help define a spending plan for increasingly scarce resources.

Dr. Tom Glynn provided an overview of tobacco research to the Subcommittee, including its history; the concentration on prevention and control; large intervention trials like COMMIT and ASSIST; R01 and RFP research on tobacco control innovations; and plans for national dissemination of research findings. Dr. David Abrams, Director of Communication and Behavioral Medicine at Miriam Hospital in Providence, Rhode Island, presented the state of the art in smoking cessation research. Ms. Malek indicated that he stressed the complexity of the issues and the contradictions between the existing data and many long-held assumptions and models about tobacco cessation. He mentioned the need for a new strategy to approach the problem and for a better balance of basic, clinical, and applied research, intimating that NCI has moved too far in the direction of application and neglected the other aspects of tobacco research. Ms. Malek said that several participants stressed the need to focus on dissemination of research results and collaboration with government agencies and voluntary organizations. Dr. Abrams said that the field is on the brink of many new opportunities after years of collecting data.

Ms. Malek told the Board she learned that smoking decline has leveled off since 1990, that remaining smokers are hard to reach and motivate, that they are highly addicted, and that they experience great difficulty quitting. These facts apply to youth starting to smoke, less-educated individuals, and smokers of lower socioeconomic status. Consequently, Ms. Malek suggested that reduction of smoking prevalence will necessitate reducing initiation, motivating cessation, and providing a variety of treatment options, including inpatient clinical care, to those having trouble quitting.

As part of his presentation to the Subcommittee, Dr. Abrams suggested rethinking the following basic assumptions about cessation: smokers can quit on their own; treatments are widely available; taxes will cut prevalence; tobacco ban policies will increase cessation; and economics justify treatment and prevention. Ms. Malek reported that more research is needed on how to prevent initiation, how to help addicted smokers by accelerating their motivation to quit, and ensuring appropriate levels of treatment and care. She said Dr. Abrams estimated that 30 to 40 percent of the 50 million U.S. smokers are heavily addicted. He noted the magnitude of the problem, citing 418,000 deaths per year related to tobacco use.

Ms. Malek referred to Dr. Glynn's summary of three areas for future NCI research: prevention, particularly among youth; nicotine dependence; and policy research. She said he emphasized application of research results and systematic reviews of trial data. She informed the Board that tobacco research policies will be discussed at a special NCAB meeting held in July to set an agenda for behavioral research.

Dr. Sigal asked if there is anything the Board can do to educate or sensitize members of Congress to tobacco-related problems. Ms. Malek suggested lobbying, but noted that the tobacco lobbies are significantly more powerful. When Dr. Sigal raised the issue of regulations in the Occupational Safety and Health Administration (OSHA) bill, Dr. Salmon asked about its current status. Dr. Sondik informed Dr. Sigal that the FDA has not retreated from its position against smoking in public areas, but Dr. Rimer pointed out that the bill is still in the deliberation stage.

Dr. Calabresi asked whether steps are being taken to apply the positive results achieved for smoking cessation among teenagers in the African American community to other groups.

Ms. Malek suggested that the subject would be addressed later in the meeting, and Dr. Rimer mentioned that Dr. Sherry Mills of DCPC has already discussed the focus groups she conducted with African American youth. Dr. Rimer proposed adding this topic to the smoking research agenda. Ms. Malek and Dr. Calabresi agreed that this is an important subject for further exploration, because smoking prevalence has increased 2 percent among White teenagers while decreasing considerably among African American teenagers.

The Board passed a motion to approve the minutes of the Subcommittee meeting.

Special Priorities Subcommittee

Dr. Wilson reported to the Board that the Special Priorities Subcommittee discussed the conference to be held in Washington next January on recruiting minorities to clinical trials and prevention trials of all types. The initial meeting, he explained, will be to define the state of the art in recruitment techniques for different ethnic and socioeconomic groups, with the goal of assisting cancer centers in recruiting these groups for care and, ultimately, incorporating them into the clinical research community. The meeting will be a one-and-a-half-day plenary session in which speakers who have been successful in recruiting minorities, and behavioral and social scientists will give advice and explain why past recruitment strategies may have failed. Dr. Wilson noted that the meeting would not address the economic reasons for why minority populations do not get involved in clinical studies, but would focus instead on education and recruitment. The January conference will be followed by a series of regional meetings and conferences to disseminate the information.

Dr. Wilson added that larger numbers of grant applications are being returned to clinical investigators for failure to meet the guidelines for involving minorities. While the rule that the study sample should reflect the population distribution has been in effect for 10 years, it has not been enforced as stringently as it is now, and investigators are learning the NCI is serious about this policy.

Dr. Rimer expressed her pleasure that the subcommittees have been making additional contributions by taking on substantive tasks and products. The Board passed a motion to approve the subcommittee minutes.

Basic and Environmental Sciences Subcommittee

Dr. Becker reported to the Board for the Basic and Environmental Sciences Subcommittee. He preceded his report with an observation that there is a conflict in timing of subcommittee meetings; he thought that several members may have been interested in attending the last subcommittee meeting but were unable, because of conflict. He continued by reporting that the Subcommittee discussed whether there are known environmental influences on breast cancer. He referred to a number of articles that link exposure to hydrocarbons, pesticides, herbicides, etc., to increased incidence of breast cancer, and the responsive articles that refute the methodology by which those earlier conclusions were reached. He noted that this

topic is particularly important in light of the large financial investment made to study the reputed high incidence of breast cancer on Long Island.

Dr. Becker said that Dr. Peter Shields of the Laboratory of Human Carcinogenesis spoke to the Subcommittee about a collaborative study on which he was working with the Department of Social and Preventative Medicine of the State University of Buffalo to examine the association of enzyme N acetyl transferase 2 polymorphism with susceptibility to breast cancer. Dr. Becker described it as a classic enzyme for the metabolism of xenobiotic compounds, particularly polycyclichydrocarbons, that prepares them for excretion and disposal.

Dr. Shields reported finding two major types of polymorphisms in White females; one with rapid metabolism of the enzyme, the other with slow metabolism. He correlated the latter with a high risk for breast cancer among women who are heavy smokers, but did not find this correlation among women with the former polymorphism. In discussing Dr. Shields' data, Dr. Dickersin pointed out that more work is needed before reaching a scientific correlation. Dr. Shields agreed that he is very cautious about predicting from the form of the enzyme to a woman's susceptibility to breast cancer from smoking. Dr. Becker also mentioned the side issues that arose as to whether women with the slow enzyme have a predisposition to smoke and whether they find cessation more difficult.

Dr. Becker reported on another speaker, Dr. Carl Barrett, Acting Scientific Director of National Institute of Environmental Health Sciences (NIEHS), who played a significant role in the final analysis of the gene sequence in BRCA-1. Dr. Barrette has been testing various agents for production of mammary cancer in rodent systems and has found 35 compounds that produce breast cancer in rodents. However, none of these compounds are known to be associated with breast cancer in human females. Dr. Barrett suggested that the animal model may be inappropriate due to subtle interactions of the stroma and epithelial tissues that affect the metabolic patterns in rodents.

Dr. Barrett further discussed his work and findings with BRCA-1, including his analysis of more than 35 breast cancers that appear sporadically, i.e., nonfamilial cancers, none of which showed a mutation in BRCA-1. This is an especially significant finding, since most tumors are extremely labile and this lability is enhanced when they are put in culture; hence, the lack of a single mutation suggests that BRCA-1 in its somatic form is highly robust and not very susceptible to environmental carcinogens in nonfamilial cases. Dr. Barrett also spoke about his work with "knockout mice" and antisense against BRCA-1 to learn more about the function of this gene, which is a zinc ring protein, making it a likely candidate for DNA binding and transcriber-modulating protein.

Dr. Becker noted that Dr. Susan Sieber discussed with the Subcommittee the coordinating efforts and money being devoted to breast cancer by several governmental and nongovernmental agencies. She reported that in FY96, the NCI and Department of Defense budgets devoted to breast cancer research will be $344.7 million and $150 million, respectively. Dr. Becker emphasized the importance of this success in organizing funding and stressed the need to further study breast cancer and narrow the enormous gaps in our understanding of its etiology, aside from the small cohort of women predisposed by germ line mutations of BRCA-1. He said that Dr. Barrett pointed out the uncertainty that remains about

how BRCA-1 acts in the carcinogenic sequence, perhaps as a predisposer of other genes that have not yet been discovered.

Dr. Sigal asked if the committee had assessed the appropriateness of NCI's funding level for research in environmental carcinogenesis. Dr. Becker answered that the committee has not yet tackled this issue and mentioned the difficulty in defining environmental carcinogenesis (i.e., does it refer only to the workplace, to air pollution in general, etc.?). He noted however, that in response to the chairperson's request, SENCAP recommendations, including this question, were distributed to the Subcommittee members. Dr. Becker agreed to take on the task of addressing Dr. Sigal's question and present the estimated figures for NCI and NIEHS environmental carcinogenesis research funding at the next NCAB meeting. Dr. Sigal requested a preliminary estimate for incorporation into the Bypass Budget, and Dr. Becker offered to enlist the help of Dr. Sieber of the DCT to arrive at a figure (using the broadest definition of environmental carcinogenesis) and circulate it to the Board with the other materials related to the Subcommittee's activities.

It was noted that some Branches from the DCT stated that they contribute to the national toxicology program and report on an annual basis about activities in chemical carcinogenesis and toxicology. A great deal of environmental exposure research is under the purview of NIEHS.

The Board passed a motion to accept the Subcommittee's minutes.

Planning and Budget Subcommittee

Dr. Sigal reported for the Planning and Budget Subcommittee and echoed Dr. Becker's comment about scheduling subcommittee meetings at overlapping times. Dr. Kalt explained that the overlaps are the result of compressing the NCAB meeting to accommodate the schedules of Board members. He noted that efforts have been made to rotate and avoid conflicts as much as possible.

Dr. Sigal directed the Board to the Subcommittee's newly created mission statement, which appeared in their notes. She indicated that the Subcommittee will advise Board members of new scientific directions and areas of emphasis, as well as examine areas that have been funded.

In regard to the Bypass Budget, Dr. Sigal raised the issue of the appropriate funding level to be requested for the 1997 Budget and asked whether the figure should continue at a flat rate. She reminded the Board that they requested $3.6 billion for 1996 and are currently funded at around $2 billion. She relayed the Subcommittee's discussions about requesting $4 billion and whether the Bypass Budget is intended to include scientific needs and present scientific opportunities to the President. Dr. Sigal acknowledged that requests for higher levels of funding would be unrealistic and poorly received, but expressed the consensus of the Subcommittee that the budget should at least remain flat.

Dr. Sigal informed the Board about the debate over style, format, and readability of the Bypass Budget and the general opinion that the document is too long and cumbersome. The subcommittee made plans to shorten the Budget and create a stand-alone executive summary

geared toward the nonscientific community, particularly Congressional leaders. She indicated that she has requested the assistance of the Office of Cancer Communications to put the Budget in an accessible format. The Subcommittee also discussed the feasibility of incorporating the SENCAP and intramural committee recommendations into the Bypass Budget. She reminded the Board of the imminent deadline for submitting the Budget and the difficulty in inserting line items once a Budget is accepted.

Dr. Rimer reported that she has requested that Dr. Day take over Dr. Calabresi's responsibilities for following up on the SENCAP recommendations and that Dr. Calabresi continue to advise the Board about implementation of the recommendations; both members agreed to comply.

The Board passed a motion to accept the Subcommittee's meeting minutes. Dr. Rimer thanked all the subcommittee chairs and co-chairs for providing substantive discussions to the Board and meaningful advice to the NCI. She announced that a meeting for the subcommittee chairs will be scheduled for June or July as part of the agenda committee meeting and that members will be polled to select a convenient time and place.

XII. CONTINUING AND NEW BUSINESS–SESSION II—DR. BARBARA RIMER

Dr. Rimer opened the continuing and new business session by stating that certain continuing business items would be considered first, including a statement by Dr. Schein on the budget crisis and a proposed NCAB response to the Bishop/Calabresi report, followed by other new business. Turning to Dr. Schein's statement, the "National Cancer Advisory Board Response to the Proposed Budgets of the NCI, "Dr. Rimer emphasized the importance of using the document in presentations to other organizations to proactively support the NIH budget. Dr. Schein explained that the drafters intended to incorporate elements of the previous morning session's discussion, and he asked the Board to review the statement and offer suggestions. The members offered several minor editorial changes and discussed whether the statement should emphasize cancer research as a top priority, or advocate funding for biomedical research in general.

Dr. Sigal asked whether the document would be formally submitted to anyone. Dr. Rimer offered to write a letter to President Clinton and send a copy of it to Secretary of Health and Human Services, Dr. Donna Shalala. She emphasized the need to rely on multipronged efforts to fight the budget cuts. Ms. Brown offered to present the NCAB's statement at an event in the Dirksen Senate Building.

Drs. Salmon and Kalt clarified the Board's role with respect to lobbying activities, explaining that the Board can make recommendations but that members may not speak individually on behalf of the Board. Dr. Kalt noted that members remain free to exercise their individual rights as citizens to lobby in person, but that they may not do so in their capacities as special government employees; on days when they are not paid a government salary, they may attend and speak at events or submit editorials to newspapers, etc. Dr. Maureen Wilson, Assistant Director, NCI, cautioned that Congress is particularly wary of government employees lobbying for their own programs, and she suggested that a non-Board member communicate their statement to avoid creating controversy. She added that the PCP will also be sending a letter to the President regarding the budget cutbacks and emphasized the need for

members to energize their constituencies on this issue, since the public is best equipped to influence Congressional action. Responding to a question by Ms. Brown, Dr. Wilson qualified her previous warning against lobbying by Board members; if a Board member happens to represent a constituent organization, such as the Venture Capital Fund, then presenting the NCAB's statement on behalf of that other entity would be deemed acceptable behavior.

Dr. Chan sought clarification of whether Board members can speak with their own local representatives. Dr. Wilson explained that Board members are free to discuss the impact of budget cuts on their respective home institutions with their Congresspersons. Dr. Becker pointed out that such activities may be considered unethical if conducted during a trip to Washington that was paid for with government funds. He questioned whether NCAB members should publicize the document, even under technically acceptable circumstances, in light of current Congressional sensitivity to even the appearance of a conflict of interest. Dr. Rabson pointed out that the President's budget is much more supportive of cancer research than the Senate budget; thus, any lobbying efforts should be directed at Senators.

Dr. Mayer proposed immediately revising and printing the budget statement for distribution to the meeting's visitors, many of whom represent powerful lobbying groups. Dr. Rimer agreed that the constituency organizations are the most appropriate advocates for the Board's statement, and she enlisted Mr. Van Nevel's assistance for disseminating the document to these constituents. The Board approved the revised statement, which read as follows:

"NATIONAL CANCER ADVISORY BOARD RESPONSE TO THE PROPOSED BUDGET FOR THE NATIONAL CANCER INSTITUTE

"Cancer remains a major cause of morbidity and death for the American public. The War on Cancer is still being actively engaged, and current cancer statistics demonstrate that the commitment of resources to this effort must remain a national priority. In this regard, the programs of the National Cancer Institute provide the essential elements for the implementation of the national strategy to prevent, diagnose and treat the large and heterogeneous groups of diseases called cancer. The American public expects that government will provide a significant portion of the required response to a problem that affects directly the lives of one out of three of its citizens. It is important to recognize that the status quo, as reflected in the current cancer mortality statistics, is not acceptable. Currently, 50 percent of Americans diagnosed can be expected to die of their disease.

"The budget proposed by the Administration and Congress, for fiscal years 1996 through 2000, will have a devastating impact on the national resources for biomedical research, and specifically for cancer research and care, that have been so carefully developed over the past three decades. The U.S. could irrevocably lose its edge in cancer research. This comes at a time when opportunities for improvement for the control of cancer, resulting from past investments in basic research, are unprecedented. The impact of the proposed budgets will place future progress in jeopardy; many programs will either be delayed or possibly abandoned, and the training of health care and research professionals required to build on the advances which have been made to date, will be severely curtailed.

"Current trends in health care delivery, and specifically managed care, represent an additional major threat to translational investigation by limiting patient access to and financial support of, clinical research.

"The American public will be poorly served if the methods for cancer prevention, diagnosis and treatment are not improved, leaving future generations dependent on current technology. The budgets under review, combined with the health care environment for clinical research, have created a potential crisis for all biomedical research and especially cancer. We call upon the Administration and Congress to give specific consideration to the future funding of the National Cancer Institute and its mission to reduce the suffering and deaths due to cancer, and its economic consequences."

Dr. Rimer thanked Dr. Schein for writing the statement and brought the Board's attention to the proposed NCAB response to the Bishop-Calabresi (Ad hoc Working Group on the NCI Intramural Program) report. She noted several minor changes from Dr. Sondik and urged the Board to move forward and operationalize the Board's response and involvement in implementing the report's recommendations. The "Proposed NCAB Response to the Bishop/Calabresi Report" was as follows:

1. June 15, 1995 (anticipated). Full text report is delivered to NCAB and NIH staff, press and public via Internet.

2. June 15-July 20, 1995. An NCI e-mail address and fax number will be set up to receive outside comments.

3. July 20-August 1, 1995. Comments on report collated and sent to members of the NCAB Activities and Agenda Subcommittee.

4. August 15-30, 1995. NCAB Activities and Agenda Subcommittee meets for a day during this period to discuss report and comments, plan report agendas for future Board meetings.

5. September 12-13, 1995. NCAB meeting. Probable FY 1996 Budget discussed at NCAB. Preliminary status report given by NCI staff at meeting, and how budget may impact on recommendation of the Working Group. New NCI Director comments on report to NCAB.

6. November 28-29, 1995. NCAB Program Review Meeting. Discussion at Board by NCI staff of proposed implementation of short-term issues, plans for revised advisory bodies.

7. February 27-28, 1996. Regular NCAB meeting. Update on plans or activities in response to the reports. Relevant BSC representatives invited to Board.

8. May 7-8, 1996. Regular NCAB meeting. Comprehensive progress report and review of implementation of plan presented by NCI. Relevant BSC representatives invited to Board.

Dr. Bishop suggested that he and Dr. Calabresi participate in the Activities and Agenda Subcommittee meeting in August 1995 to provide guidance in implementing the report. Dr. Rimer agreed and noted that the Board would seek wide involvement, through e-mail, faxes, and letters, in the implementation of the report's recommendations and would continue a dialogue with the current and new Director regarding implementation efforts. She announced that there would be further discussion of this issue at the September NCAB meeting.

Dr. Rimer then opened up discussion on future agenda items, noting that she would like further discussion on the future of cancer centers. Dr. Day suggested that the Board establish a mechanism to track the trends and impacts of managed care on clinical research and clinical care in the cancer centers. Dr. Salmon pointed out that cooperative groups and CCOPS are similarly affected by changes in the health care delivery system, and Dr. Becker commented that managed care affects not only clinical but all research. He suggested that the Board solicit brief statements from all the cancer centers about how they are being affected by managed care. Dr. Day added that the Board should address the issue of patient access to care. At Dr. Rimer's request, Dr. Sigal suggested that a speaker from an insurance company or managed care organization be present at the September Board meeting to discuss their criteria for centers of excellence. Dr. Becker thought it may be more worthwhile to hear from a consultant on managed health care, since the individual insurers all have different and constantly changing policies. Dr. Rimer said that she and a few other Board members would select a speaker to continue discussion of this topic.

Drs. Dickersin and Sigal offered the opinion that it would only be useful for the Board to hear from additional cancer center directors if they spoke directly to the issue of managed care, rather than discussing their centers' basic science activities. Dr. Day suggested finding speakers from patient advocate groups who have a different perspective than the cancer center directors and can address patient access issues.

For a future topic, Dr. Goldson suggested a presentation on the NCI as a clinical and research resource. Dr. Rimer mentioned that Dr. John Gallin could discuss the clinical center and the leadership training program for training individuals in biomedical research. Dr. Dickersin described an R21 at the National Eye Institute through which interested departments can receive 4 years of funding to pay for an experienced researcher to develop a research program and train individuals in the department. She suggested that a similar mechanism could work to train community doctors in research.

Dr. Schein proposed that the Board receive an update on the current status of clinical molecular genetics and its application in risk assessment. Dr. Rimer agreed that the Board should also hear about the studies being performed, how patients would get access, whether there should be clinical trials, and who would pay for the trials. Dr. Becker added that ethical decisions are a critical issue to address for this topic as well.

Dr. Dickersin asked whether a review of the extramural program, similar to that performed by Drs. Bishop and Calabresi for the intramural program, is planned. Dr. Sondik commented that such a review was initially planned under the SENCAP recommendations, but that it will likely take place as a consequence of the Bishop-Calabresi report.

Dr. Day suggested that the Board hear a presentation on the biotechnology industry's translational research and the mechanisms used for technology transfer (e.g., CRADAs) by the NIH and other institutions. Dr. Salmon agreed that the subject is important and timely in light of the approximately $7 billion invested in biotechnology, mostly in the early 1990s, and the current financial troubles that many biotechnology companies are facing. Dr. Schein notified the Board that he will be chairing a meeting at the White House to discuss the crisis threatening biotechnology in the United States. He explained that attrition and consolidation within the pharmaceutical industry and within the small company sector have effectively pushed the new headquarters of the newly merged entities to Europe. Despite years of U.S. investor support, and in some cases government support, companies like Genentech are now owned by European companies. Dr. Rimer asked Dr. Schein to help organize a session for the Board on this topic.

Dr. Rimer reminded the Board of the Secretary's action plan, which is scheduled for review over the summer, and the cancer control meeting in July. She asked members to relay any additional suggestions to her via telephone, fax, or e-mail.

Dr. Rimer announced the next two presentations: a follow-up on breast cancer trends and whether they are attributable to screening or treatment; and a detailed look at the COMMIT trial. Dr. Greenwald informed the Board that breast cancer was the leading cause of cancer incidence in women (46,000 deaths projected this year) and lung cancer was the leading cause of cancer death in both women (62,000 deaths projected) and men (95,000 deaths projected). He introduced Dr. Brenda Edwards, who would report on the analyses of breast cancer statistics, and Dr. Tom Glynn, who would report on the COMMIT trial (the intervention trial aimed at decreasing smoking rates in communities) in the broader context of NCI's tobacco control programs.

XIII. BREAST CANCER TRENDS AND THEIR INTERPRETATIONS—DR. BRENDA EDWARDS

Dr. Edwards began by noting that her presentation was a follow-on from Dr. Broder's presentation in January. She explained that she would present the data sources; describe the data briefly; and identify the questions or hypotheses that explain the trends by focusing on medical interventions, particularly screening, early detection, and treatment. She explained that she would conclude the presentation by briefly describing some ongoing research, or surveillance activities, to continue looking at the data.

Dr. Edwards displayed the first slide and noted that the backbone of the data sources is the Surveillance, Epidemiology and End Results (SEER) Program. Because of her clinical perspective, Dr. Edwards explained that she also looked at data from the Community Clinical Oncology Program (CCOP) evaluation study, as well as the cooperative groups, although the latter would not be included in this presentation. The data were examined in a variety of ways, including other data from a mammography benefit study, as well as a study of mammography studies. Data from the National Health Interview Survey focused on health behavior and screening behavior.

Dr. Edwards' next slide depicted the SEER backbone, which provides data from 1993. She noted ongoing studies of survival data, Black and White racial differences,

mammography, and the systems from which the data are generated. She noted that while the SEER data go back to the early 1970's, some clinical information is more recent, especially systems information.

Dr. Edwards noted that 182,000 cases of breast cancer are expected to be diagnosed in women this year; the lifetime risk is one in eight. She emphasized that incidence data have been increasing since the early 1970s and especially in the early 1980s. She mentioned the rate of 109 per 100,000 women diagnosed with breast cancer in the last 5-year reporting period and referred to a slide that included the number of deaths.

Dr. Edwards pointed out that mortality rates for the national trend essentially have been relatively stable in the United States over the past 50 years. She noted that the data are population based, rather than from a particular hospital or study.

Dr. Edwards presented summary data from 1988 to 1992, revealing a rate of diagnosis of 109 women per 100,000. The mortality rate averages 27,000 per 100,000 for White women, and is higher among African American women. She discussed relative survival for cases diagnosed from 1986 to 1991, pointing out that these dates represent the year in which the case was diagnosed, and suggested that one must think about cohort data—as in survivor data versus cross-sectional population data—when referring to incidence and mortality.

Incidence and mortality trends over the last 5 years continue to remain higher for White women than for African American women. However, mortality over the 20-year reporting period shows a crossover. While mortality was similar for both groups of women in the early 1980s, mortality rates for African American women have overtaken the age-adjusted rates for White women.

A variety of patterns across different age groups exists. For women 30 to 39, there has been a gradual decline in mortality, with an accelerated decline beginning in about 1987. The pattern is not as uniform for other age groups; for example, the 40 to 49 age group has seen a gentle decline, an increase, and now a decline again. The 70 to 79 age group featured level or flat rates in the early 1970's, followed by an increase and a decline.

Dr. Edwards cautioned that trends in breast cancer data or other cancer sites cannot be characterized by one summary figure. She pointed out that the recent declines in breast cancer mortality for all women are really driven by the rates for White women. She referred to Dr. Broder's presentation at the last meeting, and reiterated that women 30 to 39 have shown about an 18 percent decline in mortality from 1987 forward. She reported about a 5 percent decline from 1989 forward and reiterated that the decline for 40 to 49 year old has been noted since the early 1970's.

Referring to her slides, Dr. Edwards illustrated the decline in mortality for the 50 to 59 age group. Her next three slides reinforced mortality rates and represented different ways of portraying the data and the variation in rates over time among both White and African American women.

Dr. Edwards turned to rates by various age groups in breast cancer incidence from 1988 to 1992 developed from SEER Program data. She explained that age-specific incidence

rates tend to be slightly higher in younger age groups, with some crossover between ages 45 and 49. She referred to much higher incidence in White women, smaller incidence for Black women, and declines in the older age groups.

Dr. Edwards spoke of the difference in age-specific mortality rates, where the rate of death due to breast cancer among African American women shows an excess across a larger set of ages, with crossover occurring in the 65 and older age group, suggesting that mortality among older White women is greater than among older African American women. A slide depicted age distribution for both incidence and mortality, and revealed a shift at younger ages for African American women in both incidence and mortality.

Referring to her slides, Dr. Edwards displayed the U.S. female population by age and calendar year over a 20-year period based on distribution in 1970, 1980, and 1990. She explained that increased breast cancer cases and deaths among younger women may be a function both of the aging of the population and a larger bolus of women moving into their 30s, 40s, and 50s, which yield larger numbers of both cases and deaths. Nevertheless, Dr. Edwards reported, the number of cases, which is influenced by population shifts, is actually an important measure.

Dr. Edwards questioned whether changes in breast cancer mortality were due to advances in treatment, screening, and early detection; whether there is something about the biology of the tumor; or perhaps a cohort effect. She turned to data on screening information, treatment questions, and other factors that may yield information that might explain mortality rates. She displayed trends by incidence, age-specific breast cancer, and tumor size, as well as mammography facilities and analytic modeling.

Dr. Edwards displayed a slide of incidence rates from SEER and other data sets. The top two lines displayed malignant disease, the bottom two lines displayed in situ disease. The log scale depicted the dramatic increase beginning in the early 1980's of in situ disease.

She presented trend data described by the SEER historic stage in the following categories: localized (confined to the breast), regional (involving lymph nodes), and distant disease. Dr. Edwards noted a pattern across a wide range of ages, particularly for White women. She noted that the increases seen in 1974 may be attributed to breast cancer diagnoses in a couple of prominent American women, which subsequently motivated more women to be checked and drove up the incidence rates somewhat. She noted some flattening in the late 1970s, an increase in localized disease beginning in the early 1980s, and a decline in regional disease. The line depicting distant disease remained mostly flat, and unstaged disease remained approximately constant, with some variation in both directions. Dr. Edwards observed that breast cancer incidence trends by stage yielded some of the earliest clues that there might be a screening effect on reduced mortality.

In discussing staging data by White and Black race since 1983, Dr. Edwards presented trends showing shifts in the proportion of cases diagnosed with early-stage or in situ disease. She pointed to increases in situ disease that have been seen among African American women, and reported dramatic increases in stage I disease, not as much shift in stage II disease, and some decline in advanced disease.

Dr. Edwards attempted to provide information on change and stage distributions over time for a wide range of age groups among both White and Black women. She showed comparisons in data from 1978 to 1982 with data from a later 10-year period. Almost one-half of the cases in the earlier period—the late 1970s and early 1980s—for White women were localized disease. Increases in the proportion of localized cases were seen in almost every age group. Noting variations by age, Dr. Edwards reported a shift toward larger proportions of early-stage disease in younger Black women, which, however, is not as dramatic as that seen in White women.

Dr. Edwards briefly noted the trend toward an increase in localized disease and a decline in regional disease. She pointed out that approximately 50 percent of deaths due to breast cancer result from regional disease.

Referring to a slide summarizing patterns in a variety of age groups, Dr. Edwards noted the general increase in early-stage disease, particularly in later years. She noted that trends by tumor size of less than 1 and 2 centimeters show increases, and tumors of 3 centimeters or greater reveal some declines.

Dr. Edwards turned to data on breast screening from the National Health Interview Survey, a cancer control supplement funded by the NCI in 1987. She remarked that about 20 percent of women in different age groups reported having had a screening mammogram in the last year, except, possibly, for a somewhat lower rate among the very oldest women in the late 1980s. She reported the greatest increase in this health behavior between 1987 and 1990 across all age groups, though the level of reported screening was lowest among older women.

Referring to her slides, Dr. Edwards summarized previous slides and portrayed representative national data from 1987, 1990, and 1992—whether focusing on White, Black, or Hispanic women—as suggesting that, using a 2-year reference, 40 to 50 percent of women reported having had a screening mammogram; a 1-year reference yielded 35 percent. She pointed out that there have been substantial gains in screening over the 5-year period for both African American and White women. Data among Hispanic women were based on a smaller sample and more subject to variability, but national data suggest improvements among this population as well.

In discussing mammography, Dr. Edwards acknowledged the work of Dr. Martin Brown and others in regard to data on mammography facilities. She noted the tremendous increase in the number of available mammography machines. Referring to her slides, she pointed to increases in incidence that are beginning to level off, and a small, but persistent increase in mammography. She questioned how to reconcile those two pieces of information and whether incidence data could be partitioned into two parts—a true increase for factors that may be unknown and another that could be attributed to breast screening. Dr. Edwards referred to a report published this year that attempted to look at several sets of data to answer this question.

Referring to a slide, Dr. Edwards described a conceptual model of observed or empirical incidence data partitioned into screen-detected versus nonscreen-detected cases. She mentioned the importance of considering assumptions, such as the lead or lag time for picking up asymptomatic cases that would ultimately become symptomatic. She pointed to the top line,

representing an increase in breast cancer screen rates observed empirically and suggested that there may be a decline once screening by mammography is introduced into the population. She pointed to the line depicting clinical, or symptomatic cases that have been detected and noted the effect of a transient shift in the proportion of clinically detected cases and the potential return to the steady-state or baseline figure. Dr. Edwards acknowledged the particular component of the curve as hypothetical, and probably not true because it does not take into account competing risk and death due to other causes. Hence, this is a hypothetical situation and it does not return back to baseline.

Dr. Edwards cited an estimate of the data from a January 1995 manuscript that partitioned the hypothetical incidence curve into two components. She pointed, on her next slide, to a smooth line representing the incidence curve if screening or technology had not been introduced. She next pointed to the top line, representing empirical observation and to a red figure depicting clinically detected, asymptomatic cases. She acknowledged not being able to provide a quantitative number regarding the attribution, but noted that screening is believed to have significantly contributed to the shorter-term increase in breast cancer incidence data. Dr. Edwards acknowledged that, while difficult to quantify—for example, at 50 percent, 25 percent, or two-thirds—it is consistent with data that a portion of the increase is due to screening.

Looking at treatment data, Dr. Edwards noted that screening does not have a potential impact on mortality rates unless there is an attendant improvement in treatment and unless screen-detected cases are treated. She pointed out data on adjuvant therapy and mentioned a number of patterns-of-care studies sponsored by the NCI and other organizations. She acknowledged the need to resort to modeling and noted the large issue of diffusion and access to care, on which she reported having little or no data, other than from a hypothetical standpoint, on diffusion, as well as some empirical data.

Dr. Edwards referred to a slide that combined information from a number of sources, including the CCOP evaluation, which collected data from 1984 through 1989 on a number of indicator cancer sites, including early-stage breast cancer. Information was also collected through SEER in 1990 and 1992, as well as from SEER control sites for the last 2-year period. Dr. Edwards pointed to summary figures by age and node status to illustrate changes in the percentage of patients receiving adjuvant treatment. She noted dramatic increases by year beginning in 1984 through 1989 for node-negative young women. During this period, a large proportion of node-positive women received adjuvant therapy, and dramatic increases in adjuvant therapy occurred among node-negative older women. She explained that data for older women were separated from that for node-positive women based on whether they received cytotoxic therapy or tamoxifen. Dr. Edwards noted some shifts in the pattern from level to variable over the time-frame for adjuvant chemotherapy; increases were apparent for the use of tamoxifen.

Dr. Edwards pointed out that while SEER data capture information on adjuvant therapy and radiotherapy, this information is incomplete and underreported, in part because of the large movement towards outpatient therapy. She reported having more confidence in the reported figures featured on the slide, since they were collected under special circumstances.

Dr. Edwards pointed to a modeling activity undertaken in the last several months that examined the benefits of adjuvant chemotherapy on mortality trends among younger women. She turned to stage II breast cancer, depicted in young women on the slide, pointing out that an improvement in survival of 5 to 10 percentage points could be expected, depending on the length of time from diagnosis. SEER and other data suggest that the use of adjuvant therapy for this subset of patients has increased from 20 percent in the mid-1970s to 80 percent or higher in the early 1980s. She reported that one-half of the women aged 30 to 39 are actually diagnosed with stage II, node-positive disease. Dr. Edwards noted that because not all women receive the appropriate therapy and the information has entered the population data gradually, the net result may be a 3- to 6-percentage-point increase over time in the population data. Based on a model developed to assess the impact of the cancer program, this could be interpreted as an 8 percent mortality reduction by 1988 across all women ages 30 to 39 for all stages.

Dr. Edwards acknowledged that while declines in mortality could be related to adjuvant therapy, this does not entirely explain the decline, especially in recent years. She pointed to the work of Drs. Robert Tyrone and Ken Chu, among others, on cohort effects using age pericohort models, both parametric and nonparametric. She characterized their work as being within the realm of analytic epidemiology and statistical models. She noted that recently published papers, as well as several in review, essentially say three things. First, based on cohort effects—year of birth, risk factors, and external factors—a decline in mortality should be seen among women aged 60 to 69 during the 1990s, and among those aged 70 to 79 in the decade between 2000 and 2010. An examination of the data, however, revealed declines among the older age groups, which suggests that there are effects that cannot be explained from the cohort data. While there is no certainty that medical intervention—screening or adjuvant therapy—are causes, these interventions represent one plausible explanation. Dr. Edwards stated that the dynamics of all the factors affecting empirical population data are not fully understood and bear further exploration.

Although some data exist on receptor status and other possible markers, Dr. Edwards reported that work is ongoing on databases and surveillance activities that will yield information on trends. Since, at present, most of the data are not population based, she noted that she would not discuss this subject in detail.

Dr. Edwards informed the Board that she and her colleagues have been taking an operations or systems approach to studying components of mammography delivery, such as the 1992 survey of over 1,000 facilities included in a national random sample. She mentioned an ongoing, in-depth study of 1,700 cases of abnormal screening exams from a group of 50 facilities, and note that several papers have been published that are currently being analyzed.

Displaying her final slide, Dr. Edwards recognized that the interpretation of national breast cancer trends will require a much broader view beyond SEER or national mortality data, and should include the system in which the data are generated. She mentioned both the establishment of the Surveillance Consortium for Breast Cancer and an RFA initiated to examine delivery and operations of mammography, which will be linked with both pathology information and facilities, and with research on biology of screen-detected and nonscreen-detected tumors. A number of SEER investigators and DOD breast cancer grantees have been included in meetings to share definitions and activities and increase compatibility in data sharing. Dr. Edwards also mentioned work beginning at the international level on breast cancer

screening databases to look at defining mammography operations, data interpretation, and meaning on the national level.

Dr. Edwards concluded by referring to her own personal commitment, relating that two staff members with whom she works are women with breast cancer who serve to remind her that behind every number is a woman. She thanked the women for their work at the NCI, and acknowledged their help along with the remainder of her staff, in preparing her presentation.

Questions and Answers

Dr. Rimer thanked Dr. Edwards for her excellent presentation and acknowledged the amount of work that was accomplished quickly. She requested a hard copy of Dr. Edwards' slides for Board members, since there is much to digest that should be examined over time.

Dr. Day asked Dr. Edwards to speculate on the advantage to women under age 50 receiving mammograms. Dr. Edwards replied that she had a recent discussion with her 40-year-old secretary who was diagnosed with breast cancer through an incidental mammogram. She declined to speculate on Dr. Day's question, and stated that it is difficult to know whether smaller tumors are detected through screening mammograms or those done because of women's breast disease or cancer concerns either because they are at high risk or symptomatic. She noted that in the 1992 mammography facility survey, over 50 percent did not distinguish between screen and diagnostic exams. SEER and Medicare data back to the late 1980s also do not distinguish women's motives for mammography.

Dr. Becker asked Dr. Edwards to clarify whether she had shown significant incidence among all age groups of use of mammography. Dr. Edwards stated that she had, and Dr. Becker asked if Dr. Edwards believes that the incidence increase in the number of mammograms in 40- to 50-year-old is based on high risk or preexisting breast disease, or on a trend toward mammography at all ages. He suggested that there are not that many women with lesions or with conditions alerting them sufficiently to the need for mammograms to account for the incidence increase. Dr. Edwards replied that there has been a movement to educate and instruct both women and physicians to utilize mammography. She reiterated that the trends among young women under age 50 reveal an increase in localized disease and a decline in regional disease and added that those lines are not as prominent as in women over 50. She noted that patterns among the youngest women and their interpretation are different. She acknowledged the need to pay more attention to the level of the trend and the relative shape of stage-specific trends.

Dr. Maureen Wilson asked about the effort to determine why patients come in for mammograms. She wondered if the following questions were asked: "Is this time for your mammogram, or do you feel a lump?", or "Did you talk with a best friend who had a positive mammogram?" "How long has it been since you have had a mammogram?" She suggested the importance and ease of obtaining this information. Dr. Edwards remarked that CDC collects limited data on behavioral risk factors from every State. She noted that Dr. Rimer has been part of a mammography consortium group in six geographic sites that includes intervention and control groups in which screening mammography has been promoted. Pre- and postsurveys have been administered, as has a survey to determine whether such efforts

have increased the use of the Medicare benefit. She noted that one of the usual responses is "My doctor did not tell me." She acknowledged that there are a variety of routes to having a mammogram, which are shifting over time.

Dr. Rimer noted the need—in analyzing the impact of mammography on mortality rates—to distinguish between women who have routine mammograms and those having their first mammogram in the last year. She noted that about 40 percent of women age 50 and over have never had a mammogram, and that 30 to 40 percent of women nationwide have never had a mammogram.

Dr. Correa asked Dr. Edwards about changes in modalities of treatment over the years. Dr. Edwards acknowledged having noted changes, per the data she presented on adjuvant therapy. Dr. Correa then asked about changes in types of surgery, and Dr. Edwards noted increases in more conservative therapy, especially dramatic—more than 40 percent— among those with in situ disease. She further acknowledged the trend from more extensive to more limited surgery without radiotherapy; she cautioned that the trends show high regional variability, as shown in the American College of Surgeons' patient-care studies, as well as in SEER data.

Dr. Rimer referred to a "stat byte" in the *JNCI*, which showed regional distribution. Dr. Edwards noted that she had omitted that reference from her presentation because while it covered modality changes and patterns of care, the two are presumably equivalent and would not have had an impact on the mortality data.

Dr. Sondik asked if there had been any analytic work relating these factors to mortality change. Dr. Edwards replied that there is a fair amount in the epidemiology literature on classic risk factors, as well as in the national census data. She noted controversy over whether classic risk factors can predict or explain the rates and suggested that they may explain only 50 percent. Dr. Sondik clarified that he referred specifically to the change in mortality versus the change in mammography and the change in specific risk factors, such as the work of Drs. Tyrone and Chu on change in frequency. Dr. Edwards stated that this would be the group's next assignment, and that others could be encouraged to undertake such work as well.

Dr. Sondik noted the importance of Dr. Edward's data and slides and suggested writing them more formally so that they can be incorporated into the literature. He stated that this would help the reanalysis of trials, and emphasized the critical importance of getting as much information out as possible.

Dr. Rimer again thanked Dr. Edwards and invited Dr. Peter Greenwald to introduce the next speaker, Dr. Thomas Glynn. Dr. Rimer noted the importance of tobacco control in light of the negative overall findings of the COMMIT Trial and the particular difficulty of reaching heavy smokers.

XIV. IMPLICATIONS OF COMMIT FOR TOBACCO CONTROL— DR. THOMAS GLYNN

Dr. Glynn began by clarifying the actual title of his talk, Implications of the COMMIT Trial in Related Tobacco Research for Tobacco Control in the U.S., and explained that he would present his material in the context of the NCI's overall tobacco control program. He acknowledged the work of the subcommittee chaired by Ms. Marlene Malek, where some of these issues were discussed.

Dr. Glynn presented an overview of his presentation, which would include a brief status review of current trends in tobacco use, an overview and results of the COMMIT Trial, and implications of the COMMIT Trial for future action, both within and outside the NCI.

Characterizing his next slide as "upbeat," Dr. Glynn pointed out that lung cancer among males of all races began to drop from 1973 to 1989. He noted that these are the first fruits of the tobacco control effort and that these men probably stopped smoking 20 years ago, sometime between the Surgeon General's Report of 1964 and 1975. Declines in lung cancer rates have been seen primarily among 45- to 54-year-old White males; while limited, such success may continue if control efforts continue or accelerate Among women, Dr. Glynn noted the unfortunate straight line expected to continue rising until at least 2008 or 2010, when women who stopped smoking during the 1980s and 1990s will show similar declines. He reiterated that, for now, the rate for women is going to continue rising.

Dr. Glynn explained that his next few slides contained data already known by members; he noted that the 434,000 smoking-related deaths per year in the United States translate to 1,200 per day, or 50 every hour. He noted that tobacco kills more Americans each year than alcohol, cocaine, heroin, suicide, car accidents, fires, and AIDS combined.

Turning to trends in smoking prevalence, Dr. Glynn pointed to a great decline among men since 1955—53 percent to about 28 percent in 1992. This trend is holding steady. The prevalence among women in 1955 was 24 percent, with a parabola effect though the 1960s and early 1970s, and a decline to about 23.5 percent as the 1970s ended. Though current prevalence rates reflect where women were 40 years ago, the decline is continuing.

Dr. Glynn reported that in 1989, Dr. John Pierce, of the University of California, San Diego, tried to project where we would be in terms of smoking prevalence in the year 2000 and predicted that males would be at about 20 percent and females about 23 percent, for an overall rate of about 21 percent. These estimates continue to appear to be quite accurate, Dr. Glynn concluded.

Among youths, according to the high school senior survey conducted by the National Institute on Drug Abuse since 1976, there has been no decline in smoking rates among high school seniors in the past 10 years, which remain at about 20 percent. He presented everyday smoking rates, showing crossover back and forth among males and females and equality among high school seniors. Among high school dropouts, rates are in the 65 to 70 percent range. The smoking rate among Black youths has sharply declined, as reported in the popular media and the *JNCI*; whereas, rates among White youths have remained essentially the same.

Dr. Glynn acknowledged Dr. Sherry Mills, of the DCPC, who has conducted focus groups to gather qualitative data to explore these differences, and noted that extramural investigators are being encouraged to apply for grants to look at this issue in more detail. He expressed hope that the declines among Black youths will continue.

Dr. Glynn emphasized that youth need to be "hit very hard," since 90 percent of smokers begin by the age of 20 and about 3,000 youths must be recruited to smoke every day if current levels of tobacco use are to be maintained. Of those 3,000, 23 will be murdered, 30 will die in traffic accidents, and nearly 750 will die from a tobacco-related disease. He suggested that efforts to reach youth in the past few years have not been as successful as hoped.

Mentioning smokeless tobacco, Dr. Glynn showed a slide picturing children under age 18 at Yankee Stadium, sitting on cushions distributed by Skoal Bandit, captioned "Take a pouch instead of a puff." He stressed the need to target both smoking and smokeless tobacco use.

Turning to global tobacco-related deaths, Dr. Glynn pointed out that deaths worldwide are expected to exceed 3 million per year in the 1990s and 10 million per year by the year 2020. The World Health Organization estimates that 1 of every 10 million people alive today, or 500 million, will die from a tobacco-related disease.

Dr. Glynn explained that in the early 1980s, when Drs. Peter Greenwald and Joe Cullen came to the NCI, a gradual segue was occurring from research on the carcinogenicity of tobacco to approaches for helping people either not start or stop smoking if they wished to do so. The smoking tobacco and cancer program focused initially on 49 intervention trials emphasizing eight primary groups or approaches: adolescents, physicians and dentists, media, self-help strategies, Black Americans, Hispanic Americans, women, and smokeless tobacco users. Groups met many times through the 1980s to try to determine what to do about tobacco use in these eight areas. Dr. Glynn stated that the COMMIT Trials developed from those efforts.

Dr. Glynn noted that the premise of this community intervention trial for smoking cessation resulted from studying the NCI trials and studies supported by other agencies, testing them in individual communities, and trying to put all that was learned into a single community. He acknowledged the hundreds of NCI investigators—especially Dr. Terry Pechacek, who was a prime mover in the late 1980s, along with Drs. Joe Cullen, Bill Lynn, who took over the Trial, and Dr. Sylvan Green, who helped enormously in the analysis.

Dr. Glynn briefly presented the design features, explaining that sample size of 11 matched pairs of communities, or 22 communities across North America, were included. He noted that the primary endpoint involved matched-pair differences in heavy-smoker-cohort quit rates. Heavy smokers were defined as those smoking 25 or more cigarettes per day. The secondary endpoint involved differences in light- to moderate-smoker-cohort quit rates among those smoking under 25 cigarettes per day. The intervention involved 58 mandated activities, such as physician delivery of nonsmoking advice to patients and worksite interventions, over a 4-year period. The intervention was performed as a contract to enable mandated interventions.

The next slide depicted an editorial accompanying the articles summarizing COMMIT in the February *American Journal of Public Health.* He noted that the editor characterized COMMIT as a model of meticulous design, focused intervention, and careful analysis. Dr. Glynn explained that he included the slide to illustrate that the data are believable, and characterized the Trial as conservative in design and conclusions.

Dr. Glynn explained that while the Trial had some bicoastal bias, it was well distributed geographically, and included two sites in Canada. The Trial hypothesized that implementation of a defined intervention protocol (the 58 mandated activities)—delivered through multiple community groups and organizations using limited external resources—would increase smoking cessation among adult heavy, moderate, and light smokers, and would reduce smoking prevalence across entire communities. Dr. Glynn noted that two cohorts were followed throughout the trial; pre- and posttests were administered to measure smoking prevalence. Planning for the Trial took place from 1986 to 1988; field trials occurred from 1988 to 1992; and surveys and analyses were completed and reported in the past 2 years.

In reporting results, Dr. Glynn recommended looking at the numbers. He explained that among heavy smokers, 18 percent in the intervention communities stopped smoking during the 4-year intervention trial. In the comparison communities, about 18.7 percent stopped smoking, a nonsignificant difference, which suggests that COMMIT did not have an effect on heavy smokers in the intervention communities. Among light-to-moderate smokers, 30.6 percent in the intervention communities stopped smoking and 27.5 percent in the comparison communities stopped—a significant difference. The data suggest that COMMIT had a significant difference among light to moderate smokers, but not among heavy smokers. One explanation was that COMMIT did not keep up with secular trends among heavy smokers, but did outpace secular trends in light to moderate smokers.

In reviewing the conclusions, Dr. Glynn reiterated that among heavy smokers, there was a nearly identical mean quit rate in both the intervention and comparison communities; among light to moderate smokers, there was a statistically significant mean intervention effect on quit rates in the intervention communities of about 3 percent.

Little difference between males and females has surfaced in data analyzed to date. Among light to moderate smokers, the less-educated subgroup appeared more responsive to the intervention than college-educated smokers. Dr. Glynn noted that this finding was a surprise that proved useful, in identifying the current need to target the lower-educated smoker. He pointed out that smokers in the intervention communities had greater perceived exposure to the smoking-control activities, suggesting that the intervention was delivered and that recipients were aware and involved.

Dr. Glynn reiterated that there was no intervention effect on prevalence among heavy smokers and only a moderate effect among light to moderate smokers. Although the impact of the community intervention upon light to moderate smokers was modest, Dr. Glynn emphasized its importance from a public health perspective. He noted that a 3 percent quit rate among the 30 to 35 million light to moderate smokers in the Unites States would still yield nearly 1 million new nonsmokers per year, and that would result in a positive effect on morbidity and mortality 20 years from now.

Dr. Glynn emphasized that while the lack of significant intervention effect on heavy smokers is disappointing, future efforts employing additional strategies not included in COMMIT should be incorporated and rigorously evaluated. He observed that at least four lessons—and probably many more—have been learned from COMMIT. First, addiction must be addressed among heavy smokers through more focused quitting assistance. Second, community-based strategies can influence light to moderate smokers to quit and remain smoke free, defined as 6 continuous months of nonsmoking. Third, both cessation and prevention should share the focus of tobacco control efforts. Finally, future tobacco control efforts should incorporate emerging strategies, such as policy changes and economic disincentives. Dr. Glynn added that COMMIT focused on youth and prevention to only a small extent, and further prevention foci among youth is needed.

Dr. Glynn turned to the implications of the COMMIT Trial and recommendations for related tobacco-control research in the United States. He explained that he would focus first on immediate strategies, followed by implications for the current ASSIST demonstration project, research needs, and the gap between research findings and their implementation.

Regarding immediate strategies, Dr. Glynn suggested that the NCI, communities, States, and other organizations can take appropriate action and have data available to back them up. Physicians and nurses can intervene with their patients, and schools can include smoking prevention in their curricula. Since 90 percent of former smokers report stopping on their own, more self-help materials should be made available.

Dr. Glynn suggested that media campaigns and tobacco tax increases are effective, as demonstrated in both California and Massachusetts. Cessation clinics and programs, especially more intense stepped-care approaches, will have an effect, but more need to be available. Advertising restrictions can have some effect, as can legal challenges, such as the FDA's Dr. Kessler's current efforts to regulate the tobacco industry. Worksite interventions can also be effective, as can pharmacological interventions. Nicotine gum and patches are currently available, and a nicotine nasal spray will soon be available. Cigarette warning labels have some small effect, as do smoking restrictions in public places. Youth-access restrictions, agricultural policy changes, and clean-air laws also can be implemented. The actions of States and communities are key, as these are not necessarily NCI activities.

Regarding implications for the current 17-State ASSIST demonstration project, Dr. Glynn noted the joint efforts of the NCI and the American Cancer Society. He explained that the project is using what has been learned from a wide variety of trials, including COMMIT. He suggested that COMMIT can contribute extensive experience in community mobilization and intervention implementation, rigorous data on the impact of the COMMIT intervention on smoking, and lessons about what should and should not be done. The need to emphasize policy intervention, which was not emphasized in the COMMIT Trial, can be reinforced from the California-Massachusetts experience. Extensive data that are currently under analysis and will be reported over the next couple of years may be helpful to ASSIST. Dr. Glynn underscored the need to emphasize youth interventions, which COMMIT did not.

Dr. Glynn turned to his third focus, research needs, which he noted had been recently discussed in subcommittee, where three areas of emphasis—based on the COMMIT Trial experience—were developed. The first is prevention of tobacco use by children and youth;

second, nicotine addiction treatment and behavioral and biobehavioral mechanisms (now under investigation by the National Institute on Drug Abuse) and the best uses of pharmacological interventions; and third, public policy research. He posed the following examples of public policy research questions: Does reimbursing physicians and nurses for smoking intervention increase the number of interventions? What do tax increases mean?

Regarding his fourth focus—the gap between tobacco-control research findings and their implementation—Dr. Glynn suggested that lines of responsibility should be defined and resources allocated. He lamented the fact that some research with useful endpoints often does not get used. He noted that Dr. Broder dealt with this dilemma during his tenure in talking about translational research—moving from the laboratory to the bedside—and the need to move research from trials to implementation in communities. Dr. Glynn recommended increased emphasis on applied research.

In conclusion, Dr. Glynn expressed his thoughts about how to measure progress in tobacco use beyond the strict data he presented. Noting decreased sales as one measure of tobacco control success, he quoted from a *New York Times* business section article published 2 weeks prior, entitled "A low point for RJR Nabisco." He read: "RJR Nabisco hit a 52-week low after it received disappointing earnings, which is only the latest bit of bad news as U.S. tobacco sales fell, sales were weak abroad, and regulatory liabilities loomed." Dr. Glynn's final slide featured a picture from the United Kingdom suggesting that harder work is needed.

Questions and Answers

Dr. Rimer acknowledged both Dr. Edwards and Dr. Glynn and expressed appreciation for their efforts to interpret the meaning of the trials. She noted the importance of looking beyond the bottom line to results not reported in the popular media.

Dr. Rimer called upon Dr. Paul Calabresi, who noted that smoking cessation is not an all-or-none phenomenon. He asked if Dr. Glynn's data showed that heavy smokers became light smokers, or focused only on complete cessation. Dr. Glynn responded that data showed only complete cessation, and noted the value of being reminded of the importance of reduction in smoking. He added that the reduction data have not been completely analyzed. A small drop in the average number of cigarettes per person was seen. Dr. Glynn suggested that the reduction data could be extracted. Dr. Calabresi pointed out that a shift in reduction, with light smokers becoming near nonsmokers, would be a valuable finding. Dr. Glynn noted the continuing debate, referred to a meeting 2 weeks prior on harm reduction and to the question of whether to focus solely on total cessation or on cutting down as well. He added that the field has gone in the general direction of total cessation, with acceptance of cutting back if that is the only alternative.

Dr. Correa called COMMIT and ASSIST two valuable major studies that show the difficulty of combating the smoking problem. He recommended that they be continued and that a map be examined in the after-project periods. He noted that the American Southwest has some of the highest lung cancer rates. Dr. Rimer commented that the information presented to the subcommittee will be brought to the July workshop on the future direction of tobacco and behavioral-screening research to which members of the Board are invited. She noted the death toll of smoking and the need to not turn away.

Dr. Chan suggested that there is a great need for behavioral research in the areas of prevention and advertising, and into ways to influence the tobacco industry. He referred to hearing of tobacco industry attempts to remove warning labels.

Dr. Wilson questioned projections of COMMIT's effectiveness and asked whether Dr. Glynn is disappointed with the 1995 year-end numbers. Answering Dr. Wilson's second question first, Dr. Glynn stated that he is not discouraged, but is disappointed in the heavy smoker results, yet is encouraged by the significance and implications for public health of the light-to-moderate effect.

In response to the first question, there had been a 10 percent difference in expected quit rates, with a 15 percent quit rate expected in the comparison communities and 25 percent quit rate expected in the intervention communities for heavy smokers. Secular trends were better than expected, with nearly a 19 percent quit rate rather than 15 percent.

Dr. Glynn confirmed this point about secular trends and reiterated that 18 percent of heavy smokers and 27 to 30 percent of light smokers quit during the 4-year study.

Dr. Kenneth Olden suggested that, given the disparities in socioeconomic status among Black and White youth, it would be useful to have some understanding of the economics and role of tobacco pricing. Dr. Sondik noted, and Dr. Glynn corroborated, that differences are striking, but comparing the percentages of Black and White smokers in their 20s yields smaller differences. Dr. Sondik wondered if something happens in the late teens or early 20s. Dr. Glynn referred to Dr. Sherry Mills' wish to conduct focus groups with older youth and young adults. Dr. Sondik noted the Healthy People Tobacco Reviews and remarked on the complexity and dynamism of the smoking issue.

Dr. Vaitkevicius noted that the impact on Black youth has been seen primarily among high school seniors or graduates, not among dropouts. He asked to what extent the dropout rate differs among African American and White students, which he speculated might explain the discrepancy. Dr. Glynn replied that while differences in dropout rates might be important, they are not enough to explain the differences. He referred to the data on high school seniors that were confirmed by the National Health Interview Survey. Dr. Vaitkevicius asked that Dr. Glynn make available good data from meta-analysis on school program effectiveness. Dr. Glynn agreed to do so.

In response to a question by Dr. Day, Dr. Glynn stated that the COMMIT trial used a sample, while the high school senior study relied on self-reported data.

Ms. Malek questioned why California has been so successful. Dr. Glynn cited several reasons, first noting availability of funds, and the 25-cent tax passed in 1989, of which 5 cents is earmarked for tobacco control research. He mentioned staff dedication and energy, and heavy prime-time media coverage, as well as community outreach. He noted the current debate over additional tax increases. Dr. Correa noted that the youth quit rate is not as good, and Dr. Glynn agreed that efforts, even in California, have had less impact on youth.

Dr. Dickersin pointed out that focus groups have discovered that Black teenagers consider smoking "White," which implies the element of peer pressure. Praising Dr. Glynn's

slides, she wondered if showing Dr. Glynn's first slides in a high school probability and statistics course might lead to reverse peer pressure on White youth.

Dr. Wilson asked if there is a higher probability that a White female smoker would be able to quit than a Black female. Dr. Glynn noted little difference in Black and White females' success in quitting. Dr. Rimer agreed, and referred to studies in which Black females were more able to quit.

Dr. Chan asked about data from Canada, where cigarette taxes are higher. Dr. Glynn responded that in some provinces, cigarette taxes have led to prices as high as $6.00 to $7.00 a pack, noting that sharp declines in smoking have been seen in many groups, including youth. He mentioned rollbacks because of U.S. cigarettes crossing the border, and suggested that youth in the case of such high prices, would not be able to afford cigarettes.

Dr. Rimer referred to research by Dr. Ken Warner, Professor of Economics, University of Michigan, and others on the impact of price increases on smoking and effects upon initiation. She called upon Dr. Calabresi for a final question. He requested copies of Dr. Glynn's slides and a hard copy of his presentation. Acknowledging the quality of his presentation, Dr. Rimer asked that Dr. Glynn make them available. Dr. Rimer closed by thanking the NCI presenters and the Board, acknowledging with appreciation their time and effort.

XV. ADJOURNMENT—DR. BARBARA RIMER

In closing, Dr. Rimer thanked the Board members and NCI staff for their participation and emphasized that Dr. Broder and Dr. Chabner will be missed and thanked them for all their work on the National Cancer Panel. There being no further business, Dr. Rimer adjourned the 94th National Cancer Advisory Board meeting at 1:05 p.m.

August 7, 1995
Date

Barbara Rimer
Dr. Barbara Rimer, Chairperson