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

Summary of Meeting
September 12-13, 1995

Building 1, Wilson Hall
National Institutes of Health
Bethesda, Maryland

Department of Health and Human Services
Public Health Service
National Institutes of Health
National Cancer Institute
National Cancer Advisory Board

Summary of Meeting[1]
September 12-13, 1995

The National Cancer Advisory Board (NCAB) convened for its 95th regular meeting at 8:00 a.m., September 12, 1995, in Building 1, Wilson Hall, 3rd Floor, National Institutes of Health (NIH).

NCAB Members

Dr. Barbara K. Rimer (Chairperson)
Dr. Frederick F. Becker
Dr. J. Michael Bishop
Dr. Richard J. Boxer (absent)
Mrs. Zora K. Brown (absent)
Dr. Kenneth K. Chan
Dr. Pelayo Correa
Dr. Robert W. Day
Dr. Kay Dickersin (absent)
Mrs. Barbara P. Gimbel
Dr. Alfred L. Goldson
Mrs. Marlene A. Malek
Ms. Deborah K. Mayer
Dr. Sydney Salmon (absent)
Dr. Philip S. Schein
Dr. Ellen V. Sigal
Dr. Vainutis K. Vaitkevicius
Dr. Charles B. Wilson

President's Cancer Panel

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

Ex Officio or Alternate Ex Officio NCAB Members

Dr. Robert Delap, FDA
Dr. Marilyn A. Fingerhut, NIOSH (absent)
Captain Bimal C. Ghosh, DOD
Ms. Rachel Levinson, OSTP
Dr. Hugh W. McKinnon, EPA
Dr. Lakisma C. Mishra, CPSC
Dr. Kenneth Olden, NIEHS
Dr. Raymond L. Sphar, DVA
Dr. P. C. Srivastava, DOE
Dr. Ralph Yodaiken, DOL (absent)

Members, Executive Committee, National Cancer Institute, NIH

Dr. Richard Klausner, Director, National Cancer Institute
Dr. Alan S. Rabson, Deputy Director, National Cancer Institute
Dr. Edward Sondik, Associate Director for Strategic Planning, National Cancer Institute
Dr. Jerry Rice, Acting Director, Division of Cancer Etiology
Mr. Philip D. Amoruso, Associate Director for Extramural Administrative Management
Ms. Maryann Guerra, Associate Director for Intramural Administrative Management
Dr. Marvin R. Kalt, Director, Division of Extramural Activities
Dr. Robert E. Wittes, Acting Director, Division of Cancer Treatment
Dr. Peter Greenwald, Director, Division of Cancer Prevention and Control
Mrs. Iris Schneider, Executive Secretary, Asst. Director for Program Operations and Planning

[1] For the record, it is noted that members absented themselves from the meeting when discussing applications (a) from their respective institutions or (b) in which conflict of interest might occur. This procedure does not apply to en bloc actions.

Liaison Representatives

Dr. John Currie, American Association for Cancer Education, Inc.
Dr. Edwin A. Mirand, Association of American Cancer Institutes
Dr. Marc E. Lippmann, American Association for Cancer Research
Dr. Robert Martuza, American Association of Neurological Surgeons
Ms. Kerrie B. Wilson, American Cancer Society
Dr. John Laszlo, American Cancer Society
Dr. Robert W. Frelick, Association of Community Cancer Centers
Dr. Stanley Zinberg, American College of Obstetricians and Gynecologists
Dr. Bernard Levin, American Gastroenterological Association
Dr. Edward P. Gelmann, American Society of Clinical Oncology, Inc.
Dr. Stanley Order, American Society of Therapeutic Radiologists
Mr. James Kitterman, Candlelighters Childhood Cancer Foundation
Ms. Jean Whalen, Leukemia Society of America, Inc.
Dr. Margaret Foti, National Coalition for Cancer Research
Ms. Dorothy J. Lamont, National Cancer Institute of Canada
Dr. J. David Beatty, National Cancer Institute of Canada
Dr. Tracy Walton, National Medical Association
Dr. Eve I. Barak, National Science Foundation
Ms. Mary Baroni, Oncology Nursing Society
Ms. Pearl Moore, Oncology Nursing Society
Dr. Jeffrey Norton, The Society of Surgical Oncology, Inc.
Dr. Marston W. Linehan, The Society of Urologic Oncology

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

Dr. Barbara Rimer called to order the 95th meeting of the National Cancer Advisory Board (NCAB). She acknowledged Dr. Richard Klausner, the new Director of the National Cancer Institute (NCI), who would later address the Board. She announced the newest member of the Board, Dr. Richard Boxer, a clinical urologist from Milwaukee, Wisconsin, who was unable to attend the meeting, but had expressed his particular interest in trans-NIH initiatives in prostate cancer. Dr. Boxer replaced Dr. Paul Calabresi, who recently became a member of the President's Cancer Panel (PCP).

Dr. Rimer introduced guests representing a number of respected organizations and societies 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 asked for a motion on the minutes from the May meeting, which the Board unanimously approved without change. She asked the Board to inform her of any conflicts with the meeting dates set for 1995, 1996, and 1997, noting that the dates are scheduled as 3-day meetings, but are intended to be 2-day meetings when possible, with Monday evenings reserved for committee meetings. Dr. Rimer emphasized the importance of being present for the upcoming meetings, as the NCI will be undergoing a process of self-examination and strategic planning.

Dr. Rimer reminded the Board to check outside the door for messages between sessions. She noted that four members were absent from the meeting, making everyone's presence essential for a quorum, particularly at the closed session that was scheduled to begin at 3:15 p.m.

Dr. Rimer announced her intent to keep the meeting on schedule, and requested that all presenters confine their remarks to the time allotted. She also requested that Board members inform Dr. Kalt during the coffee break of any grant applications they wished to discuss in the closed session. She noted that there was a full schedule of committee meetings and reminded the Board that the meeting was being televised on closed-circuit television. She emphasized the importance of speakers' use of their microphones for purposes of transcribing the minutes.

As an overview, she informed the Board that the meeting would include an update on the PCP by Dr. Harold Freeman, presentations by Dr. Klausner on both his vision of the National Cancer Plan and the Von Hippel-Lindau (VHL) gene, presentations from two cancer education organizations, an update on legislative affairs, and an update on a behavioral research conference held during the summer. She mentioned a shift in the schedule toward fewer presentations and longer discussion times to allow the Board to focus in depth on presented issues.

Dr. Rimer introduced Dr. Freeman, Chairman of the PCP, to update the Board on the Panel's latest activities.

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

Dr. Freeman thanked Dr. Rimer and joined her and the Board in welcoming Dr. Klausner as Director of the NCI.

Dr. Freeman reported that the PCP held a meeting on June 6th on Acquired Immuno Deficiency Syndrome (AIDS)-associated neoplasms, in conjunction with an NCI-sponsored workshop on Kaposi's sarcoma. The meeting intended to explore the impact of AIDS on the mission and goals of the National Cancer Program, and focused on malignancies that impact the duration and quality of life of Human Immunodeficiency Virus (HIV)-infected individuals; advances and opportunities in treatment; and epidemiology, clinical aspects, and psychosocial complications.

Dr. Freeman mentioned the increased risks for HIV-positive individuals to develop certain malignancies: Kaposi's sarcoma, 40,000-fold increased risk; systemic non-Hodgkin's lymphoma, 191-fold; and primary central nervous system lymphoma, 3,900-fold. (The risk for invasive cervical carcinoma remains undetermined.) He acknowledged progress in palliation of symptoms and improved patient functioning, but stated that no cure has been found for Kaposi's sarcoma, a malignancy that is often complicated by the herpes virus. Similarly, he mentioned that anogenital malignancies may be complicated by the human papilloma virus. Dr. Freeman named several chemotherapeutic agents being studied, including tumor necrosis factor inhibitors, angiogenesis inhibitors, hormonal agents, cytokines, TAT inhibitors, and retinoids.

With respect to HIV-positive children, Dr. Freeman noted that cancer is less often the AIDS-identifying event than among adults, which may reflect the accelerated course of AIDS among the pediatric population. Burkitt's lymphoma, immunoblastic lymphoma, and primary central nervous system malignancies are more common among AIDS-infected children than among the general population.

Dr. Freeman predicted that the prolonged survival of HIV-positive individuals will eventually lead to an increase in the number and types of cancers associated with HIV will, whose emergence may be detected with greater accuracy by the Multi-State AIDS/Cancer Match Registry, developed by the NCI.

Dr. Freeman informed the Board of several Panel recommendations, including one that research on AIDS-related malignancies focus attention on treatment of the underlying HIV disease. He pointed out that this endeavor may require special training of AIDS oncologists who can focus on clinically relevant endpoints in AIDS-associated malignancies, therapeutic interventions in HIV-infected populations, and enhanced coordination of clinical trials to maximize use of established registries and tissue banks.

Other recommendations include improvement of screening, inclusion of viral agents in studying anogenital cancers, and efforts by NCI both to balance intra- and extramural efforts and to coordinate efforts with the Office of AIDS Research and the AIDS Clinical Trials Group.

The PCP held another meeting on July 20th to hear from experts in the field about progress and challenges in leukemia. Dr. Freeman explained that tremendous progress has been made since the 1940s, when leukemia was almost always fatal and clinical intervention was deemed the least promising of treatment options. He pointed out the fact that therapy-related leukemia can be a complication of the use of cytotoxic drugs or radiation for treatment of other cancers or immunological disorders among 5 to 15 percent of patients.

Dr. Freeman elaborated on the progress in treating leukemia, which began with the use of chemotherapeutic drugs in the 1950s and improved through gradual refinement of their use, as well as combination with cytokines. He praised the courage and optimism of investigators who challenged prevailing medical practice to test innovative therapeutic options for a disease that affects only 7 percent of the population, but remains a leading cause of cancer deaths.

Dr. Freeman mentioned that all trans retinoic acid has been found to induce remissions in adults with acute promyelocytic leukemias and was recently recommended by the Food and Drug Administration (FDA) for relapsed patients.

He asserted the continuing need for biological and chemotherapeutic discoveries, and expressed the fear of researchers that their efforts at innovation will be stymied by restrictions in federal funding for drug development, translational research, and clinical trials. The Panel is also concerned that managed care will increasingly limit access to investigative clinical trials; this lack of support may ultimately lead to suboptimal treatment, since improved therapies cannot be tested. Dr. Freeman opined that managed care poses one of the greatest threats ever to the mission of the National Cancer Program.

Dr. Freeman suggested that the cancer research community focus increased efforts on educating the public, patients, insurers, physicians, and especially legislators on the value of supporting clinical research. He proposed reviewing the process of disseminating results of clinical research and examining the methods of communication, which would be a topic of discussion at the next PCP meeting on "The Information Superhighway: What Does It Mean for Cancer?"

Dr. Freeman also recommended coordinating efforts of professional societies, academic institutions, and federal policymakers to ensure appropriate minimum standards of care as guidelines for insurance support of clinical trials. Noting that the NCI cannot handle this task alone, Dr. Freeman advocated forging a public/private partnership to develop incentives for providers, payers, and patients to participate in clinical research.

Dr. Freeman informed the Board that the Panel sent a letter to President Clinton apprising him of their concerns that medical progress against cancer—particularly research progress—will be stunted by the effects of two developing trends: massive cuts in federal funding for training and research (especially translational research), as well as potential cuts in Medicare and Medicaid; and, on the other side, the movement towards managed care, which emphasizes cost containment at the expense of research, teaching, and high-quality care.

Dr. Rimer thanked Dr. Freeman for his presentation and noted that the Board would later address some of the issues he raised regarding managed care. She introduced Dr. Klausner, who was appointed by President Clinton in August, and shared his background with

the Board. Dr. Klausner, she said, received his undergraduate training at Yale University and his medical training at Duke University, where he wrote a successful medical textbook as a student. He did a residency and fellowship at Massachusetts General Hospital and came to the NIH in 1979 as an intramural researcher, where he was highly successful. In 1984, Dr. Klausner became chief of the Cell Biology and Metabolism Branch in the National Institute of Child Health and Human Development, where he made scientific strides in multiple areas of cell biology.

Dr. Rimer mentioned Dr. Klausner's authorship of several books and more than 250 papers. He was elected to the National Academy of Sciences in 1993, has held numerous journal editorships, and served as past president of the American Society for Clinical Investigation. Dr. Rimer noted that Dr. Klausner continues to be a science director in his own lab, and since being named Director of NCI, has already made significant changes. She expressed her pleasure that Dr. Klausner immediately sought to establish a close relationship with the Board, representing a new direction and important step in collaboration to meet the goals of the National Cancer Plan.

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

Dr. Klausner stated that for the past month, since starting his new position, he has spent an enormous amount of time meeting with people from many of the communities that affect and are affected by the National Cancer Plan and the National Cancer Institute, articulating his vision for the NCI and listening to their ideas. He said that it has been encouraging and moving for him to learn of the great desire on the part of virtually everyone to contribute to the revitalization of the National Cancer Institute.

Dr. Klausner explained that he planned to do three things during his remarks: describe the major principles that he sees as guiding the NCI; report on existing and proposed structures to enact those principles; and describe the activities that will be required for those structures to work.

Before beginning, Dr. Klausner acknowledged the steady hand and calm determination with which Dr. Edward Sondik has guided the NCI through its recent transition, providing leadership and stability. Dr. Klausner thanked Dr. Sondik for the grace and openness of his welcome. Dr. Klausner turned his attention to describing the status of the intramural research program and responding to some of the issues raised by the report on intramural research from the Ad Hoc Working Group on the NCI Intramural Program chaired by Drs. Michael Bishop and Paul Calabresi (also referred to as the Bishop-Calabresi report).

To introduce the first principle guiding the NCI, Dr. Klausner stated that the essential task for the leader of the Institute is to clearly formulate and articulate the Institute's goals and how to achieve them. This requires three things, he said: first, a clear and consistent vision of priorities, principles, and processes; second, the assumption of a proactive approach instead of a crisis-oriented, defensive approach; and third, a planning process that is open to many voices and sources of expertise in the cancer community and rooted firmly in the recognition of scientific opportunity and areas of need. He added that the planning process must integrate long-, mid-, and short-term issues and align itself with a clear and rational way of defining,

presenting, and analyzing the budget. Dr. Klausner noted that the budget is the sole property of the entire Institute and not a collection of private reserves or entitlements.

A second principle, Dr. Klausner continued, is that the NCI needs to be well integrated into the many communities that it serves. Because the Institute must be open in attitude and structure, he said, it needs advisory processes that are actively engaged in both critique and planning and truly incorporated into the life of the institution.

Institutionally, Dr. Klausner stated, the NCI must reform itself by becoming a meritocracy, relying on a system and process of accountability that allows the pursuit of excellence in terms of achievements and not simply promises. This system of accountability, he continued, should be fair and clearly articulated, and it should include rewards for achievement.

As an institution of science, Dr. Klausner said, the NCI's structures and processes must serve science, both intramurally and extramurally, and not the other way around. He suggested that this is a good time to confront the tendency of all large institutions toward bureaucratization. What the NCI can and cannot do, he argued, is limited not so much by regulations and laws as by the will and imagination of its leadership and their ability to ensure that it functions in a way consistent with its goals and purpose.

An institution of science, Dr. Klausner continued, must be modeled on the habits and values of science, including openness to individual contributions from all levels of the institution and from all communities and perspectives. He added that decisions must appeal to evidence, not to authority. This, he stated, is what distinguishes a scientific institution from a political or religious one.

Dr. Klausner turned his attention to recent changes within the NCI, reminding the Board that behind organizational charts there are always individuals. He said he is pleased to report the extraordinary enthusiasm of individuals throughout the community who have agreed to come to serve the Institute. His first appointment, Dr. Klausner explained, was Dr. Alan Rabson as Deputy Director. The response to this appointment, he noted, has shown the universal respect and admiration that the NCI and all of its communities have for Dr. Rabson, who has been described as a model for the type of person who should be running the Institute. Dr. Klausner thanked Dr. Rabson for his role as a source of knowledge and wisdom.

Dr. Klausner presented an overview of the NCI's reorganization into seven Divisions, of which two and one-half are intramural Divisions. He observed that many have felt for a long time that the responsibilities of the intramural and extramural programs should be separated; this was also, he noted, a clear and unmistakable recommendation of the Bishop-Calabresi report. Dr. Klausner stated that the NCI has largely, but not entirely, accomplished that goal.

Two new Divisions, Dr. Klausner explained, will encompass the majority of the intramural program and will have only intramural responsibilities; a third will have both intramural and extramural components. The first two are the Division of Basic Sciences and the Division of Clinical Sciences. The third new Division, Dr. Klausner continued, is the Division of Cancer Epidemiology and Genetics. These three Divisions, he stated, represent a

rational division of the NCI's functions as a research institution into three major areas—research in the laboratory, in the clinic, and in the community.

The Acting Director of the Division of Basic Sciences, Dr. Klausner announced, is Dr. George Vande Woude, who has taken on this responsibility with remarkable vigor and great vision. The Acting Director of the Division of Clinical Sciences is Dr. Philip Pizzo, whom Dr. Klausner described as an extraordinary clinical researcher with a commitment to mentoring and training.

Dr. Klausner noted that the creation of the Division of Cancer Epidemiology and Genetics demonstrates the growing importance of population-based studies and studies to improve the definition of cancer risk and causation, as well as the overwhelming importance of genetics. This Division, he explained, will have both intramural and extramural components. Its Acting Director is Dr. Joseph Fraumeni, a recent recipient of the General Motors Award who, Dr. Klausner noted, is one of the developers and founders of the important field of molecular epidemiology in cancer. Dr. Klausner added that Dr. Fraumeni is being assisted in setting up this new Division by Dr. Alan Knudson, a special consultant to the Director who has come to the NCI for a year from the Fox-Chase Cancer Center. Dr. Klausner stated that Drs. Vande Woude, Pizzo, and Fraumeni are working very closely together to ensure that these three new programs are integrated. Dr. Klausner thanked these individuals for their efforts in transforming the National Cancer Institute, observing that a feeling of change within the Institute is very clear.

The four extramural Divisions, Dr. Klausner continued, include the Division of Cancer Prevention and Control (DCPC), which will continue to be led by Dr. Peter Greenwald. The Acting Director of the new Division of Cancer Treatment, Diagnosis, and Centers, which, Dr. Klausner explained, also includes training, will be Dr. Robert Wittes. For the new Division of Cancer Biology, under which Dr. Klausner expects the Frederick Cancer Research and Development Center to be housed in the future, an Acting Director has not yet been selected. Finally, Dr. Klausner added that Dr. Marvin Kalt will continue to Direct the Division of Extramural Activities.

Dr. Klausner turned his attention to four new advisory boards that are being initiated to improve linkages between the decisionmaking and planning processes with both the extramural and intramural research communities. There will be a single Board of Scientific Counselors (BSC), he explained, who will be advisors for all of the intramural activities of the NCI. The Board of Scientific Advisors (BSA), he continued, will serve as advisors for all extramural activities. Dr. Klausner described his goals for these two boards as overseeing the Institute's programs as a whole rather than acting as advocates for different fiefdoms within the Divisions. In addition to overseeing reviews and critiques, Dr. Klausner explained, these boards will be asked to establish menus of projects aimed at proactively determining the directions the NCI will take in light of the major thrusts, mechanisms, and goals confronted by the Institute.

For example, Dr. Klausner related, the Board of Scientific Advisors will be asked during the coming year to undertake a comprehensive review of issues such as cancer centers, clinical trials and cooperative groups, developmental therapeutics, and other important topics. The Board of Scientific Counselors, he continued, will become involved in the planning process to determine the size, structure, and functions of the intramural program.

Dr. Klausner announced that three individuals have been recruited to serve in leadership roles to help these Boards accomplish their expanded tasks, noting that in November these individuals are scheduled to report on their activities to the NCAB. A Subcommittee on Basic Sciences within the Board of Scientific Counselors, Dr. Klausner stated, will be chaired by Dr. Edward Harlow, who has agreed to come to the NCI for a year on a sabbatical. Another group within the Board of Scientific Counselors, the Subcommittee for Clinical Affairs, will be chaired by Dr. Martin Abeloff, who will be able to commute to accomplish this work. The chair of the Board of Scientific Advisors, Dr. Klausner continued, will be Dr. David Livingston, who will begin a sabbatical with the NCI at the beginning of October.

Dr. Klausner explained that the NCI is now in the process of obtaining approval of the charters for these new Boards and developing lists of individuals who will be asked to serve on them once the charters have been approved. Members of the current Boards, he noted, will be asked to serve as interim members of the new Boards until the full membership of each new Board is in place, which is expected to take 4 to 6 weeks.

Next, Dr. Klausner addressed the need to obtain input and advice from the intramural community. He reported that he has introduced a unique new governance structure involving two new internal advisory boards, which will be made up of individuals who work in the intramural and extramural programs. The chair of the new Intramural Advisory Board will be Dr. Claude Klee and the chair of the new Extramural Advisory Board will be Dr. Fay Austin. The members of these boards have already been chosen, Dr. Klausner noted, and the boards will begin meeting soon. He added that charters for these boards have been written and promised to provide NCAB members with copies of these charters.

Dr. Klausner explained that the functions of these boards will be twofold. First, they will advise the Division Directors, the Deputy Director, and the NCI Director on issues they feel are important for the smooth and effective operation of their programs. Dr. Klausner described them as filters that are needed in the process of making decisions and formulating policies by providing feedback on the effects of those decisions and policies on those who do the Institute's work. Second, Dr. Klausner continued, they will provide an open forum for communication from the entire community to the leadership that does not depend on going through the hierarchical chain of command. These boards will set their own agenda, he noted, and their chairs will sit on the Executive Committee in order to become involved in all aspects of planning and decisionmaking.

Dr. Klausner added that two new administrative structures have been instituted. The Office of Extramural Administration, he reported, will be headed by Dr. Philip Amoruso, and the Office of Intramural Management will be headed by Ms. Maryann Guerra.

Dr. Klausner stated that there would not be enough time to go into detail about the planning process, but announced that during the upcoming Planning and Budget Subcommittee meeting he would present his views about processes being put into place for long-, mid-, and short-range planning. He reported that these remarks would include his thoughts on how the Bypass Budget should look in the future and what it should accomplish. In order to provide oversight for the planning process, Dr. Klausner added, he has asked Dr. Edward Sondik to take on the role of Associate Director for Strategic Planning.

Turning his attention to the recent Bishop-Calabresi report on the intramural program, Dr. Klausner emphasized how insightful and articulate the report is and how useful it has been. He stressed the fact that he intends to respond to the report, and, in fact, the response has already begun. The first issue for the intramural program, Dr. Klausner stated, involves the internal scientific structure; the goal, he said, is to simplify that structure, encourage communication, and ensure the integration of strong basic, clinical, and population-based approaches to cancer research. The Directors of Divisions involved in the intramural program are working together to ensure that the principles and structures that apply to one Division apply to all Divisions. An example of this, Dr. Klausner explained, is a recent meeting to develop an overall plan for an intramural cancer genetics program that will operate across Divisions, including activities such as training for counselors.

Dr. Klausner reported that the simplification of internal structure will result in the elimination of internal programs that formerly operated as subprograms within the overall intramural program. The bureaucracies representing programs such as the Biologic Response Modifiers Program and the various carcinogenesis programs, he said, will be gone.

Information is being gathered, Dr. Klausner announced, regarding the issue of stewardship of resources and, by implication, the size of the intramural program. He stated that he is working with Division Directors to establish a detailed snapshot of the demographics of the intramural program, including numbers of principal investigators, the number and positions of their staff, how much space they use as groups and individuals, and—importantly—what their resources are in terms of operating expenses, contract expenses, salaries, and benefits. Dr. Klausner explained that beginning in October, each laboratory will have its own budget, which will be carefully followed. He noted that this will be a new situation for some of the laboratories.

In early November, Dr. Klausner reported, the leadership of the intramural program will participate in a retreat to examine the demographics of the program, look through the reviews of each program for the past several years, develop a plan for the redistribution of resources, and begin the process of setting goals regarding the size of the intramural program in terms of a percentage of the total Institute budget.

Another critical issue being addressed is career development, including training, recruitment, and quality control for career development activities. Clearly defined, written standards are being developed, Dr. Klausner said, for decisions about the recruitment of tenure track individuals, including the definition of tenure track. Criteria for promotion, within both junior and senior positions, are being reviewed, he added, and a clear process for promotion review will be developed that will involve individuals from the NIH and the extramural community as well as the intramural program.

Dr. Klausner announced that an ombudsman will be appointed for the intramural program, whose charge will be to oversee the integrity of career development and the quality of life of postdoctoral fellows and trainees. Dr. Klausner expressed his belief that the intramural program always has provided, and must continue to provide, an extraordinary opportunity for young people to begin their careers with a unique freedom of resources.

Another issue related to the fundamental principles of meritocracy, excellence, and accountability, Dr. Klausner continued, is the review process. He stressed the importance of

clearly articulating the definition of the review process, both for reviewers and for those being reviewed. As important as the review of science, Dr. Klausner argued, are the review of each program's utilization of resources in terms of its accomplishments and the review of stewardship. Leadership and management, he said, will be reviewed in terms of mentoring and the commitment to career development for all individuals at the Institute. The position of laboratory Chief, Dr. Klausner noted, is a position not of power but of responsibility. He added that structural issues regarding laboratories and branches will be under constant review. Questions that will be asked, he said, will include whether laboratories and branches should automatically continue when their chiefs leave the NCI or whether some restructuring is appropriate.

Turning to the principle that all aspects of the institution should serve science, Dr. Klausner observed that within the intramural program, it has often been unclear whether the institution is serving the science or the science is serving the institution. The first step in addressing this issue, he stated, is to acknowledge that the institution is a community of peers who should have the authority to manage personnel and budgets for their own programs. This means that to the full extent possible under law, management of laboratories and clinical programs will be delegated to the scientists who run those programs. Dr. Klausner explained that Dr. Shalala, Secretary of Health and Human Services, will be announcing a new set of delegations of authority that he and NIH Director Dr. Harold Varmus had requested.

With authority, Dr. Klausner continued, comes the responsibility for oversight and stewardship, which requires an administrative structure that will allow the delegation of authority to work. Dr. Klausner explained that the first charge of the new intramural and extramural advisory boards will be to work with administrative staff to establish a clear set of streamlined rules and guidelines so that people know what is expected of them. A high priority, Dr. Klausner stated, is to provide the Institute with a state-of-the-art information management system.

Dr. Klausner reviewed the dramatically altered administrative structure he has proposed for the intramural program. This structure, he explained, is designed to facilitate the delegation of authority. It is also designed, he said, to ensure that administrative and support staff feel themselves to be an integral part of the science, are appreciated, and function in a way that enables science rather than presents hurdles for scientists to overcome. Dr. Klausner added that this principle also applies to the extramural program as well and will be applied as the Institute takes a careful look at clinical trials, cancer centers, and the grant process.

The current administrative structure, Dr. Klausner observed, is extremely hierarchical, so that to get things done in the laboratory, scientists must go through multiple levels. He described this as a stochastic process in which a scientist tries to get something done, learns that the attempt did not succeed, and must try again and again. In the current structure, many elements are separated and isolated. Personnel issues, for example, are isolated from budget issues, in spite of the fact that personnel decisions involve costs. Another effect of the increasingly hierarchical nature of the administrative structure, Dr. Klausner noted, is that career development decisions for support personnel are based on how many people an individual supervises. He stressed that in the future, career development will not be based on the number of people supervised or the amount of money controlled, but on the importance of an individual's work.

The new administrative structure, which Dr. Klausner described as a model for other Institutes, will be a flat structure in which many administrative functions will be performed in the laboratories and branches. To accomplish this goal, he said, the responsibilities of Branch Secretaries will be redesigned. In addition, a new position—the Laboratory Manager—will be developed to provide an interface between the laboratory and administration. Given clear regulations, access to an information management system, and the responsibility to manage budgets with no hidden costs, much of what normally has been accomplished through multiple structures can happen at the level of the laboratories.

Dr. Klausner explained that, essentially, the entire administrative structure of the intramural program will consist of a single middle level, comprising what will be called "administrative resource teams" with team leaders. Each of these teams, he said, will have expertise in personnel management, financial management, information support services, administrative services, procurement, contracts, and other areas. Some teams may not have specialists in every area, but will share with other teams. A number of laboratories and branches, Dr. Klausner explained, will be able to turn to a particular team; the team's goal is to make things happen or to explain clearly why something cannot be done.

The administrative teams, Dr. Klausner continued, will report to Ms. Guerra in the Office of Intramural Management; however, team members will be reviewed not only by Ms. Guerra but also by the scientists they serve. Promotion, he emphasized, will depend on the quality of each individual's work and its importance. Dr. Klausner expressed his belief that within this interactive administrative resource team approach, there will be greater flexibility and opportunity for individuals to advance and to have a voice in how their jobs change. Dr. Klausner stated that he has spent a great deal of time with the individuals in these positions, and stressed the importance of their understanding of and participation in the process of developing the new structure. He emphasized the importance of working together to predict the consequences of these changes.

Another way to ensure that the institution is serving science, Dr. Klausner stated, is through the work of the Intramural Advisory Board, which will meet on a monthly basis and will establish subcommittees based on its needs. These scientists will tell the Institute whether the new structure is working, indicate what the scientists' needs are, and provide input for the development of resources such as the information management system.

Dr. Klausner then addressed the issue of the intramural program as a community of scientists. He acknowledged that most individuals involved in the program do not know what others in the program are doing, since there is no annual report or other central source of information. Dr. Klausner announced that the Division Directors involved in the intramural program will oversee the development of a readable and useful annual report, which will help scientists keep up with what their colleagues are doing and will also be useful in recruitment and other endeavors.

Many mechanisms for interaction will be explored, Dr. Klausner noted. In December, he announced, the first intramural retreat in the Institute's history will take place, during which all principal investigators will present posters and talk to each other.

Dr. Klausner turned his attention to the Frederick Cancer Research and Development Center. As mentioned earlier, the Frederick Center will report to the Division of Cancer

Biology, which is part of the extramural program. Dr. Klausner acknowledged that some might question this move, since there are many intramural laboratories within the Frederick Center. He expressed his belief that the Institute should closely examine the opportunities provided by the Frederick Center. There is a growing need, Dr. Klausner stated, to develop national resources that are available to both the intramural and extramural communities. The Frederick Center, he suggested, should not be a service center for the intramural program but should become a resource that is neither intramural nor extramural, but instead serves the entire NCI community. It remains to be seen, Dr. Klausner added, whether the national resources needed by the community are all located at Frederick or are disseminated throughout the country in cancer centers or other facilities. The types of resources needed, he related, include informatics, complex genetics, animal models, developmental therapeutics, and developmental diagnostics.

While there is a great deal of discussion about translational research, Dr. Klausner stated, the NCI is limited in its ability to conduct translational research when the fundamental intellectual infrastructure does not make it clear who is responsible for developing these resources. He argued that it is difficult to conduct complex molecular-based family studies, for example, because no one is developing the mathematics and software that are required. Animal models, he added, are becoming more important, but also too expensive, for many members of the community. Dr. Klausner suggested that the community should come together to think about the types of intellectual infrastructure that the nation needs. He expressed the desire to see concepts developed based on the opportunities provided by the Frederick Center.

Dr. Klausner observed that the NCI is a continually changing institution that must be reformed and "re-formed" to improve its ability to provide knowledge needed to reduce the burden of cancer. The Institute has already begun, he said, to put change into effect and is seeking assistance from within and outside the community. Dr. Klausner acknowledged the fact that change will not be easy, due to challenges to the health of virtually all aspects of the institution. He concluded by asserting that he looks forward to working with the NCAB to confront these challenges.

Questions and Answers

Dr. Rimer stated that Dr. Klausner has done a fantastic job so far in reinvigorating those already at the NCI and in forming an extraordinary integration of outstanding people into the Institute.

Dr. Day mentioned that the NCAB was involved last year in a controversy concerning mammograms, during which the NCI formulated a policy, submitted it for review by outside advisors, and brought it to the Board for approval. He asked Dr. Klausner what his approach would be in handling questions that are generic in nature and fall into the realm of health policy. Dr. Day noted, in light of Dr. Klausner's comments on the science-based nature of the institution, that questions concerning issues such as mammograms for women under the age of 50 are scientifically ambiguous.

Dr. Klausner stated that he has real concerns about the NCI, which is first and foremost a research institution, becoming a standard-of-care, regulatory, certifying, or policymaking institution. He said that he sees the Institute's role as an honest broker of knowledge that then

allows the larger community to address issues such as standards of care. It can be difficult to maintain credibility, Dr. Klausner suggested, if the Institute is drawn into such issues. The NCI does have a role, he continued, in making sure that information and knowledge are disseminated and readily available, which includes helping the larger community understand the situation when knowledge is unclear and can lead to controversies.

Dr. Klausner noted that a similar situation occurred recently surrounding issues related to tobacco use. He and Dr. Varmus, he reminded the Board, wrote letters to the President on this subject. These letters were written by scientists who had been appointed to advise the President on health research, Dr. Klausner stated, in order to clearly articulate the status of data on this subject, not to argue for specific regulatory steps.

Ms. Mayer asked whether Dr. Klausner's vision for the NCI is similar to or different from a vision of the National Cancer Program. Dr. Klausner replied that the National Cancer Program is much larger than the NCI and deals with many of the issues raised by Dr. Day's question. The National Cancer Program, he said, has to deal with actions taken by private individuals and private groups, corporations, the health care system, the insurance industry, and other government agencies, and involves issues such as health care reform and insurance reform. The NCI, he added, has an essential role to play in the National Cancer Program, but it is important to address the responsibilities and structures that allow the NCI to perform its role.

Dr. Sigal asked Dr. Klausner to describe his vision for interaction between the NCAB and the NCI Director, as well as between the Board and other organizational components of the NCI. Dr. Klausner said that he sees the NCAB performing a variety of functions. He also suggested that one of the things the NCAB needs to do is decide for itself what it can accomplish. He frankly observed that the NCAB agenda is a very heavy one; while all the issues addressed are important, he said, there is a need to step back and decide which are the most important for the Board to address.

Dr. Klausner added that the most important task for the NCAB is to become a real part of the planning process, which has been difficult because there has not been a focused planning process. He promised that there will be a defined planning process and stressed that the NCAB is very essential to the process that he hopes to see created for development of the budget and the Bypass Budget.

Other issues the NCAB might want to address, Dr. Klausner suggested, include the impact of managed care and health care reform on the National Cancer Program. He recommended that the Board pick a relatively small number of such issues in order to be most effective in its efforts.

Dr. Rimer mentioned that she has mailed some proposed goals for the coming year to Board members, and suggested that members give additional thought to these goals based on Dr. Klausner's remarks.

Dr. Schein suggested that there is a risk associated with the changes that Dr. Klausner described. Noting that the review and reprioritization of programs will involve the Institute's most senior, and perhaps most productive, scientists for a year or longer, he asked how this can be accomplished while the important work of the Institute continues.

Dr. Klausner said that the Institute is aware of this concern, but noted that the proposed changes have been under discussion for several years and expressed confidence that the Institute will be able to accomplish these changes without disruption. He added that the current system, in which issues such as personnel policy and the review process have been unclear, has been harmful to progress and productivity. Dr. Klausner stated that there are good models for the changes NCI is trying to implement and that the existing groundwork simply needs to be acted on in good faith. He also expressed confidence that the individuals involved in the intramural program desperately want these changes and have been coping for years with a system that does not work for them.

Dr. Klausner assured the Board that the Institute is working to ensure that issues do not "fall through the cracks" as these changes are being made. He suggested that the separation of the intramural from the extramural program is occurring so smoothly that most people will not notice the change, other than the fact that they communicate with different people than in the past. The implementation of the flat structure for administrative functions, reviews of the extramural program and cancer centers, and other restructuring activities, Dr. Klausner continued, are also not expected to affect ongoing, day-to-day work. He stated that he has not spoken to a single cancer center director who has not asked him to take a hard look at the bureaucracy associated with achieving and maintaining cancer center status.

Dr. Chan asked what kind of changes will occur in the grant application and approval process. Dr. Klausner replied that the approval process for grants is being discussed. Concerning the planning process, he said, the Institute must look through the budget and make sure that the necessary amounts are being placed in the appropriate mechanisms to support the NCI's priorities. He argued that too much money is being placed into Requests for Applications (RFAs) and contracts as opposed to the investigator-initiated research project grant (RPG) pool. Once these prioritizations are made, Dr. Klausner added, the entire budget can be examined and adjustments made. He stressed the fact that the budget will no longer be divided into different "pots," such as cancer control. The Institute will continue to fund research in cancer control and prevention, Dr. Klausner asserted, as part of its efforts to achieve the goals of the grants program as a whole.

The crisis of low funding rates for grants, Dr. Klausner noted, is overwhelmingly an issue of the lack of sufficient funds. In addition to making sure that money is used as well as it can be, he suggested, this situation can be improved by addressing issues such as investigator stability. One of the greatest threats to investigator stability, Dr. Klausner stated, is the "long queue" phenomenon associated with the grant application process, in which investigators learn that if an application is amended enough times, it will eventually be funded. This is a burden for study sections, Dr. Klausner asserted. The Institute, he proposed, should also reexamine the application process in terms of budget detail. The use of modular grants is being discussed, Dr. Klausner reported, as a means of reducing the amount of time investigators must spend on financial management and oversight. He proposed experimenting with modular grants, which take less time and would allow investigators, as well as the study sections, to focus on science instead of detailed financial management.

Dr. Klausner stressed the need for setting priorities that make it possible to identify applications that should, but cannot, be funded and develop a quick process for funding them as soon as money is available. Then, he proposed, the study sections should clearly explain why each unfunded application is not being funded and direct the applicant to address these

issues specifically in an amendment. Dr. Klausner expressed the opinion that the number of amendments should be limited to two and that a second amendment should be submitted only at the invitation of the Institute. These types of changes, he suggested, would address problems such as the demands on the study sections and the turnaround time for the grant process.

Dr. Rimer observed that one of the major recommendations of the Subcommittee to Evaluate the National Cancer Program (SENCAP) Report concerned these issues, adding that a poll of the Board's subcommittee chairs indicated that their highest priority is to address the problems with grants administration.

In response to comments made by Dr. Correa, Dr. Klausner stressed that the Institute will continue to address and fund research in a complete range of issues related to cancer, such as chemical carcinogenesis and nutritional aspects of cancer. He acknowledged the possibility of anxiety related to the fact that a molecular biologist has assumed the leadership of the NCI; on the other hand, he suggested, if an oncologist had been appointed, then basic scientists might be experiencing anxiety. He emphasized, however, that the Institute's advisors represent the full range of communities and research interests, from basic laboratory research to clinical research and population-based research. He offered the opinion that the establishment of a Division of Epidemiology and Genetics is very important, but asserted that he has no preset agenda concerning which areas of science are important or unimportant. His only agenda, Dr. Klausner assured the Board, is that the Institute must have a good advisory structure that can discuss areas of importance and opportunity.

Dr. Klausner stated that the Institute must be very careful to avoid developing a stochastic or *ad hoc* decisionmaking process that is based on the last workshop that produced an RFA or an investigator's position in the queue. He promised that the Institute will take a broad view of the whole research portfolio, and the institution will not become the National Institute of Cancer Molecular Biology. He reiterated the significance of the fact that all of the interested communities, including the consumer community, are extremely well represented on the NCI's advisory boards.

Dr. Freeman expressed his appreciation for Dr. Klausner's statements concerning the National Cancer Institute as a scientific endeavor. He noted, however, that the Institute operates in the context of a larger society that has concerns about social, political, and economic issues. Dr. Freeman asked Dr. Klausner, in his role as an important spokesman to the country, to address his beliefs concerning some of these issues. He reminded Dr. Klausner that he will be challenged with these issues when he goes before the Congress.

Dr. Klausner first reminded the Board that one of his first efforts as NCI Director was to write a very visible letter to the President, with Dr. Varmus, on exactly these sorts of issues. He said that he will continue to speak out on issues related to the responsibility of health care providers and insurers and on the fact that the goals of the National Cancer Program cannot be accomplished simply by gaining knowledge.

While the central function of the Institute is the acquisition of knowledge, Dr. Klausner asserted, another very important function is the dissemination of knowledge. He expressed his strong belief that the Institute's responsibility is not merely the dissemination of information but real public education. He observed that education is defined not by what we say, but by

what the public hears. This means, he continued, that the Institute's educational approach must be based on an understanding of cultural and individual aspects of its audience, empowering people to make decisions within the context of their communities and their own lives.

Dr. Rimer observed that when Dr. Klausner spoke about Dr. Knudson and Dr. Fraumeni working with other Divisions, the Division of Cancer Prevention and Control was not mentioned. She stressed the importance of working with DCPC as well as with other Divisions. Dr. Klausner agreed, noting that his previous remarks had been focused on the intramural program. He said that all of the extramural programs will be working together on the duplication within programs in areas such as biostatistics and clinical trial designs. Dr. Klausner pointed out that part of the function of the Extramural Advisory Board will be to bring together staff members from these Divisions. He added that the Division Directors have been working extremely well together and that any future structural changes will come from them.

Dr. Klausner offered a brief remark on the subject of AIDS research. He said that he met with Dr. Paul, Director of the Office of AIDS Research; Dr. Anthony Fauci; Dr. Varmus; and the Executive Committee recently to lay out a set of principles on how the NCI will approach planning, decisionmaking, and evaluation of its AIDS portfolio and coordinating that portfolio with the goals of the NIH and the National AIDS Program. In fact, Dr. Klausner reported, the NCI has already shifted funds from intramural to extramural AIDS-related research. He emphasized the fact that a dialogue has been established that will become part of an ongoing discussion and decisionmaking process about the integration between the goals of the National Cancer Program and the Office of AIDS Research.

Dr. Becker raised the issue of the availability of money for research grants, acknowledging that no quick answer will be possible. He said that one point made by the Bishop-Calabresi report is that the intramural budget of the NCI, as a percentage of the total research budget, is much greater than that of most other Institutes; the NCI proportion, he stated, is estimated to be 22 to 24 percent, compared with an average of 11 percent for other Institutes.

Dr. Becker observed that reports concerning the support of intramural labs in the public press have led to adversarial relationships with investigators who missed funding of R01 grants by a tenth of a point. He suggested that a shift of a small percentage of intramural support to R01s that are not earmarked for a specific type of research would result in an increase in the number of external R01s. Dr. Becker argued that the impact of such a shift on the external community, especially on young investigators who time after time miss by a tenth of a percentile point, would be extraordinary.

Stressing the fact that he does not expect a plan to be in place now, Dr. Becker suggested that Dr. Klausner has the power to meet the recommendations of at least two separate boards to reduce the intramural budget, and he expressed his opinion that funds removed from that budget should be diverted into the unrestricted R01 pool.

Dr. Klausner stated that he has told the intramural community that the fraction of the NCI budget that goes to intramural research is too large and will be reduced and to transfer that money into the investigator-initiated RPG pool. He said that he is not prepared to cite exact numbers and expressed some doubt about the accuracy of the numbers quoted by Dr. Becker,

since the way different Institutes measure contracts varies. Dr. Klausner noted that, as requested in the Bishop-Calabresi report, a more detailed plan for reducing the intramural budget will be available by next spring, and he guaranteed that the funds will be transferred to investigator-initiated research.

IV. LEGISLATIVE UPDATE—MS. DOROTHY TISEVICH

Ms. Tisevich, legislative liaison for the NCI, presented an update on current Congressional issues, including the proposed Government-wide furlough and the 1996 appropriation process. She informed the Board of House approval for a bill that would increase NIH funding 5.7 percent over the fiscal year 1995 level, with a slightly lower increase in funding for NCI. She added that the Senate Appropriations Subcommittee on Labor, Health, and Human Services is expected to mark up the bill in mid-September—probably for a smaller increase—with a full Senate vote to follow shortly thereafter. The final amount of funding will likely be settled in conference.

Ms. Tisevich displayed a list of issues that the House had identified for the NCI to address—breast cancer, prostate cancer, minority populations, leukemia, neurofibromatosis, nutrition, translational research, coordination of the National Cancer Program, and policy research on tobacco—noting that the full text was attached to the Legislative Update. She also listed issues for the NIH—pediatric research, gastric cancer, diagnostic radiology, clinical research, nutrition, AIDS research and funding, and achieving a balance in the research portfolio.

Ms. Tisevich drew the Board's attention to an issue of concern to the NCI and the extramural community, the House report language regarding a grant awarded to Dr. Stanton Glantz at the University of California at San Francisco. She read aloud from the report, "The committee was disturbed to learn that NCI had funded a research grant studying tobacco industry campaign contributions to state legislators and voting records of those individuals on tobacco control initiatives."

"While the committee is not rendering judgment on the merits of the grant proposal, it feels strongly that such research projects do not properly fall within the boundaries of the NCI portfolio, especially when nearly three-quarters of approved research projects go unfunded."

"Accordingly, the committee does not provide any further funding for this research grant within the NCI appropriation."

Ms. Tisevich remarked that the Senate's reaction to this provision is unknown, and the issue may be resolved in conference. She added that the grant has been funded for 2 of its 3 years at a cost of about $220,000 per year, with the third year's funding due next July. The grant has resulted in publications in several peer-reviewed journals. She explained that the NCI regards the House language as a clear expression of Congressional intent, and will decide on a plan of action after the Senate responds to the matter.

Ms. Tisevich mentioned an amendment adopted during full committee markup that was introduced by Representative Ernest J. Istook (R-OK) and two cosponsors, which would

affect the award of federal funds to institutions that engage in political advocacy. She read the following excerpt from the bill, "Tens of thousands of special interest groups representing the entire political spectrum receive more than $39 billion in federal grants each year. While no one knows exactly what happens with all this money, we do know that large sums are being spent wrongly on political advocacy."

"This bill puts a stop to taxpayer-funded political advocacy. This bill attacks the problem both directly and indirectly. It directly prohibits any recipient of a federal grant from spending any grant funds on political advocacy. Because money is fungible, however, it also indirectly attacks the problem by setting limits on the amount of political advocacy that a grantee can perform with non-grant funds."

Ms. Tisevich elaborated on the bill's reporting requirements for grantees and federal agencies and its enforcement provisions by agency inspectors general and audits by an arm of Congress, the General Accounting Office. She promised to keep the Board updated on the Senate's response to this language and any differences that are worked out in conference.

Turning to the subject of a government furlough in the event an appropriations bill is not enacted and the debt ceiling is not raised, Ms. Tisevich told the Board of efforts to agree on a continuing resolution that will allow some agencies to continue to operate. She hypothesized that the disparity in White House and Congressional views over certain federal programs and funding levels may yield a continuing resolution that provides continued funding for current programs, but at a fixed level below the current figures.

Ms. Tisevich said that Dr. Klausner met with key Congressional leaders to share his vision of the National Cancer Institute and the National Cancer Program and discuss some of the issues that will be raised when the NCI is up for reauthorization next year, although substantial efforts on reauthorization will not start until January, during the second session of the 104th Congress. She reminded the Board of the provisions that were added to NCI's statutory authorities at its last reauthorization—the earmark for cancer control, separate authorization of appropriations for breast and women's cancers and prostate cancer, several reporting requirements, developmental research plans and progress reports, etc.—and noted that both the appropriations and authorizing committees are interested in reducing earmarks.

Moving to the issue of new legislation, Ms. Tisevich described a bill that Senators Tom Harkin (D-IA) and Mark Hatfield (R-OR) are expected to introduce that would increase the cigarette tax by 25 cents per pack. The estimated annual revenue of $5 billion would be placed in a trust fund for biomedical research. She reminded the Board of a bill the senators introduced last year that would have set aside a percentage of health insurance premiums for a similar purpose.

She also mentioned a bill introduced by Representative Martin Meehan (D-MA), the "Freedom from Nicotine Addiction Act of 1995," which calls for the reduction and eventual elimination of nicotine in tobacco products. The "Pesticide Safety and Right-to-Know Act of 1995," introduced by Representative Henry Waxman (D-CA), would require labeling of food that has had pesticides containing known or probable carcinogens applied to it. This bill would also require determination of whether dietary exposure to a pesticide chemical under the

tolerance being prescribed is reasonably anticipated to cause breast cancer or serious reproductive disorders in any individual.

Ms. Tisevich referred the Board to the materials that were attached to the Legislative Update—summaries of the bills her office is tracking and relevant language from the House appropriations report—and invited the members to contact her office for further information.

Questions and Answers

Dr. Rimer thanked Ms. Tisevich for her presentation, and Dr. Ellen Sigal opened the discussion by asking about the status of cancer coordination. Ms. Tisevich deferred to Dr. Klausner, who expressed his opinion that Congress is seeking a report from him about coordinating the needs of the National Cancer Plan. He told the Board that he had met the previous day with the PCP and suggested that the PCP and the NCAB collaborate on this report to formulate clear statements about the requirements of a functional National Cancer Plan.

Dr. Rimer asked whether Congress has ever singled out an individual grant in previous legislation. Ms. Tisevich knew of only one such occasion, in which Congress directed the Child Health Institute to unfund an awarded project to study sexual behaviors and practices among adolescents. The sex survey project was funded by a combination of grants and contracts. She added that NCI is not legally obligated under the Public Health Service grant policy statement to provide future years of federal support for research; funds may be withheld for unavailability, as in this case.

Dr. Freeman said that Dr. Kessler concluded that nicotine is an addictive substance, which makes tobacco addictive, and asked whether the White House has plans to regulate it. Ms. Tisevich responded that Dr. Klausner may know more about the White House's stand on this issue. On the Congressional level, she noted that Representative Waxman, one of the most outspoken proponents of tobacco control, was replaced as chairman of the Subcommittee on Health and the Environment. The parent committee is now chaired by Representative Thomas Bliley (R-VA), who is sympathetic to the tobacco industry. Ms. Tisevich admitted that there continues to be some Congressional effort to control tobacco, but that she doubts the prospects for success of these efforts.

Dr. Philip Schein asked whether the bill restricting political advocacy by recipients of federal grants has undergone legal review. Ms. Tisevich answered that the Department of Health and Human Services has looked at the provision, which would apply across all federal agencies, but plans to defer to a broader review of the scope and implications by the Justice Department. She pointed out that the Senate is not expected to include this level of detail in its appropriations bill, so this particular provision may not be in the final version after conference. Dr. Rimer suggested that NCI's participating organizations should examine this bill, since it may have serious consequences. Dr. Schein expressed concern over the threat to free speech, and proposed offering a statement to Congress, if necessary.

Dr. Michael Bishop asked whether the NCI has taken a public position on the appropriateness of Dr. Glantz's grant. Dr. Klausner said that this is a difficult question and raises the problem of defining the NCI's boundaries. He offered the example of studies about

the economics of unemployment or poverty, which can be high-quality research that has enormous impact on health, but may be too far outside the Institute's scope and limited resources. He suggested that the NCAB's role is to use its best judgment in deciding whether to fund studies at these "boundaries," independent of whether the study is important, whether the research is good, and whether it impacts health or cancer. While these are important issues that may affect NCI's funding potential, with respect to the specific grant, Dr. Klausner opined that the NCI should stand behind the thorough review process that the grant went through to be accepted.

Dr. Greenwald pointed out that the grant had a broader scope than to simply assess the influence of tobacco money on the legislative process. He expressed his opinion that there is important research in policy development and structural change in society that is appropriate as cancer control research, and this should be the outer boundary of what the NCI supports. Furthermore, while it may be the most sensitive, policy research may also have the greatest impact, so it should not be excluded.

Dr. Bishop commented that the grant was most likely singled out, not because of its scientific content, but due to Dr. Glantz's other controversial activities. Dr. Greenwald agreed, noting that Dr. Glantz is both an effective activist and a good scientist. Dr. Rimer asked whether the NCI is the best fit for this grant, since it deals with policy issues. Dr. Day reminded the Board that they had all voted to approve the grant in question.

Dr. Rimer then announced that there would be a brief recess.

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

Dr. Rimer announced that Dr. Schein accepted her invitation to serve as chair of the Subcommittee on Clinical Investigations. She expressed her opinion that he is ideally suited to take on the important mission of new agent development.

Dr. Rimer opened the floor for new business, but no new items were offered. She thanked the Board members who wrote letters to President Clinton about the nicotine issue, showing that the NCAB will take a stand on such science issues.

Dr. Rimer announced that the Board would hear from representatives of two organizations that work closely with the National Cancer Plan; the National Coalition for Cancer Research (NCCR) and the American Association for Cancer Education (AACE). These presentations, along with similar previous and future ones, are being given in response to requests by the Board. Dr. Rimer welcomed and introduced Dr. Margaret Foti.

VI. REMARKS AND DISCUSSION: NATIONAL COALITION FOR CANCER RESEARCH AND AMERICAN ASSOCIATION FOR CANCER EDUCATION, INC.—DRS. MARGARET FOTI AND JOHN CURRIE

Presentation by Dr. Foti, National Coalition for Cancer Research

Dr. Foti thanked Drs. Rimer and Klausner and the members of the Board. She introduced her presentation on the NCCR's activities, programs, and public education campaign as "The National Coalition for Cancer Research: A Partnership in Advocacy for Cancer and Biomedical Research."

As background history, Dr. Foti told the Board that the NCCR was founded and incorporated in 1986 to strengthen the National Cancer Program through public education and communication about the value, accomplishments, and promise of cancer research. The NCCR sought to ensure reauthorization of the NCI and respond to research funding needs, as well as provide a strong collective voice to advocate research to find a cure for cancer.

Dr. Foti showed a slide with the NCCR's current mission statement—to provide a forum for a group of diverse cancer-concerned organizations to advance cancer research through collaborative action in such areas as public education and advocacy, leading to the eradication of cancer and its effects. She mentioned the strong active leadership of the organization, and recognized the public education campaign efforts of Dr. Day, an NCAB member who served as President of the NCCR from 1992 to 1994. Dr. Foti reviewed the NCCR's growth from 12 to approximately 20 member organizations, both lay and professional, representing tens of thousands of cancer survivors and their families, children with cancer, researchers and health care professionals, cancer centers, and volunteers.

Dr. Foti mentioned several of NCCR's activities and accomplishments, such as providing input on budget and appropriations through public witness testimony, meeting with members of Congress, and developing policy statements. To support public education efforts, the NCCR monitors and reports to its member organizations on legislative initiatives, which also assists them in improving their advocacy activities. Dr. Foti listed some of the initiatives in which the NCCR has been involved: health care reform, the Hatfield-Harkin health research fund, reimbursements for clinical trials, indirect cost reimbursements, and the clinical study section.

The NCCR is currently working on a public education campaign called "Research Cures Cancer" that was started in 1992 by Dr. Sigal and Ms. Dana Fields, vice president and publisher of *Rolling Stone*. Dr. Foti explained that the campaign included multimedia public service ads created by the Fallon McElligott agency, which has received numerous awards. The campaign is intended to focus national attention on the need for more cancer research to prevent and cure cancer and to emphasize the progress that has been made through previous research.

Dr. Foti elaborated on the components of the campaign: six public service announcements (PSAs) appeared on 300 television stations in the top 50 metropolitan areas; radio ads played on the top five stations in the top 20 radio media markets; dioramas appeared in 16 major airports; and brochures were supplied to those who called the 800 number in the

PSAs. It is estimated that the number of individuals exposed to these messages may soon reach 90 million. Dr. Foti recognized the assistance of volunteer collaborators, such as Mr. George Brown, who placed ads in the *Wall Street Journal* and the *Investors' Business Daily*, as well as Dr. Terry Leltman and his staff, The V Foundation, Glaxo, AACI, the cancer centers, and NCCR member organizations. Dr. Foti explained that they cannot determine how successful the outreach has been, because the PSAs could not specifically seek funding contributions, due to the NCCR's 501(c)(3) status. She then showed the Board the airport diorama and a video of the PSAs.

Dr. Foti emphasized that the campaign is moving to the grassroots level to mobilize the cancer research community and educate policymakers. She mentioned that the NCCR intends to target a few geographic areas with the assistance of some of its member organizations. She suggested the need for a sophisticated approach to deal with current problems, and invited Board members to collaborate on future initiatives.

Presentation by Dr. Currie, American Association for Cancer Education, Inc.

Dr. Currie, president of the American Association for Cancer Education, described the history of his grassroots organization, which began in 1946 as the Coordinators of Cancer Teaching (CCT), chaired by Dr. Samuel Harvey. In 1966, the AACE replaced the CCT, and has met annually since then to exchange information, hold symposia, offer papers and posters, and provide an opportunity for cancer educators to meet.

Dr. Currie noted that the AACE's history parallels the cancer education programs of the NCI, beginning with undergraduate training grants in 1948, clinical cancer grants in 1956 and from 1975 to 1983, and the current R25 cancer education grants. He described the Association's two awards: the Margaret Hay Edward Achievement Award, which was awarded in 1995 to Dr. Daisilee Berry; and the Samuel Harvey lecture, the highlight lecture of each annual meeting, to be delivered by Dr. Martin Abeloff at the Moffitt Cancer Center in Tampa this November. The 50th annual anniversary meeting will be held in Chicago next October.

Dr. Currie explained that the AACE's 400 plus members are not only physicians, but also nurses and other professionals involved in cancer education. The Association has sections in many aspects of cancer education: basic science, community, education evaluation, dental oncology, gynecologic oncology, international, oncology nursing, palliative oncology education, pathology, pediatric, preventive oncology, psychosexual, public and patient education, radiation, and surgical.

Dr. Currie reiterated the AACE's purpose of fostering cancer education and providing a forum for papers and presentations through its annual meeting and journal, the *Journal of Cancer Education*. He distributed copies to the Board, noting that the 10-year-old journal is peer reviewed and indexed, and serves as a vehicle for announcements of the Cancer Training Branch and the European Association of Cancer Education, both of which have a close alliance with AACE. He mentioned the educational surveys and symposia that the AACE sponsors and its promotion of R25 submissions. Dr. Currie described other AACE liaisons with the American Cancer Society, the American College of Surgeons Commission on Cancer, the American Society of Clinical Oncology (ASCO), the Association of American Cancer

Institutes, the International Society of Nurses in Cancer Care, the International Union Against Cancer (UICC), the NCAB, the National Coalition for Cancer Research, the Oncology Nursing Society, and the Society of Surgical Oncology.

Dr. Currie concluded that the AACE seeks to increase involvement with its liaisons and expand its membership, and invited them to join and assist in furthering cancer education.

Dr. Rimer thanked Drs. Foti and Currie and announced a presentation by Dr. Klausner on the function of the Von Hippel-Lindau gene, with an introduction by Dr. Alan Rabson.

VII. FUNCTION OF THE VON HIPPEL-LINDAU GENE—DR. RICHARD KLAUSNER

Dr. Alan Rabson presented an introduction on the initiation of research related to the von Hippel-Lindau gene at the NCI. Dr. Berton Zbar, then Director of the Laboratory of Immunobiology in the intramural program at NCI, became interested in characterizing cancer-related genes that would present alterations in their structure and function. Because of the extensive availability of kidney cancer tissue at NCI and the evidence in the literature indicating that patients with kidney cancer exhibited t(3;8) translocations, Dr. Zbar decided to investigate the gene(s) involved in kidney cancer. While presenting a seminar to investigators of the Biological Response Modifiers Program, he was apprised of the existence of the VHL syndrome—a genetic disease, identified by Drs. Eugene Hippel and Arvid Lindau in 1895, characterized by congenital angiomatosis of the retina and cerebellum. Kidney cancer is also considered a common clinical manifestation of this disease.

Dr. Zbar, in collaboration with Dr. Marston Linehan and other scientists, initiated investigations of the VHL syndrome at NCI using NIH's Clinical Center. The team of NCI investigators performed genetic linkage studies of affected families and successfully cloned the VHL gene on chromosome 3. Dr. Rabson introduced Dr. Richard Klausner, stating that at the same time that the team of NCI investigators was studying the VHL gene, Dr. Klausner, then at the National Institute of Child Health and Human Development, was also investigating the structure and function of the same gene.

Dr. Klausner indicated that for several years he and Dr. Linehan maintained close communication regarding their findings on the VHL gene. He stated that a collaboration has recently been initiated between the two groups to complete the identification of the kidney tumor suppressor gene, the VHL gene, and to establish a potential new tumor suppressor pathway. Dr. Klausner explained that tumor suppressor genes are genes whose loss of function is associated with a predisposition to, and perhaps the rate-limiting step for, the development of cancer. Dr. Klausner indicated that the number of tumor suppressor genes being identified is steadily increasing.

Dr. Klausner referred to Knudson's two-hit hypothesis for tumor suppressor gene inactivation (based on the retinoblastoma gene) and indicated that the VHL gene clearly illustrates all aspects of this hypothesis. By studying the karyotype of families with kidney cancer, investigators observed that a balanced reciprocal translocation from chromosome 3p to 8 was present in one family. Other families with hereditary clear-cell carcinoma of the kidney—the most common form of kidney cancer—also exhibited balanced translocations of

3p, but to other chromosomes. Patients with sporadic or nonfamilial kidney cancer were also studied. Their tumors were analyzed for cytogenetic changes; investigators found a loss of heterozygosity on the 3p chromosome of sporadic kidney cancer cells. More than 90 percent of patients with sporadic clear-cell renal carcinoma—which represents 90 percent of the 27,000 new cases annually of kidney cancer in the United States—exhibit loss of heterozygosity on the 3p chromosome.

Dr. Klausner indicated that approximately 5 to 10 percent of common cancers are developed as part of inherited familial syndromes, such as the VHL syndrome. In these syndromes, a clear Mendelian simple inheritance pattern can be identified for the cancer. Dr. Klausner explained that different familial forms of kidney cancers exist. In the familial kidney cancer setting, kidney tumor suppressor gene abnormalities are present in one of the alleles in germline cells; these patients also show loss of the wild-type VHL allele inherited from the unaffected parent, which results in loss of heterozygosity, ultimately leading to development of cancer. The probability of developing cancer is significantly higher in individuals, who originally exhibit loss of one allele compared with normal individuals who would have to exhibit two mutational events in a somatic cell to develop sporadic kidney cancer.

Dr. Klausner noted that the VHL syndrome is a rare disease with a birth frequency of approximately 1 in 35,000. Approximately 60 percent of all individuals affected by the VHL syndrome will develop renal cell carcinoma before the age of 60. VHL-related kidney cancers are characterized by early onset and are multifocal and bilateral in origin. Dr. Klausner added that the genetic linkage studies performed at the Clinical Center revealed that the gene for the familial form of kidney cancer associated with VHL disease is the same gene involved in the sporadic form of kidney cancer. Dr. Klausner illustrated the distribution of familial mutations in the VHL gene, which occur mainly in exon 1 and exon 3. In contrast, VHL gene mutations detected in sporadic kidney cancer occur with significant frequency in exon 2. Mutations in the VHL gene are detected in 90 percent of all cases of sporadic clear-cell renal carcinoma.

Dr. Klausner explained that since the sequence of the VHL gene does not resemble that of any other gene whose function is known, the VHL has been defined as a pioneer gene. The VHL gene is highly conserved in closely related animals. Cell biology studies have indicated that the VHL gene product is localized both in the nucleus and the cytoplasm. Preliminary biochemical studies revealed that the VHL protein formed complexes with two other proteins and that this interaction was disrupted when naturally occurring VHL mutations were present, suggesting that these proteins are potentially involved in the normal tumor suppressor function of VHL. Purification and sequencing of the two proteins surprisingly revealed that both proteins were subunits of a complex called elongin, the nature of which Dr. Klausner then proceeded to explain. Transcription is the principal point at which gene expression is controlled. The process of transcription elongation in eukaryotes involves RNA polymerases and certain mechanisms to control initiation of transcription. The RNA polymerase responsible for transcribing certain genes requires activation through one of several transcription factors; the most important of these transcription factors is known as elongin. Elongin was originally described as transcription factor SIII by Drs. Ronald C. and Joan W. Conaway; they identified a three-subunit elongation complex composed of elongin A, B, and C that activates transcription elongation by RNA polymerase II.

Dr. Klausner stated that the purification and sequencing studies revealed that the two proteins found in association with the VHL protein were two of the three subunits of the elongation complex, elongin B and C. These studies also showed that elongin A is never found associated with the VHL protein; instead, elongin A stimulates transcription elongation. Dr. Klausner indicated that the addition of purified VHL protein into a transcription elongation assay containing the elongin complex (A, B, and C) completely inhibited transcription by blocking elongation. The VHL protein was shown to contain a 15 amino acid peptide sequence in which many of the naturally occurring mutations cluster; this region shares sequence identity with elongin A. Dr. Klausner explained that a small peptide containing this sequence was synthesized to determine whether it would mimic the effect of the whole VHL protein; specifically, block the assembly of the elongin complex and inhibit elongation. Results demonstrated that the peptide did block the assembly of elongin, inhibiting transcription elongation.

Dr. Klausner stated that the VHL gene may represent a novel pathway for tumor suppressor activity. He indicated that only a small number of tumor suppressor gene pathways may exist and to develop cancer, several, if not each, of these pathways might have to be disrupted. Dr. Klausner wondered whether mutations in the VHL gene reflect only early predisposition to developing cancer and whether the VHL gene pathway can be modified to prevent tumorigenesis. He stated that mutations in the VHL gene are detected early in the development of renal cancer when the tumor is virtually localized in the kidney. Studies are ongoing to determine whether a diagnosis of kidney cancer can be made by analyzing cells that are sloughed into the urine.

A pseudo gene therapy experiment has been performed in nude mice, in which renal cancer cells expressing no VHL gene from a patient were implanted into the mice and large tumors subsequently developed in these animals. Renal cancer cells obtained from sacrificed mice were transfected with the VHL gene and implanted into other animals; the latter did not develop any tumors. Dr. Klausner indicated that histological examination revealed no ingrowth of fibroblasts or blood vessels surrounding the renal cancer cells. The introduction of the VHL gene into the cancer cells did not affect their cell cycle, since the cells maintained their ability to grow in soft agar. These data suggest that the VHL gene specifically inhibits the ability of the cancer cells to be tumorigenic.

Dr. Klausner added that each tumor suppressor pathway identified to date appears to function as a guardian of specific regulatory mechanisms that are normally tightly controlled to regulate the normal function of cells. He mentioned the p53 and retinoblastoma genes as examples of other tumor suppressor pathways.

Dr. Klausner noted the cellular localization of the VHL gene product—nucleus and cytosol—and stated that one of the gene product's functions appears to be related to cell-to-cell adhesion and signal transduction. He explained that when VHL-expressing cells are grown in culture and these cells are not in contact, all the VHL protein is localized in the nucleus; however, when cells are in complete contact, the VHL protein is entirely localized in the cytosol. The VHL gene appears to be the first gene identified in which its regulatory mechanism involves sensing contact between cells. Dr. Klausner speculated that the VHL tumor suppressor pathway will be shown to involve many genes, some of which will be tumor suppressor genes and others will be oncogenes. The VHL tumor suppressor pathway

will be shown to be part of the unidentified signaling pathway for tissue organization that has to be maintained in a normal cell.

In conclusion, Dr. Klausner stated that the recent findings on the VHL gene will force investigators to study in more detail transcriptional control, particularly the mechanisms that control elongation. The VHL gene has unraveled a novel tumor suppressor pathway that might be involved not only in kidney cancer but in multiple, if not all, types of cancers.

Questions and Answers

Dr. Day questioned whether the first studies using lymphokine-activated killer (LAK) cells—in conjunction with interleukin (IL)-2—were performed with renal carcinoma cells and then asked Dr. Klausner to speculate about the interaction between these cells. Dr. Klausner indicated that he and his coworkers have recently cloned a new gene which appears to regulate the VHL pathway; the gene encodes interleukin 4 (IL-4). He then explained that it is unclear whether the cytokines act directly on the renal cancer cells—which contain cytokine receptors—or act through the immune system. This is an area that requires a more mechanistic investigation.

Dr. Goldson suggested that, based on Dr. Rabson's extensive knowledge of the Institute's history, Drs. Rabson and Klausner prepare a historical overview of the NCI that could be recorded for posterity.

VIII. BEHAVIORAL RESEARCH AND MEETING SYNOPSIS—DRS. NORMAN ANDERSON, BARBARA RIMER, AND PETER GREENWALD

As background, Dr. Greenwald noted that the September 1994 SENCAP Report, *Cancer at a Crossroads*, included recommendations for application of basic research, which inherently involves the fields of behavioral and social sciences. In response to these recommendations, NCI sponsored a workshop entitled, "Behavioral Research in Cancer Prevention and Control," held July 6-7, 1995. Dr. Greenwald said that he and his copresenters would be reporters on the workshop and then introduced Dr. Norman Anderson, Director of the new NIH Office of Behavioral and Social Sciences Research.

Presentation by Dr. Anderson

Dr. Anderson thanked the NCAB members for the opportunity to address the Board. He explained that he took leave from Duke Medical Center, where he is a faculty member in the Department of Psychology, to act as the first Director of the new Office of Behavioral and Social Sciences Research. The Office was created by Congress in 1993 to "provide a prominent focus within NIH for coordinating behavioral research conducted and supported by NIH institutes and centers." Congress charged the Office with designing a plan that would: evaluate the role of lifestyle factors that complement the effects of medicines and contribute to the promotion of good health; foster a comprehensive research program; expand NIH support for behavioral and social sciences research; supplement current Institute research and training programs; promote cross-disciplinary research; and integrate a biobehavioral perspective into research regarding good health and disease prevention, treatment, and cure. Dr. Anderson

began his work as Director of the Office in July 1995. The Office is staffed by one other individual, Dr. Virginia Cain, who is a sociologist and veteran at NIH.

Dr. Anderson presented his view of how the fields of behavioral and social sciences integrate into the overall mission of NIH. He asserted that behavioral and social sciences research is vital for determining health outcomes. Behavioral, social, and genetic factors are intertwined—behaviors can affect genetic predisposition, genetics can contribute to behavioral concerns, and social and environmental factors can influence genetic susceptibility. These factors all affect biologic and other health outcomes.

Dr. Anderson suggested that this model of the interactive role of the behavioral and social sciences with other health-related fields should be embraced as part of the philosophy of NIH. Accepting this model as part of NIH's philosophy would necessitate supporting behavioral and social sciences research, particularly in terms of identifying new behavioral and social risk factors for disease. He pointed out that while previous efforts to discern behavioral risk factors associated with the leading causes of death have been successful—for example, smoking, poor diet, and lack of exercise—other behavioral risk factors should be explored.

Support for research to explore the effects of biologic, behavioral, and social interactions is necessary as well. Interdisciplinary research will allow a more thorough determination of the factors that influence health outcomes. Dr. Anderson provided NCAB members with an example of multidisciplinary work from his personal experience. Despite his training as a clinical psychologist, he directs a noninvasive cardiovascular psychophysiology laboratory at Duke, where he collaborates with nephrologists, cardiologists, and hypertensionologists to study the issue of hypertension among African Americans. He stated that the new Behavioral and Social Sciences Research Office will support research that follows this example of multidisciplinary work.

The integrative model also suggests additional points of intervention in terms of behavioral factors that go beyond traditional pharmacologic agents, providing further opportunities for positive health outcomes. Dr. Anderson added that the conduct of basic research regarding the behavioral and social sciences should be a priority. Basic research acts as the foundation for any field and, therefore, study of the basic behavioral and social processes is crucial to the development of effective interventions.

Dr. Anderson outlined several of the tasks that the Office is currently involved in. As mandated by Congress, their first task was to create a standard definition of behavioral and social sciences research. He explained that Congress intended for the Office to assume a leadership role in defining what is and is not included within these fields of research. The next task involved using that definition to draft a report regarding the current level of funding for behavioral and social sciences research across all NIH Institutes and Centers. Dr. Anderson recognized that each Institute already determines their expenditures related to these fields, but stated that Congress requested that this assessment be conducted using a standard definition for all Institutes. In the future, the Office, in conjunction with members of the scientific community, will develop a strategic plan for behavioral and social sciences research at NIH that will include specific evaluation criteria and timeframes.

Dr. Anderson indicated that the Office has a limited budget for funding small grants, as well as workshops, conferences, and fellowships. The primary focus of the Office's work, however, will entail working with the various Institutes at NIH to enhance their individual behavioral and social sciences portfolios. He announced that discussions between himself and Dr. Klausner have already occurred regarding the process for involving his Office in integrating additional behavioral and social sciences research into NCI's portfolio. The Office will also assist in implementing several educational efforts to increase public awareness of not only the methods that the fields use, but the numerous and sometimes dramatic discoveries that have resulted from this type of research. Dr. Anderson credited behavioral and social sciences research with determining that smoking is an important risk factor for a multitude of illnesses, as well as that diet contributes to health. Behavioral and social sciences researchers also found that stress can produce negative physiologic effects and that exercise is a vital element of good health.

Two mechanisms have been established to fulfill Dr. Anderson's role as the principal advisor to Dr. Varmus, the Director of NIH, regarding issues related to the behavioral and social sciences. Dr. Anderson's office will sponsor a speakers' series that will convene the top scientists in these fields each month to discuss their work. Dr. Varmus will be present at these seminars. In addition, Dr. Anderson will schedule regular, informal briefings between extramural scientists and Dr. Varmus, providing unprecedented access to NIH leadership for behavioral and social science researchers.

In response to a question posed by Dr. Bishop, Dr. Anderson noted that estimates indicate that between 2 and 10 percent of the total budget is devoted to behavioral and social sciences research, depending on how the fields are defined.

Presentation by Dr. Rimer

Dr. Rimer stated that the "Behavioral Research in Cancer Prevention and Control" workshop was envisioned as a first step in a trans-NIH strategic planning process for behavioral research. In preparation for the meeting, a series of review papers was commissioned. Topics included tobacco research, genetic testing, diet and cancer, cancer screening and patient issues, and quality of life. The papers will be presented in a supplemental issue of *Preventive Medicine*, disseminated to members of the research community, and made available at the May NCAB meeting. Dr. Rimer also indicated that the recommendations generated at the workshop will be distributed to NCAB members within the next month.

The goal of the workshop was to determine what has been achieved in the fields of behavioral and social sciences research and what directions the fields should move toward in the future. Based on this examination, a comprehensive strategic plan will be developed for behavioral and social sciences research.

Dr. Rimer characterized the progress that has been made in behavioral and social sciences research as mixed—certain areas are very strong, while others are weak. She began with a discussion of the prevalence of smoking in America, particularly among specific populations. Currently, 25 percent of the adult population in the United States smokes, and while large initial decreases in the proportion of adults who smoke have been achieved, the prevalence is currently at a plateau. Of particular concern is the fact that 19 percent of

American high school seniors smoke, and that a disproportionate number of these adolescents are also dropouts. This fact attracted interest to this area not only among Board members, but within President Clinton's administration as well. Dr. Rimer informed members that efforts to prevent adolescents and younger children from initiating smoking have not been very successful. In addition, significant racial differences exist regarding smoking prevalence, with smoking reported among about 32 percent of African American males, particularly blue-collar groups. Efforts to reduce the prevalence of smoking have not appreciably impacted this group. Furthermore, the gap between the percentage of men and women who smoke has become smaller, as an increasingly larger number of women are initiating the behavior. Regarding diet, only 23 percent of Americans consume the recommended number of servings of fruits and vegetables each day.

Dr. Rimer moved to a discussion of current practices regarding cancer screening. Since 1992, approximately 22 percent of American males have been screened for colorectal cancer, with approximately 14 percent having had a fecal occult blood test (FOBT) and 11 percent receiving a proctoscopy. Dr. Rimer reported that standards for evidence of colorectal cancer during screening procedures will soon be upgraded and that the Institute needs to examine these modifications.

A paper written by Drs. Breen and Kessler that will soon be published in the Centers for Disease Control and Prevention (CDC's) *Morbidity and Mortality Weekly Report* presents the latest data regarding screening among women. Approximately 67 percent of American women have recently received a Pap test, 50 percent have had a clinical breast exam, and 36 percent have had a mammogram. She indicated that these data represent a doubling of the baseline figures from 1987; however, improvement in screening compliance rates is still needed. Dr. Rimer asserted that it is a misconception that the goal of getting a preponderance of women to have mammograms has been achieved—nearly 40 percent of women in their 60s and 70s have never been screened, and the percentage of individuals who have never been screened in other age groups varies from 25 to 37 percent. Many others have not been screened on a regular basis. Dr. Rimer reiterated that these areas, as well as others, were reviewed in the papers that will be published in *Preventive Medicine*.

Dr. Rimer indicated that workshop participants made recommendations in the various areas of behavioral research, some of which overlap. She explained that the scope of behavioral research is very wide, including basic behavioral research, interventions, high-risk populations, clinical populations, clinical research, community-based research, health services, policy research, and communications research. The meeting convened 75 of the nation's top behavioral scientists. Numerous discussion groups were held to allow scientists to not only comment on their own areas of behavioral research, but on other domains as well.

Dr. Rimer reported specific recommendations that were representative of those developed by the workshop participants. For example, the interplay between diet and genetics, particularly in terms of how diet alters genes or exacerbates certain genetic mutations, needs to become the focus of research. Regarding smoking cessation, the etiology of weight gain during cessation, which is more common among women, and the reasons that nicotine replacement therapies are only effective for some individuals should be explored. Dr. Rimer suggested that some basic mechanisms may explain these phenomena. She added that at any one time, only 15 to 20 percent of smokers are ready to cease smoking. Very little data exist

regarding methods for motivating cessation among those smokers who are not even considering stopping the behavior. She added that to have an impact on the groups that are currently smoking, research examining this reticent group is necessary. Researchers have yet to elucidate the process that occurs between smoking initiation and addiction. Behavioral researchers should collaborate with scientists who are studying the recently discovered lung cancer genes to try to understand the interaction between genetic susceptibility and the detrimental effects of prolonged tobacco use. In addition, data are increasingly suggesting that individuals who are depressed are more likely to smoke; however, the cause of this association is unknown. The interaction should therefore be examined.

Dr. Rimer then outlined some of the participants' suggestions regarding high-risk populations. She underscored the need to target intervention research toward developing methods for reaching high-risk women who have never been screened for cancer or who are screened very irregularly. Attention also needs to be focused on effective methods for inhibiting tobacco use among adolescents. Dr. Rimer pointed out that tobacco-related interventions for adolescents need to be implemented in locations other than schools, as many young smokers may not attend school.

Long-term survivors of cancer also need to be studied as a high-risk population. Appropriate interventions, particularly in terms of diet, exercise, and strategies for avoiding second cancers, should be designed for this population. Targeted interventions for individuals who are at high risk for developing cancer should also be created. Dr. Rimer informed the Board that one of the overall conclusions arrived at by workshop participants was that risk factors should be viewed as being interrelated. Research should be conducted regarding how to combine self-help interventions, which are preferred by most smokers, and effective techniques for motivating smoking cessation among heavily addicted smokers. Dr. Rimer remarked that very limited knowledge exists regarding effective methods for helping heavily addicted smokers stop the behavior, despite the significant success public health practitioners have achieved in motivating moderate smokers to stop smoking.

Dr. Rimer indicated that efforts to educate the public in terms of making good decisions about receiving various cancer screening tests should be implemented; many of the techniques that are currently being promoted among the public are still unproven. In particular, as genetic tests become available, methods for educating both the general public and high-risk individuals to help them make informed choices about the tests need to be developed. Currently, there is very limited knowledge regarding strategies for helping individuals decide whether to receive genetic tests and how to interpret results. Dr. Rimer pointed out that behavioral scientists will act as the bridge between the geneticists who develop the tests and the individuals who must decide whether to use them.

Managed care will pose new challenges to disseminating cancer prevention strategies. Developing methods to integrate preventive and primary care will become increasingly important. Dr. Rimer reported that another area addressed by workshop participants is the lack of monitoring of cancer prevention and control among physicians. Less than one-third of physicians currently use a tracking system, and even fewer are using computerized systems. Mechanisms for integrating alternative models of cancer prevention services, particularly those that target specific populations or types of delivery systems, into managed care settings need to be created.

Developing culturally relevant measures for assessing quality-of-life issues among members of various populations is important. While many quality-of-life measures that have been developed appear to accurately predict health status, they have not yet been modified to be appropriate for certain populations.

Dr. Rimer stated that methods for assessing dietary intake that do not require hospitalization need to be developed. Practical methods for measuring consumption, such as identifying a biological marker of fat consumption, would facilitate the process of determining the impact of an altered diet. Technological advances, such as interactive, portable computers, may be utilized to overcome some of the obstacles inherent in dietary assessment. Dr. Rimer concluded that one of the most important areas of behavioral research will involve improving the ability of the scientific community to accurately communicate risk messages to the general public.

Presentation by Dr. Greenwald

Dr. Greenwald presented a discussion of appropriate next steps regarding the conduct of behavioral and social sciences research, both on a trans-NIH level and at NCI as well. Regarding trans-NIH initiatives, one suggestion involves the establishment of behavioral and social sciences intervention programs. The programs would be composed of multidisciplinary teams, which could potentially be organized under program project grants and be directed by members of the NIH Institute that specializes in the primary focus of each one. For example, if a program were primarily concerned with cancer, then NCI staff would direct it. The other recommendation for trans-NIH work is to conduct basic behavioral research. Dr. Greenwald stated that this type of research might be funded through the fixed price mechanism proposed by Dr. Varmus—for example, grants of $150,000 each.

Dr. Greenwald requested that a working group consisting of members of the NCAB and the Board of Scientific Advisors be established to conduct an in-depth review of the current state of behavioral and social sciences research at NCI, identify gaps, and formulate a strategic plan for future research in these fields. The plan would be presented at the May NCAB meeting and delivered to the BSA both as a report and for concept approval of any recommended initiatives that require funding. Dr. Greenwald cited program announcements (PAs), requests for applications (RFAs), and training initiatives as items that may require BSA concept approval. One of the issues that this working group would address is the criteria for determining when an RFA is an appropriate mechanism for stimulating an area of research in these fields. Dr. Greenwald also indicated that he and Dr. Vince Cairoli discussed expanding the R25 Cancer Education Program to involve training efforts, particularly in terms of "cross-training."

Dr. Greenwald concluded his presentation by recommending that the reports of external reviews, conducted by working groups, become the foundation of NCI's strategic plan. The plan could include reports from the Bishop-Calabresi Ad Hoc Working Group; the suggested working groups in the areas of the behavioral and social sciences, and of clinical trials in prevention and early detection; and any additional working groups that are formed. A procedure for periodic rereview could be established to provide updated information for the strategic planning process.

Questions and Answers

Dr. Ellen Sigal asked whether collaborations with the private sector have been considered as an option for conducting behavioral and social sciences research. This would allow large organizations with an interest in the outcome of the research to fund some of the work, which tends to be expensive because the studies typically need to be large to be meaningful. Dr. Greenwald replied that if feasible such collaborations would be appropriate, particularly for studies that explore structural change, such as whether clinical trials can be integrated with managed care; however, this alternative has not received much attention. Dr. Rimer commented that discussions with the Robert Wood Johnson Foundation have been held regarding a collaboration in tobacco research. She added that in her experience, managed care organizations have not been willing to fund research and, therefore, they probably are not practical solutions for ameliorating the NIH budget constraints. Dr. Sigal remarked that she believes that Kaiser-Permanente is currently funding some behavioral studies and that other managed care groups are exploring the possibility of supporting certain research. Dr. Rimer responded by stating that most of the meaningful research conducted by these organizations is funded by NIH or other government-supported mechanisms.

Dr. Wilson suggested that as trends move toward population-based capitated health care, behavioral research should become a higher priority. In addition, as more individuals preveiously receiving Medicare begin to be covered by capitated care programs, efforts to reduce the costs for providing health care to these individuals will gain more attention. Promoting healthy behaviors within a targeted population is a highly efficient means for lowering health care costs. Outcome research and report cards comparing various populations who receive capitated care will recommend those organizations whose patients appear to be healthiest. Therefore, behavioral research may become more valued within a managed care environment.

Dr. Rimer replied that it is not yet clear whether managed care organizations will make genuine efforts to promote healthy behaviors, or if simple approaches, such as mass distribution of brochures and fliers, will be utilized. She commented that the report card mechanism will increase accountability and possibly result in better efforts from these groups, particularly in terms of tobacco counseling and cancer screening.

Dr. Klausner supported the idea of developing a strategic plan for behavioral and social sciences research. He also underscored the importance of refining methods for communicating risk information to the general public. Questions, such as whether discussions of risk behaviors should be limited to cancer-related health effects and how members of the public react to different messages, need to be addressed. Dr. Klausner added that communicating conflicting or varying risk reports to the public has undermined their faith in these reports. Dr. Rimer agreed with Dr. Klausner and added that unclear reports cause individuals to overestimate the risks associated with certain behaviors and underestimate risk linked to others. Dr. Greenwald suggested that communications research could play a vital role in achieving accurate portrayal of risk to the public.

Dr. Harold Freeman asked which disciplines are primarily involved with the conduct of behavioral research. Dr. Rimer replied that behavioral research is an umbrella term that involves scientists from numerous disciplines, including anthropology, health education,

ecology, health policy/services, sociologists, and economists. Dr. Greenwald added that geneticists are becoming increasingly involved in behavioral research as they explore methods for informing individuals about their work, as are pathologists.

Dr. Freeman suggested that research should focus on how individuals perceive information they receive, instead of on what various messages state. For example, a recent University of Michigan study evidenced that only 4.5 percent of African American adolescents smoke, which is a 15 percent decrease (from 20 to 4.5 percent) in a 15-year time period. The proportion of White adolescents who smoke has not decreased at all, remaining steady at 20 percent. Dr. Freeman indicated that this variation is probably not related to educational factors, but cultural aspects. The findings of the study suggest that an ethnological/cultural perspective, as well as a psychological approach, should be employed when exploring why individuals act in a certain manner. He emphasized the need to involve disciplines that assume a broader, more cultural perspective, such as anthropologists and ethnologists, to provide a better understanding of individuals' values, behaviors, and motivations for changing behaviors. Dr. Rimer agreed with Dr. Freeman, stating that the most outstanding behavioral scientists are those that work to discern cultural values and then design appropriate interventions based on this knowledge.

Dr. Philip Schein asked whether any organization, such as NCI or the American Cancer Society, is actively involved in providing tobacco prevention teaching aids, educational materials, slide kits, and other tools to school systems. He indicated that his sense is that while substantial and effective efforts have been made to communicate risk information regarding HIV and other sexually transmitted diseases to school-aged children, a similar level of effort has not been achieved in regard to tobacco prevention. Dr. Greenwald replied that tobacco prevention teaching modules for schools have been developed and field tested. One type of module involves the conduct of five educational sessions in the 7th grade, with reinforcement in the 10th grade. Smoking rates are monitored at graduation and certain of these modules have been shown to be quite effective. Dr. Greenwald explained that the availability of educational materials has not been the problem. The real challenge has been negotiating the fragmented school system. Each community has a school board that is responsible for supporting the implementation of these technologies, which makes dissemination and adoption much more difficult.

Dr. Schein also asked whether the American Cancer Society's massive population-based data collection effort that explored the associations between lifestyle factors and cancer risk has been completed, and whether the data are available for study and evaluation. Dr. Rimer responded that a great deal of data have been collected through these population studies in terms of lifestyle factors and cancer risk and that the findings of some of these studies have been published. A representative of the American Cancer Society added that more data will be made available in the future.

Dr. Schein recommended that NCI make it a priority to promote the use of effective teaching modules among the various school systems. He suggested that the Administration would probably be willing to support this effort.

Dr. Chan asked whether the nation's smoking prevalence rates among adolescents have been compared to those among Canadian youth. Dr. Greenwald stated that after Canada raised

the tobacco tax, substantial decreases in smoking prevalence among youth were noted, although the accuracy of these figures was confounded by individuals crossing the U.S./Canadian border to purchase cigarettes. Dr. Greenwald suggested that if the United States raised the tobacco tax as well, which has been shown to have the most profound effect on youth purchase, a very effective measure for reducing smoking prevalence among adolescents would be achieved. Dr. Rimer commented that Dr. Richard Peto's compendium of international smoking rates contains data that relate smoking rates among various age groups around the world. Dr. Chan offered that his recent unofficial surveillance of Canadian youth suggested that smoking prevalence among adolescents in Canada is significantly lower than in the United States.

Dr. Greenwald remarked that international data indicate that while the United States has only 5 percent of the world's female population, it accounts for 50 percent of tobacco-related deaths among women. Currently, the United States has one of the highest proportions of female smokers in the world. Dr. Greenwald expressed his concern regarding the potential for the proportion of female smokers in developing countries to increase as international tobacco companies begin to market their products in these nations. He added that NCI should become involved in influencing policy related to this concern. Dr. Rimer announced that she and Ms. Marlene Malek and Dr. Susan Blumenthal, Director of the Office of Women's Health (OWH), have begun discussions about a collaborative effort to sponsor a summit on women and tobacco that will focus attention on attempts to expand the tobacco market in developing countries as an important national policy issue.

IX. CLOSED SESSION

The afternoon session of the first day of the meeting was closed to the public because it was devoted to a meeting of the Special Actions Subcommittee. A total of 1,020 applications were received, requesting support in the amount of $259,742,077. Of those, 1,020 were recommended as being eligible for funding at a total cost of $235,789,839.

X. SUBCOMMITTEE REPORTS

Dr. Rimer gave the Board a preview of what they would be covering that day—subcommittee reports, managed care, a presentation about collaborations with the Office of Women's Health, upcoming program reviews, and peer review and reinvention at the NIH.

Activities and Agenda

Dr. Rimer informed the Board about the issues the chairs had discussed at the July meeting. She mentioned the desire to take on a more proactive, strategic role, which Dr. Klausner will support. Consequently, agendas for future Board meetings will have fewer presentations and include more time for planning substantive activities and discussing major scientific issues of cancer control. Dr. Rimer said that she and Dr. Kalt are working on an efficient way to track the recommendations and suggestions offered by the Board. She told the Board of a plan to mentor new members about their role and how to use it effectively.

With respect to suggestions for meeting topics, Dr. Rimer noted that they will be discussing managed care, as was suggested, and plan to discuss the biotechnology industry

and interaction with the NCI at a future meeting. She mentioned other suggested topics, including monitored payment for clinical research, new developments in tobacco policy, genetic testing, definition of and gaps in basic science, and recommendations regarding hormone replacement therapy and associated risks for cancer and coronary disease.

The Board passed a motion to accept the minutes from the subcommittee meeting.

Basic and Environmental Cancer Research

Dr. Becker explained that there is a public perception that the NCI and the government in general are too dismissive of the carcinogenic threat from environmental hazards. He noted that people define "environment" differently, but that he would not include hazards in the social environment, like diet and cigarettes.

Dr. Becker acknowledged Dr. Susan Sieber for her help in organizing the presentations of representatives from several regulatory- and research-oriented government agencies. The presenters spoke about their agencies' involvement in environmental research studies in the various subclasses of occupational, agricultural, water, air, etc. He noted the difficulty agencies have in identifying funds spent in each subarea of environment.

Dr. Becker said that the Department of Energy's (DOE) representative discussed their interest in low-level radiation effects and the eradication of super dumps. He also mentioned DOE's extensive biological research, including the Genome Project.

From the Occupational Safety and Health Administration (OSHA), the speaker described the approximately 5-year-long process by which the agency develops industrial standards for various agents.

The subcommittee also heard speakers from the National Institute of Occupational Safety and Health (NIOSH), which surveys and assigns risks and has more than 100 cancer projects, many subcontracted to NCI; the National Risks Management Research Laboratory, which is part of the Environmental Protection Agency (EPA) and conducts many studies of environmental hazards; and the National Institute of Environmental Health Sciences (NIEHS), which focuses its research on genetic risk. There were two speakers from the NCI—one from the Chemical and Physical Carcinogenesis Branch and one from the Environmental Epidemiology Board.

Dr. Becker concluded that although the speakers could not identify the exact amounts being spent on research in each category, the Board may be able to extract interpretive data with further efforts. One wrinkle he mentioned is that some projects may not be testing carcinogenicity directly, but may still be relevant. Dr. Becker also noted the high level of interagency cooperation that occurs through interagency committee meetings to discuss environmental hazards, and he suggested publicizing these events. He emphasized the importance of information exchange and the need to put information into a form that is meaningful to the lay public. He suggested organizing the materials provided by the speakers into a format in which total expenditures by agency in each area can be assessed, and presenting that information to the Board in February.

Dr. Becker observed that the meeting had been valuable, and he appreciated the contributions of the agency representatives. He told the Board that they would receive a 7-page appendix of excerpted materials from the subcommittee presentations later that morning.

Dr. Rimer mentioned the possibility of using the RaDiUS system for tracking cancer-related federal research and aggregating information. Dr. Becker agreed that may be useful, but noted that the output will depend on the input and corresponding information may not match; i.e., a project's dollar value may be assessed in terms of human resources when it does not have a set grant budget.

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

Cancer Centers

Dr. Day told the Board that the subcommittee had discussed changes in the elements for review of applications for comprehensive status. He reminded the Board that before the May 15, 1995, deadline, the Cancer Centers Program eliminated Element 4, which required participation in "high-priority" clinical trials, as defined by the NCI and cooperative groups. That element was included under Element 3, clinical research, and changed to suggest, not require, participation in or encouragement of patients to enter high-priority clinical trials. The criteria for review were ultimately changed to delete reference to high-priority clinical trials and, instead, include a bullet on allocating patients to clinical trials, including those with high-priority status. Dr. Day asked the Board to vote to approve the wording, since it is the NCAB's role to set the criteria.

The subcommittee also discussed comprehensive reviews, which the Board had already covered in its closed session, and clinical research in the cancer centers, which Dr. Becker said he planned to discuss later. The Board passed a motion to accept the minutes and the language changes in the comprehensiveness criteria.

Clinical Investigations

Dr. Schein explained that the minutes of this subcommittee were not yet prepared, but he referred to the topics discussed at their meeting. He expressed his hope that attendance might improve with better scheduling. Dr. Schein told the Board that the meeting began with a restatement of the mission of the clinical trials program, stating that the overall mission of the National Cancer Program cannot be fulfilled unless there is a strong, effective national resource available for translating laboratory-based advances in cancer biology into practical new standards for cancer prevention, diagnosis, and treatment. He added that the committee will work closely with the NCI to ensure an effective, focused, and adequately funded program to support that mission. He emphasized giving clinical trials a priority commensurate with the responsibilities they will have in changing national cancer statistics.

Dr. Schein said that Dr. Wittes prepared a review of the reorganization of the programs that focused on clinical investigations, and Dr. Klausner also spoke on this subject. The subcommittee discussed coordination and linkage between the intramural and extramural programs, which has been effective in the past. Dr. Schein mentioned the new ideas coming

from intramural programs that require testing in larger clinical trials. He also suggested that closer cooperation is needed between the cancer centers and the cooperative groups.

Another priority identified by the subcommittee is the prioritization of resources for clinical investigation. Dr. Schein said that discussion of the strategy focused on the incidence and importance of specific tumors. He cited the subcommittee's strong belief that a program dedicated specifically to lung cancer is needed to effectively improve national cancer statistics on incidence and survival. The subcommittee also expressed concern over the possibly insufficient priority given to pancreatic cancer, which is increasing in incidence and is difficult to diagnose and treat.

Dr. Schein said that the committee also discussed the budgetary allocation and mechanisms for funding clinical investigations, as well as concerns in the extramural community about obtaining grants for R01s. He mentioned a recent closing of 15 investigational new drugs (INDs) by the NCI, which he fears may be interpreted as NCI phasing out its commitment to clinical therapy development. Dr. Schein said he was assured that the NCI holds about 170 active INDs, which indicates a strong involvement in this arena, and that 60 were closed out as part of a housecleaning effort. He requested that the committee receive a list of the active INDs and the 15 closed out.

The subcommittee also dealt with a request from the NCAB working group on implementation of the SENCAP recommendations. Dr. Schein said they felt that translational research should be made a priority in terms of encouraging collaboration between basic scientists and clinical investigators, and to provide a mechanism for ensuring that their mission can be fulfilled. The other area considered a priority was support for the development of implementation access to new cancer care technologies and therapies.

Dr. Rimer assured Dr. Schein the Board would receive the minutes that morning. Dr. Bishop asked whether the subcommittee discussed the status of plans to revitalize the Clinical Center. Dr. Klausner said that issue has not been decided because of the unresolved budget issues. Dr. Bishop asked whether the Board's exercise of influence would be helpful. Dr. Schein spoke about scrutiny of the intramural program's productivity and changes in its administration, as well as the unique value of the Clinical Center for conducting translational research and the importance of preserving that intramural facility. Dr. Klausner agreed with Dr. Schein's statements and mentioned that Dr. Philip Pizzo, in response to a recommendation in the Bishop-Calabresi report, had established a protocol review board of intra- and extramural investigators. One of the tasks of this group is to provide a quality control review of the protocols in the Clinical Center and to coordinate intra- and extramural activities to facilitate communication, prevent duplication, etc.

Dr. Klausner asked whether Dr. Schein's subcommittee or the NCAB as a whole plans to interact with Dr. Varmus' clinical investigations and clinical research working group. Dr. Schein said that the subcommittee discussed designating a liaison from the Board to the NIH committee, since they will undoubtedly be addressing many common issues. Dr. Klausner agreed to assist in facilitating this endeavor.

Dr. Klausner also suggested analyzing the data collected on RPG support for clinical research, specifically patient-oriented research. He felt that the NCI should continue to gather

such informative data to provide guidance in handling patient-oriented research under the current granting system. Dr. Schein estimated that large amounts of funds are allocated, but expressed doubt that the majority is being spent on high-quality, high-priority clinical research. He proposed increased scrutiny and tighter standards, and mentioned the concern in the extramural community that new research concepts and new protocols are difficult to get through the current Cancer Therapy Evaluation Program (CTEP) mechanism. He described the process as long, difficult, and reinforced by the fact that intramural investigators sometimes use extramural mechanisms as well. He told the Board that these issues are part of his full agenda to ultimately create a focused, efficient, and adequately funded program. Dr. Klausner endorsed these efforts and told Dr. Schein that his subcommittee should be involved in creating the charge to the Board of Scientific Advisors to oversee a review of the clinical trials mechanisms, infrastructure, etc.

Dr. Calabresi asked Dr. Klausner about the status of the integration among the Navy Branch, the Bethesda Clinical Center, and the Frederick clinical program. Dr. Klausner explained that there is substantial activity, but it is still in an early stage. He explained that Dr. Martin Abeloff is chairing an international search for a permanent director of clinical sciences, and complimented the work of Dr. Pizzo as acting director.

Planning and Budget

Dr. Sigal expressed her pleasure at the subcommittee's change in attitude, which she attributed to Dr. Klausner's energy and excitement. She told the Board that the House markup of the President's budget included an increase of 5.7 percent, which will allow for a 25 percent success rate in RPGs. The increase may go down; nonetheless, Dr. Sigal estimated that the NCI budget for 1996 will be adequate. She warned that future budgets may not be as generous.

Dr. Sigal expressed her optimism for the Bypass Budget, which will be made shorter with more realistic funding requests. She said the document will address the opportunities and the consequences of not doing research, and she thanked Dr. Klausner for his role in making the kind of format and content changes that the subcommittee has long advocated.

Dr. Sigal announced that Dr. Sondik will head a thoughtful and comprehensive new strategic planning process, incorporating the input from members of the Boards of Scientific Counselors and Advisors, the Executive Committee, and the NCAB.

Dr. Rimer mentioned discussion of involving the Board in the substantive development of the budget. Dr. Sigal agreed that this is an important change, adding that the NCAB will be incorporated into the process so that the Planning and Budget Subcommittee will have time to participate in a meaningful way.

The Board passed a motion to approve the subcommittee minutes.

Special Priorities

Dr. Rimer complimented Drs. Wilson and Gray and Ms. Mayer and Ms. Schneider on their work in planning a special meeting on recruitment and retention of minorities. Dr. Wilson explained that the newly formed subcommittee is dedicated to both women and minorities. He expressed the sentiment of the subcommittee that they should become more than simply a well-informed group, and seek to make a substantial impact on a selected few important issues.

The primary goal of the upcoming conference is to improve recruitment and retention of minorities in clinical trials. Dr. Wilson said that the subcommittee decided to hold a conference in which knowledgeable speakers would clearly define the problems, identify the definable minority groups, address the legal issues, and explain the cultural and behavioral factors that come into play. Dr. Wilson handed out a draft of the program for the conference, which will take place on January 26 and 27, 1996, in Washington, DC. Invitations will be sent to ensure participation by various groups, but the conference will be open. Dr. Wilson suggested that Board members send the names of organizations they would like to see invited to Ms. Schneider to be certain they are on the invitation list.

Dr. Wilson highlighted two important issues that were not discussed—one being ethical issues in recruiting minorities. He expressed concern that clinical investigators may be offering minorities unrealistic expectations in order to obtain their participation and meet goals for minority recruitment. The role of the local institutional review board should be to make it known that such unethical practices will not be tolerated. A second issue of concern to Dr. Wilson was defining the term "minority" and standardizing the terms used to refer to various groups.

Dr. Bishop asked whether the subcommittee had discussed changes in the political climate regarding affirmative action, particularly with respect to NIH policies on requirements in training grants. Dr. Wilson responded that the subject did not arise, and that he views NIH's and NCI's commitment to this issue as remaining firm.

Dr. Kalt treated the conference focus as separate and distinct from Dr. Bishop's question, noting that the topic of diversity in clinical research is always valid because of the underlying biological differences across populations and the need to ensure applicability of clinical trial results to the population as a whole. The issue of training initiatives and the need for diversity among researchers is an arguable necessity to do business; cultural sensitivity is obviously important in social and behavioral research, and it is also an important element of research design, the infrastructure, etc. Dr. Kalt said there have been no legal challenges to NCI's current policies and practices, so they will be examined for appropriateness when they arise.

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

Dr. Klausner asked Dr. Becker whether the Basic and Environmental Research Subcommittee dealt with questions of comparing methodologic problems and challenges in looking at environmental risks for cancer. Dr. Becker said that the presentations were quite brief, and that some speakers emphasized differences in their approaches. Dr. Klausner

mentioned that he has asked the National Academy of Sciences about applying Geographic Information Surveys (GISs), which developed as a marketing information methodology, to chronic diseases and environmental risk.

Dr. Klausner introduced and welcomed Dr. Alan Knudsen to the NCI. Dr. Rimer joined him in welcoming her former mentor from Fox Chase Cancer Center, and described Dr. Knudsen as one of the individuals who fundamentally changed our understanding of cancer. Dr. Becker informed the Board that Dr. Knudsen won the highest award from M.D. Anderson at its conference on genetics and won the Berkner award for 1995.

Dr. Rimer introduced Drs. Day and Kimes, noting that they would discuss a questionnaire sent to the cancer centers to assess the impact of managed care on their activities.

XI. IMPACT OF MANAGED CARE ON CLINICAL RESEARCH—DRS. ROBERT DAY AND BRIAN KIMES

Dr. Day began by reviewing the recent history of health care reform. During the past several years, health care reform has been a prominent issue. A few years ago, the Administration introduced a massive proposal for reform which, after heated debate, was not enacted. Dr. Day suggested that the unknown impact of instituting broad reform of health care, particularly cost containment and an employer-mandated provision for funding, led to its defeat.

The debate, however, caused clinical researchers to become extremely concerned about patient access to specialized care in an environment of managed care, which would potentially place limits on an individual's choice of provider. The future of the support that insurance companies had traditionally provided for clinical research was also in question. The importance of this support was highlighted by the following example. When Dr. E.D. Thomas began performing bone marrow transplants in Seattle in the late 1960s, NCI provided all of the funding for care of those patients. Today, NCI grants include $500,000 a year to support patient care costs, and the remainder—which is approximately $90 million annually—is covered primarily by third-party payers. Researchers are worried that this funding source may disappear. Patients are concerned that their ability to access care at a facility that will provide the best care for their specific condition will be diminished in the managed care environment. Advocacy groups are working to protect the rights of patients to be able choose appropriate facilities.

Dr. Day explained that point-of-service issues, such as the ability of patients to seek care from providers outside of a managed care plan when their condition warrants this action, were among the obstacles to the adoption of health care reform last year. Both patients and providers voiced their concerns to Congress. It became clear that many unforeseen problems would surface in a total managed care environment. However, despite the lack of federal legislation and the repeal of State health care reform laws, rapid expansion of managed care is occurring in various areas of the nation.

In response to the growth of managed care, Dr. Day continued, a survey containing five basic questions related to the impact of managed care was developed and distributed to 42

cancer centers. Excellent response rates were achieved for the survey, primarily as a result of the efforts of program staff in contacting the individual centers.

Dr. Day outlined the survey results to each of the five questions. The first question asked the centers to characterize—*more*, *less*, *the same*—any change in patient population size. He informed NCAB members that some centers reported increases, which was unanticipated, while a smaller proportion indicated that they had experienced a decrease, and a large proportion reported no change in the size of their patient population. Dr. Day added that future surveys will attempt to quantify these responses.

The second question asked the cancer centers to describe—*more*, *less*, *the same*—the number of individuals eligible for trials and the number of individuals who entered trials. The responses to this question also suggested that no major changes had occurred. He reiterated that at this point most data are qualitative.

The next question probed fluctuations in reimbursement denials and requested documentation of these changes. Fifteen centers reported no difference in the number of denials, 10 increased, one decreased, and seven indicated that they did not have the necessary data to answer the question. Many of the denials represented partial denials, where certain tests or drugs may not be covered, but the rest of the patient care cost was reimbursed. Dr. Day added that in the future, more quantitative data will be collected and analyzed.

Question four asked the centers to characterize changes in reimbursement. Most of the centers reported decreases in reimbursement, which is consistent with the experience of most physicians who are currently practicing medicine. Dr. Day commented that the fact that no center reported an increase in reimbursement is a revealing piece of information that he would address when he presented his conclusions.

The final question required centers to describe positive or negative changes that had occurred related to patient care financing and delivery. Most of the centers reported more time is needed to resolve reimbursement issues. Dr. Day remarked that his personal experience supports this response. A great deal of time is required to negotiate with insurance companies for patients who require specialized care, particularly when a patient receives care at a facility not affiliated with their insurance provider. Major costs are also associated with the effort attending physicians must expend to justify each patient's plan of care for insurers. Dr. Day pointed out that these costs are not included in health care cost figures and, therefore, are costs that the health care provider or the patient must fund. Other costs, such as a patient leaving the hospital earlier after a procedure, or having outpatient surgery to avoid having to stay in the hospital, are also not included in health care costs. Dr. Day stressed that, consequently, total costs of care are underestimated.

Dr. Day indicated that strategies to handle changes in the health care environment are being actively developed, as almost all cancer-related clinical researchers are affected by reductions in reimbursements for cancer care. He informed members that a number of cancer centers and their affiliated organizations are proposing to form a network that will provide full management and care for patients who are diagnosed with cancer, at a negotiated rate. The coverage will be part of an overall insurance package that will be available through either the primary national insurance companies or the major national employers who are self-insured. It

is becoming increasingly necessary for medical schools to develop affiliations with community hospitals and providers to provide students with opportunities for clinical training. The effort to develop strategies to cope with changes in the health care environment is also not included in estimates of total health care costs; however, it is a valid and substantial cost.

Dr. Day suggested that quality of care may be jeopardized by the reported changes in the health care environment. He pointed out that this is a qualitative, not quantitative observation. Dr. Day suggested that as cost containment becomes essential, work by important ancillary personnel, such as social workers, occupational therapists, and skilled nurses will be eliminated. He underscored that, currently, most centers are effectively coping with the new health care environment, primarily by actively seeking strategies for reducing costs, such as forming networks.

A marked decrease in the discretionary revenue that is available to support clinical researchers for the portion of their time that is devoted to academic studies has occurred. Consequently, discretionary support for trainees or new investigators has diminished and faces further reductions. Dr. Day indicated that this is one of the primary issues facing clinical researchers.

Dr. Day remarked that several centers have begun to use their general clinical research centers to conduct Phase I and II studies. In the past, the clinical research centers were not used as much because the cancer center could accommodate all of the patients; however, some of these research centers have begun to care for cancer patients and are therefore attractive mechanisms for conducting cancer research. In addition, Dr. Day pointed out that cost containment pressures often lead to increased efficiency, of which multidisciplinary clinics are an important aspect. Multidisciplinary clinics usually provide better patient care and may act as better resources for research.

Networking will improve relationships between researchers and primary care physicians, who are important because they are not only the primary source of patients for cancer centers, but also provide continuing care for patients once they leave the center. Protocol discipline will be challenged by networking, because laboratory tests will be conducted at different centers as each patient progresses through their care. Care may be provided by a managed care facility, primary care provider, specialist, or cancer center, and, therefore, standardization will be difficult. However, networking will allow researchers to form closer ties with primary care physicians, who can then be encouraged to offer various cancer preventive services.

Dr. Day reported that the primary finding from this survey is that cancer centers are not yet facing a crisis; however, the data indicate the situation may worsen. He indicated that the centers will continue to be surveyed semiannually or annually, to allow them to quantify results, refine the questions, and develop a database. These data will be integrated with the information collected through standard reporting from the cancer centers, particularly the number of patients eligible for trials, the number of patients entering trials, and the breakdown by organ site. The combination of information will potentially allow NCI to track trends related to the impact of managed care. Dr. Day allowed that some information will necessarily be qualitative; however, efforts to get quantitative data will be made. He concluded by

reemphasizing that monitoring the effects of managed care on clinical research is one of the most important issues in cancer research.

Questions and Answers

Dr. Rimer asked participants to limit their discussion to policy issues that the NCAB can address. Dr. Sigal commented that the data reported by the survey seem to be inconsistent with information from other medical institutions. She stated that it does not seem possible that 10 of the cancer centers reported no change in reimbursement. Dr. Fred Becker remarked that the wording of the question may have allowed an incomplete picture to be presented; for example, if a cancer center was historically reimbursed at a low percentage, but experienced no decrease, then the center would have replied that their reimbursement remained stable. Therefore, responding that no change had occurred was not necessarily a positive answer. Dr. Rimer suggested that perhaps the appropriate individuals at the centers had not completed the surveys, or that they may have answered the questions without actually researching them.

Dr. Brian Kimes offered that the survey should be viewed as a preliminary attempt to characterize the various effects of managed care on cancer centers. He stated that while some of the responses were extremely detailed and well thought out, others were quite cursory. Dr. Kimes added that the responses can only be as good as the survey itself, which, by necessity, was prepared in haste. In the future, the survey questions will be more carefully constructed.

Dr. Rimer commented that it was an outstanding initial effort. Dr. Klausner agreed that the survey was an excellent start and represents a valuable effort, but cautioned that when collecting this type of data, a very serious attempt to be accurate must be made. He pointed out that, in effect, the survey had concluded that no crisis exists; however, this conclusion may not be entirely accurate.

Dr. Klausner suggested that several important lessons are provided by this initial survey. If the NCI is going to collect these data, then a very detailed plan of the study, including methods for designing the questions and collecting and analyzing the data, needs to be developed. He pointed out that the preliminary questionnaire can be used to assess how certain questions might be reworded. In addition, the survey suggested other areas that might merit surveillance, such as the amount of time individuals devote to work other than actual clinical research (i.e., justifying patient protocols to insurance companies, etc.). Dr. Klausner stated that it seems very important to characterize changes in this area. Survey information regarding effective strategies that are being employed by various cancer centers to offset reductions in reimbursements is also quite valuable for other centers. Finally, the survey raises the issue of the relationship between institutions that have cancer centers, but may or may not have general clinical research centers.

Dr. Day responded to these comments by stating that there is considerable geographic variation in the effects associated with managed care; for example, the severe changes experienced at the Arizona center are not consistent with those in Nebraska and Colorado. He asserted that the amount of change that a center experiences is related to the degree of managed care penetration in that area. In certain areas, such as Massachusetts and California, nearly 50 percent of the population is covered by managed care plans, while managed care represents only 5 to 10 percent of the populations of other areas. Dr. Day added that it will be difficult to

persuade teaching hospitals to respond to requests for information that require tracking of costs related to specific diagnoses, or by a patient's geographic residence. Hospitals' financial systems track information related to the cost of tests and the date that care is provided; they do not necessarily link this information to particular patients or their type of care. Dr. Sigal commented that there are sources of published data that collect information related to this topic, which she is willing to discuss at another time.

Dr. Kimes reaffirmed Dr. Day's comments regarding the variable capacity of the different centers to collect data. Some of the centers have clear, close links between their patient and research population bases, while others have more difficulty identifying this link because of the institution's inherent organization. This is one of the longstanding challenges to the reliability of any clinical database.

Dr. Becker agreed with Dr. Day's perspective that there is tremendous variation among the centers, which may be responsible for the observable variation in responses to managed care. He asserted, however, that while only 25 percent of Houston's population is covered by managed care, in 14 months the Houston cancer center's income decreased by 34 percent. Moreover, predictions of trends related to managed care are that penetration will occur at an increasingly rapid rate and that this will be multiplied by predatory pricing practices, whereby hospitals will be forced to competitively bid for contracts with managed care organizations, who will award them to the lowest offeror.

Dr. Becker suggested that the discussion should focus on the impact of managed care on the monies available for clinical research at cancer centers, which is a manageable topic, and not consider the overall impact of managed care. The amount of money available for clinical research is partially dependent upon the amount the center devoted to clinical research prior to the influx of managed care; an estimation of the change in income for a specific cancer center may not provide this information. Therefore, it is important to collect data that indicate how much of the center's budget was allocated to clinical research in the past and how much the center will be able to devote to this area of research in the future. Many centers may need their residual funds in order to continue functioning and, therefore, may no longer be able to support clinical research. Dr. Becker concluded by stating that he believes that if the survey data indicate that there is no crisis, then they are wrong. Anecdotal information from certain areas of the country can readily support this conclusion, and Dr. Becker predicted that other areas will soon be in crisis as well. As crisis strikes, significant reductions in clinical research will occur, as many millions of dollars are invested in this area. Therefore, it is highly important to address this specific topic.

Dr. Wilson remarked that in light of the fact that managed care has existed in California for the longest time and at the highest penetration levels, fairly strong conclusions regarding the impact of managed care in other areas of the nation can be reached by studying their experience. He asked whether data from California were included in the survey. Dr. Kimes confirmed that the University of California at San Diego (UCSD), the University of Southern California (USC), and the the University of California at Los Angeles (UCLA) all contributed data to the survey. He pointed out that none of these clinical centers reported reductions in the number of patients entering clinical trials. All of the California cancer centers indicated that they are having difficulty getting reimbursed by the insurance companies and having trouble negotiating the changing system, but none reported a decrease in patients. Dr. Kimes

remarked that he is particularly surprised by the response from UCSD, which does not reflect the concerns that investigators from this center have been informally voicing. Dr. Day agreed with Dr. Kimes' surprise at UCSD's response, and added that the response from Irvine also failed to include the concerns that have been voiced.

Dr. Rimer suggested that this may indicate that the survey's questions need to be reworked. Dr. Day asserted that he does not believe that the data are inaccurate, but that there are substantial geographic variations. He added that while Dr. Becker's dire predictions may come to fruition, they also may not, because there are conflicting trends. One thing that is definite is that practicing medicine and caring for patients has lost its profit margin. Since the cost of health care has not decreased, these profits must be filtering into other health care-related industries. Dr. Day added that where the profits have gone is a topic for another discussion, but stressed that the single most important message from this survey is that funding for clinical research and training will decrease as the overall income decreases.

Ms. Debbie Mayer emphasized the point that a great deal of effort is spent not only trying to get reimbursement, but also in recruiting and retaining patients in clinical trials. It is important to monitor how many patients are screened and actively recruited as compared with how many enter and remain in the trials. Managed care may significantly increase the effort needed to recruit the same number of individuals to clinical trials.

Dr. Wittes suggested that the results of the survey can potentially be read in several different manners, and that he believes they do reveal a crisis. Those organizations that report change, all report unfavorable ones; and a preponderance of centers indicate that they are encountering substantial problems. Therefore, despite the fact that some centers have experienced no changes and that the total number of patients is slightly increased, these findings are not as important as the other indications. Dr. Wittes asserted that more than data collection is necessary; otherwise, NCI's only achievement will be to document the destruction of the clinical trial system.

Dr. Day asked Dr. Wittes for his ideas regarding what should be done to preserve clinical trials. Dr. Wittes admitted that at this point his ideas are not fully formed, as this is an extremely complex problem that involves numerous issues. For example, strategies for preserving cancer center-based programs in innovative clinical research will be different from those that are used to protect the cooperative clinical trials. Dr. Wittes offered that the second issue, that of preserving cooperative clinical trials, seems to be more manageable, as it is conceivable that national consensus or even legislation could be used to force managed care organizations to fund these efforts. This is primarily true because both the general population and managed care organizations benefit from the conduct of these trials, particularly those that have endpoints that are relevant to third-party payers, such as outcome and cost-effectiveness measures. Preserving funding for innovative clinical research will be much more challenging.

Dr. Day pointed out that the largest national third-party payer, Medicare, specifically excludes reimbursement for experimental or investigative efforts. He suggested that the NCI should work to change this.

Dr. Schein read a statement from a letter sent to him by Dr. Sidney Salmon. In the letter, Dr. Salmon indicated that at the last Subcommittee on Budget and Planning meeting, he

stated that NCI should include a major portion of clinical research expense in the Bypass Budget request. During the past 25 years, the NCI has progressively reduced its funding of patient costs for clinical research related to cancer treatment, but not for cancer prevention. Treatment-focused R01s, P01s, and cooperative group grants at NCI represent a minor expenditure at this point. The difficulties that are being experienced at the Arizona cancer center reflect this trend.

Dr. Schein suggested that two other factors should be explored by the surveys. The extent of cost-shifting to other industries, such as pharmaceuticals, should be examined. It is possible that the fact that a crisis has not been revealed by the survey data may partially be a result of increased support from the private sector. Indeed, a large portion of clinical research that is currently conducted, particularly in terms of cancer treatment and diagnostic technologies, is funded by the private sector. This buffering action may be decreased as cost containment spreads to the private sector as well. Dr. Schein summarized by stating that a complex interaction of factors is occurring, each of which must be individually identified.

Dr. Schein also pointed out that the influx of managed care is occurring in a highly regulated environment. A survey conducted by the Lasagna Committee indicated that about 75 percent of the use of FDA-approved cancer therapies was for off-label indications, which involves the use of a proven technology for a condition for which it was not formally approved. The FDA typically provides a narrow label for an approved drug, while the agent's potential use as recognized by the medical literature may be much broader. For example, Taxol was approved only for treatment of ovarian cancer; however, its efficacy has been clearly demonstrated in other cancers, such as lung and breast. These other indications may be approved in time; however, no quick method exists for doing so. Dr. Schein asked how closely third-party payers read the narrow FDA indications and adhere to reimbursing only costs for cancer therapies that are used for indications approved by the FDA. Dr. Schein added that because Dr. Paul Calabresi recently attended a meeting that discussed this topic, he might be able to address this question.

Dr. Calabresi indicated that his experience and contact with other investigators reveals a great deal of concern in several parts of the country regarding reimbursement for clinical research. At the President's Cancer Panel meeting in July, one investigator from Southern California commented that if a node-positive woman is treated with CMF or CAF as therapy, her health care costs are reimbursed. However, if the investigators wish to conduct a trial to see which therapy is more effective and more cost-effective, the patients' costs will not be covered. This anecdote seems inconsistent with the survey data, which Dr. Calabresi added, simply may not accurately reflect the level of personal concern that currently exists regarding funding for clinical research. He supported the concerns that Drs. Wittes, Schein, and Becker had shared with NCAB members.

Dr. Wilson stated that two primary issues affect clinical research income at cancer centers—reimbursement of patient costs and communication of technological information to insurers. In California, the level of reimbursement for each patient has decreased at least 34 percent with no change in patient access to trials. In the future, gaining access to freestanding cancer centers may become more difficult. However, if and when trials are conducted in facilities that treat multiple diseases, these problems may be eliminated.

The other problem involves poor communication of technological advances to third-party payers. Theoretically, there is no reason for an insurance company not to support a trial that seeks to identify the more effective, or cost-effective, of two or more therapies or screening tests, as the benefits from these results would be passed onto the third-party payer. Clearly, a trial that demonstrates that a screening test is not cost-effective and thereby eliminates its use saves insurance companies a great deal of unnecessary expense. These questions can only be answered through clinical trials and, therefore, if insurance companies do not want to support them, then the NCI has not effectively marketed clinical trials.

Dr. Vaitkevicius remarked that it is important to differentiate between the various types of clinical trials that are conducted. He added that his center attracts a great deal of patients because the center participates in clinical trials. Consequently, the center subsidizes these trials as much as possible; however, to be able to subsidize the maximum number of patients for as long as possible, the least expensive trials are receiving the most support for accrual. Therefore, the total number of trial patients may not be an accurate measure for assessing access to a trial, as cost considerations exist as well.

Dr. Wittes commented that the data related to the number of patients accrued to clinical trials should not provide relief for concerns about the future of clinical trials. He informed members that the presentations at Dr. Varmus' blue ribbon panel on clinical investigations were primarily negative, with one presenter, Dr. Haile Debas, Dean at the University of California at San Francisco, stating that if effective recommendations are not developed and implemented soon, the nation's academic health centers will be in real jeopardy.

Dr. Wittes suggested that those centers who reported that their accruals have remained steady may not have noticed other factors indicating that clinical trials research is slowly being undermined. They are also having to work very hard to maintain the status quo. Dr. Wittes also announced that the clinical research community must assume part of the responsibility for motivating insurers to support clinical trials. Some insurers have been willing to form partnerships with clinical researchers. For example, several companies were willing to support health care costs for breast cancer bone marrow transplant trials that explored clearly defined questions and offered strong prospects for answering these questions. The process for developing and executing these trials has been quite lengthy, however, and if clinical researchers want to encourage future partnerships, then they are going to have to make the process simpler and quicker. Moreover, the clinical research community needs to establish its credibility within the insurance industry.

Dr. Goldson suggested that the scientific community begin to approach third-party payers, starting out with smaller matters. For example, the NCAB could target a few very specific tumor sites, such as lung and esophagus, that have not responded well to technologies that insurers are currently funding. By asking insurers to devote the money to new clinical trials that they were previously giving to these ineffectual therapies, NCI could potentially encourage the support of a few trials. This would be particularly effective if the costs associated with the trials could be streamlined by only including essential follow-up tests, which may allow the trials to be more consistent with managed care spending philosophies. As NCI gains the confidence of the insurance industry, support for other trials could potentially be garnered.

Dr. Rimer requested that individuals begin to focus on recommendations for improving the survey and tracking system for clinical research needs, since the discussion thus far had primarily been a debate about whether good data can ever be accrued or whether more data are needed. Dr. Rimer suggested that the survey be viewed as a preliminary data collection instrument that can now be refined. She called for recommendations for questions that will provide better data. Dr. Rimer also indicated that the data collection process should be viewed as ongoing to be able to provide not only NCI and NIH with continual feedback regarding clinical research needs, but also the insurance industry. A tracking system must be established that includes all the various factors that have been cited as indicators of changes in clinical research needs. For example, physician investigators are reporting that because revenues are down, they have to work later to see more patients; this type of information needs to be tracked as well. Dr. Rimer stressed that action needs to be taken soon, or clinical research programs may begin to fall apart.

Ms. Mayer suggested that reimbursement, recruitment, and retention costs be examined, in the best, average, and worst case scenarios. Dr. Sigal reiterated that at the last meeting she had suggested that some NCAB members meet with representatives from some of the major insurers and managed care organizations to try to establish grounds for partnerships. She stated that if a meeting like this cannot garner support for clinical research, then perhaps legislative action is needed. Indeed, the Harkins-Hatfield bill presented the possibility of establishing a set-aside for clinical trials by third-party payers. Dr. Sigal stressed that it is obvious that a major problem exists, regardless of the accuracy of the survey data; therefore, discussions with the major insurers and managed care organizations should begin immediately.

Dr. Calabresi responded to Dr. Sigal's comments by indicating that during the SENCAP meetings, both Blue Cross and Aetna representatives had discussed funding clinical trials—they were against funding Phase I trials, undecided about Phase II, and very positive about supporting Phase III clinical trials. Dr. Calabresi stated that the representatives expressed the belief that Phase I trials are more research-oriented trials, which NIH should support. He commented that their stated position is clearly not supported by their actions. Insurance companies are going to have to be convinced of the fact that for certain cancers, the best possible treatment is through clinical trials.

Dr. Schein requested that the next questionnaire be reviewed more broadly, so that additional feedback regarding the type of data that should be collected is received. This may help to improve its comprehensiveness. Dr. Schein also stated that it would be helpful to include data regarding who responded from each institution, whether it was a clinician or an administrator. He affirmed Dr. Vaitkevicius' comments by stating that the NCAB should be concerned that expense, rather than need or scientific merit, may become a consideration when deciding which clinical trials to initiate. The questionnaire should collect more qualitative information about the type of research each cancer center is doing, the types of trials they are willing and able to conduct, and who is supporting the research. Also, the issue of funding from the private sector, such as pharmaceutical companies, should be probed. Dr. Schein concluded by stating that the state of the art needs to advance, primarily through additional exploratory work for which it is difficult to acquire reimbursement.

Ms. Fran Visco remarked that it is crucial that discussions with third-party payers continue regarding their reimbursement of health care costs associated with clinical trials. She asserted that the NCAB must address the issue of primary care physicians who treat patients off-protocol with therapies that are available through clinical trials. She cited the example of bone marrow transplants, for which insurance carriers are willing to help fund clinical trials. Primary care physicians are supporting lawsuits that women initiate to get reimbursement for bone marrow transplants that are performed outside of protocol. Some physicians even advertise that they will perform this procedure off-protocol. Ms. Visco asserted that this issue must be addressed.

Dr. Wilson suggested that the NCAB convene the leaders of managed care organizations, present the current concerns related to funding for clinical research, and explain the benefits of clinical trials to their own companies. If they cannot be convinced of the trials' value, then the NCAB clearly needs to give further consideration to exactly what the benefits of clinical trials are, not only for the general population, but for third-party payers as well. He recommended that the Board also solicit these leaders' advice on how clinical researchers can work with the managed care system. By framing clinical trials as something that are beneficial to their companies, as opposed to simply a huge expense, there is a greater chance that they will support these efforts. Dr. Wilson added that, in the final analysis, either managed care organizations will voluntarily support clinical trials because they are convinced that it is an effective, and cost-effective, step to take, or their support will have to be mandated through legislation. Garnering support for such legislation would be extremely difficult and unlikely to succeed.

Dr. Day pointed out that the Federal Government is a primary health care payer through Medicare, which it completely controls through the Health Care Financing Administration (HCFA); Medicaid, which receives about half of its reimbursement funds from federal money; the Federal Health Employees Benefit Program; the Department of Defense, which covers military dependents and retirees; and other programs. These programs represent a large proportion of the nation's health care insurance coverage and, therefore, should be immediately presented with the concerns discussed at this meeting. HCFA would be an excellent place to start since it is in the same department as the NCI and it handles Medicare, which has specific exclusions for clinical research, even though 50 percent or more cancers occur in individuals who receive Medicare. Dr. Day recommended that the Board or Dr. Varmus meet with each of the federal insurers and discuss the issues surrounding third-party payer support for clinical trials.

Dr. Kimes reaffirmed his support of the findings from the cancer center survey, which has been confirmed through anecdotal information from university deans, who have a different perspective then center directors, since they oversee their institutions' economic situation in a more significant manner. Dr. Kimes also questioned the value of any survey data, particularly if managed care is growing as quickly as discussed at this meeting. By the time the data are collected, it may be too late to use them effectively. Dr. Rimer pointed out that there is no reason why the surveys cannot be completed by several individuals from each center, which might ensure that a broader perspective is reflected in the data.

Dr. Klausner provided his perspective on the need to balance action and data. He recognized that the impact of managed care on clinical research is an extremely complicated

issue. Concentrated efforts, as well as hard data, will be necessary to convince either insurers or Congress of the need to find funding for clinical trials. He assured NCAB members that, right now, Congress will not propose a new tax to fund clinical research; therefore, other strategies must be pursued. Dr. Klausner asserted that NCI cannot just present insurers or managed care organizations with an explanation of the benefits of medical advances and then expect them to offer support for clinical trials. This is particularly true because some individuals believe that the development of medical technology is responsible for the increase in health care costs. He explained that while education is important, clear, meaningful data must be included in the effort. The data must address the problem that is being presented. For example, if the threat is that the academic health centers are going to collapse, then data that support this assertion must be provided. While the situation is probably not that extreme, data that specifically document the extent of the demise of academic health centers, as well as the threat to the ability to conduct clinical research and train new investigators need to be presented. Dr. Klausner supported the previous assertion that asking cancer centers whether they are accruing patients at the same rate as in prior years will not provide NCI with useful information.

Dr. Sigal commented that accurate data are necessary and achievable and added that data banks do exist that can act as resources for rapidly attaining information related to the effect of managed care on clinical trials. She supported the idea of holding discussions with third-party payers and remarked that while it is important to speak with federal entities that provide insurance, these agencies typically move slowly in implementing changes. Dr. Sigal suggested that NCAB follow all three courses of action and added that any data that are collected should be obtained from experts to ensure they are meaningful.

Dr. Day expressed concern over some of the reactions to the survey data and reiterated that his experience confirms the accuracy of the data. To verify this point, he asked whether cooperative group accrual rates are decreasing. Dr. Wittes indicated that the groups are having more difficulty accruing participants, but stated that he does not know whether the enrollments are actually declining. Dr. Rimer clarified that Board members are not questioning the accuracy of the data, but whether the information reveals the entire story of the state of clinical trials research.

Dr. Day asserted that the questions that were asked by the survey were answered accurately. If different questions need to be asked, then they would have to be directed to other sources. He reminded members that the survey inquired about changes in the number of patients enrolled into clinical trials. Consistent with the experience at his cancer center, no decreases in enrollment have been experienced yet. Indeed, his center has seen increased activity lately. Dr. Day offered that he does not question the demise described by university deans regarding the potential collapse of discretionary funding, since reimbursement at teaching hospitals has declined by approximately one-third for each case. He suggested that these changes may require deans to dramatically alter the way in which they manage their institutions' funds and that training activities may have to be reduced, but declared that this still does not signify the end of clinical research or academic medical centers. Dr. Day reiterated that discussions should be held with HCFA and other federal insurers, particularly as a result of the large proportion of cancer patients these groups cover and Medicare's specific exclusion of coverage for experimental or investigative therapies. He emphasized that the issue that should be discussed is whether clinical research will continue to be reimbursed and thereby allow clinical trials to continue. The survey data indicate that the changes encountered due to

the expansion of managed care are variable by State and region, but that, currently, the effects are not drastic. Dr. Day supported this conclusion by stating that the cooperative group trials have not experienced decreased enrollment either. He added that many of those individuals who responded to the survey were administrators, who deal with issues of reimbursement and enrollment daily, not the center directors.

Dr. Becker supported Dr. Klausner's earlier points by describing portions of effective testimony from 20 years ago, when researchers testified before Congress about the importance of basic research—the budget for which Congress was threatening to reduce. The most salient presentations were those that detailed specific cost savings that were gained by the introduction of technologies developed through basic research. He suggested that the NCAB use a similar strategy and discuss clinical trials in terms of exact dollar amounts saved through related discoveries. Dr. Becker recommended that specific medical benefits from clinical trials in terms of quality-of-life improvements, life expectancy, and other definable measures, could be presented to more informed audiences. He assured members that these approaches will provide the most persuasive argument for supporting clinical trials.

Dr. Rimer asked that a subgroup of the NCAB review the survey in light of the discussion. While it is clear that additional data are needed, the Board needs to be aware that they cannot excessively resurvey the centers. She emphasized that this is an extremely important issue that will not be solved through a single discussion or survey. Dr. Rimer indicated that the survey has provided a foundation upon which further work can be built and expressed her appreciation for the efforts undertaken to conduct the survey.

Dr. Day asked whether any action will result from the survey's findings. Dr. Rimer replied that the survey will be viewed as a first step. Dr. Day pointed out that Medicare is scheduled to receive a large budget reduction as part of the process of balancing the budget. He suggested that a group speak with the Senate Finance Committee and the House Ways and Means Subcommittee that handles Medicare to attempt to convince them to remove from the policy the exclusion for coverage of investigative therapies. Dr. Day emphasized that the Committees would not have to commit to providing reimbursement for all clinical trials-associated health care costs, but simply that these costs would not be automatically excluded.

Dr. Klausner stated that Dr. Day's request is reasonable. He reiterated Dr. Becker's point that specific cost savings data must be presented to Congress or third-party payers to garner their support for clinical trials research. Data related to medical benefits alone are not sufficient. Dr. Klausner added that data that relate to the urgency of the situation must also be collected.

Dr. Day remarked that an exhaustive study was completed last year in Washington State to estimate the cost of research health care. By compiling data regarding all protocols that involved human subjects from committee reviews, the research subjects were matched to patients who received similar health care. Research care was shown to represent .5 percent of the cost of health care, which may be an overestimate. Dr. Day indicated that the figures are being reexamined and added that he would be pleased to share the information with NCAB members.

Dr. Wittes informed members that legislation to protect NIH and pharmaceutical company clinical trials is being provided by a coalition of cancer organizations. He characterized the language of the bill as "well considered." Dr. Rimer concluded the discussion by stating that the leaders of the National Cancer Plan need to act as advocates for reimbursement of health care costs associated with clinical research.

XII. NCI PARTICIPATION WITH OWH ON THE NATIONAL ACTION PLAN ON BREAST CANCER—DR. SUSAN BLUMENTHAL AND MS. FRANCES VISCO

Dr. Rimer began this section of the meeting by highlighting the ongoing collaboration between NCI, the NCAB, and the Office on Women's Health to develop and implement the National Action Plan on Breast Cancer (also referred to as "NAPBC" or "Action Plan"). She reminded members that during the previous day an inventory of the proposed awards related to the Action Plan was presented to the NCAB, and stated that a strategic planning meeting was scheduled for the following week to discuss strategies for continuing the effort. Dr. Rimer underscored the role of the NCI and the NCAB in fostering efforts related to the Action Plan. She announced that an update of efforts related to the Action Plan would be presented by Ms. Frances Visco, of the President's Cancer Panel, and Dr. Susan Blumenthal, Deputy Assistant Secretary for Health.

Presentation by Ms. Visco

Ms. Visco introduced herself as one of the cochairs of the Action Plan as a result of her position as President of the National Breast Cancer Coalition. She stated that Dr. Blumenthal is the other cochair. She indicated that since the history of the Action Plan has been presented at previous meetings, she would provide only a brief overview of the activities that have taken place in the past. As a result of the National Breast Cancer Coalition's campaign gathering more than 2.6 million signatures of individual support for making breast cancer a top priority, a conference was held by the Secretary for Health and Human Services. This conference led to the formation of a steering committee and working groups, each of which has developed a strategic plan for its specific area. Ms. Visco indicated that she would provide a recent update of the working group activities and that Dr. Blumenthal would detail the proposals that received funding in August.

Ms. Visco briefly described three of the six priority areas of the Action Plan, which include to: 1) establish a National Biological Resource Bank, which will ensure that resources are available for all areas of breast cancer research, an effort cochaired by Drs. Alan Rabson and Susan Love; 2) promote consumer involvement in decisions affecting the development and implementation of breast health-related services, an effort cochaired by Ms. Jan Hedetniemi, NIH, and Ms. Jane Reese-Coulbourne, from the National Breast Cancer Coalition (Ms. Visco remarked that Project LEAD, which was described in *Oncology Times*, will be vital to the success of efforts related to this priority area.); and 3) examine the etiology of breast cancer, including identification of current research, research gaps, and development of strategies to address those gaps.

Ms. Visco informed members that she would devote the remaining portion of her presentation to providing a more detailed update of the activities related to the other three

priority areas. The first of these priorities is to formulate a long-term plan that addresses the health needs and the ethical, legal, and policy issues of individuals who carry breast cancer susceptibility genes. The working group in this area is cochaired by Dr. Francis Collins of the Human Genome Project and Ms. Mary Jo Kahn from the Virginia Breast Cancer Foundation. Ms. Visco stated that the working group held a workshop on July 11, 1995, in conjunction with the Ethical, Legal, and Social Implications ("ELSI") task force from the Human Genome Project. The conference involved representatives from the insurance industry, government, and the scientific and legal communities and focused on the interaction of genetic information and health insurance. An overview of existing State and pending federal legislation was presented. Based on this information, gaps in legislation were identified and methods for closing them were discussed. Ms. Visco remarked that, in response to earlier discussions related to invoking the support of the insurance industry, discussions with industry representatives during the workshop revealed that while insurers are aware of the economic benefits of clinical research, they will only support it if all of the various companies act in unison. She asserted that this will occur unilaterally only if insurers are compelled to do so.

Ms. Visco presented drafts of the recommendations that emerged from the workshop and the working group. Participants recommended that insurance companies be prohibited from using genetic information to limit coverage or deny eligibility, enrollment, or continuation of benefits. They also recommended that the use of genetic information to establish differential rates or premiums be proscribed. Finally, the participants recommended that insurance companies be restricted from requesting or requiring genetic information to determine an individual's health status.

The next working group has been concerned with strategies for optimizing information dissemination, and is cochaired by Dr. Anna Chacko from the Brooke Army Medical .Center and Ms. Arlyne Draper, President of the Women's Cancer Task Force, Y-Me, San Diego Chapter. Their strategic plan includes an effort to develop a home page for the Internet for the Action Plan. The group also plans to publish an inventory that contains abstract information of funded grants that have emerged from the Action Plan. Ms. Visco reported that the working group is planning a workshop that will focus on identifying barriers to accessing the "information superhighway" and mechanisms for overcoming the obstacles. They also intend to identify and coordinate all breast cancer-related information that is available through the information superhighway, as well as to provide methods for evaluating the various data.

The final working group focuses on clinical trials and is cochaired by Dr. Kay Dickersin from Arm-in-Arm, which is a breast cancer support group in Baltimore, Maryland, and Dr. Leslie Ford from NCI. This group has been working to overcome barriers to clinical trials participation. One of their strategies is to establish a clearinghouse with information regarding the availability of clinical trials. The clearinghouse will act as a resource for women who have questions about clinical trials. The working group is also forming a list of speakers who can present information about the benefits of clinical trials to communities or professional groups. Ms. Visco informed members that the group is also working in conjunction with a public relations expert to design a marketing plan to demystify clinical trials and increase awareness of their availability. The strategy will employ the use of community leaders as recognizable spokespersons to promote clinical trials. Workshops that explore cost factors and reimbursement issues, as well as the status of informed consent and whether it should be altered, are planned.

Ms. Visco announced that the steering committee has scheduled a strategic planning session on September 19, 1995, to address the issue of garnering support and funding for programs that are not research oriented. Ms. Visco thanked Dr. Blumenthal and members of the steering committee and working groups, who have volunteered an enormous amount of time to this effort. She thanked Dr. Edward Sondik for providing his office's computer and technical support for the steering committee meeting, which she indicated saved participants many hours of work.

Presentation by Dr. Blumenthal

Dr. Blumenthal expressed her pleasure at being invited to inform NCAB members about the grant programs affiliated with the National Action Plan on Breast Cancer. She thanked Ms. Visco for the leadership role she has assumed in breast cancer activities and welcomed Dr. Klausner, whose "intelligence, vision, and leadership are three powerful tools we now have in the fight against breast cancer." Dr. Blumenthal commended the efforts of several NCI staff members in relation to the recent grant review process, including Drs. Edward Sondik, Sheryl Marks, Paulette Gray, and Karen Hardy, as well as members of her own staff, including Dr. Suzanne Haynes, Ms. Maria Klebanoff, and Ms. Jennifer Eggers, and Dr. Debra Saslow.

Dr. Blumenthal stated that the goal of the National Action Plan on Breast Cancer is to foster national efforts to identify and resolve priority issues related to breast cancer etiology, prevention, detection, and treatment. The Action Plan has fostered a unique public-private sector collaborative effort to develop strategies, policies, and activities to further breast cancer awareness, research, services, and policies. Related efforts have involved consumers, numerous federal agencies, researchers, and representatives from private industry.

Dr. Blumenthal reported that in April 1995, the NAPBC announced that $8.5 million in fiscal year 1995 funds were being allocated to support administrative supplements, new innovative small grants, and approved but unfunded grants from all federal agencies. The Action Plan solicited both investigator-initiated research and outreach programs that related to breast cancer and targeted one or more of the Plan's six priority areas.

Dr. Blumenthal outlined the timeline for activities related to the solicitation and review of the grants. She reiterated that the RFA for the innovative small grants and the PA for the administrative supplements were announced in April. The applications were reviewed in July and August. Working group meetings were held at the end of August to rank the applications in terms of their applicability to each of the Action Plan's six priority areas. The steering committee then reviewed the applications and their rankings by the working groups and made funding recommendations. Dr. Blumenthal commented that the grants should be paid by the end of the fiscal year. She added that the grant program was designed to provide support for innovative pilot research and outreach projects that might not only result in the development of essential new knowledge related to breast cancer, but also stimulate research in new areas.

Dr. Blumenthal shared portions of the grant solicitations in terms of each of the six priority areas. Regarding information dissemination, applicants were asked to propose novel strategies and mechanisms for distributing information and increasing communication among scientists, consumers, and health care practitioners in relation to breast cancer. Applicants

addressing the biological resource bank issue were asked to propose a plan for establishing a national resource for biological materials that would be available for numerous areas of breast cancer-related research. The priority area addressing consumer involvement asked applicants to present a plan for ensuring consumer participation, including advocacy groups and women with breast cancer, in the development and implementation of programs related to breast cancer research, service, delivery, and outreach. The fourth priority area called for applications that would increase the scope and breadth of etiologic research in terms of biologic, epidemiologic, and behavioral research pursuits. Specific areas that were mentioned included the effects of radiation, electromagnetic fields, chemicals, hormones, personal risk factors, viruses, and gene-environment interactions. Applications that would overcome barriers to women's participation in clinical trials were solicited as another priority area. Finally, applications that address the health needs and legal, ethical, and policy issues of individuals who carry breast cancer susceptibility genes were solicited.

The grant review process for the administrative supplement applications involved the organization of four ad hoc review panels by the U.S. Public Health Service's Office on Women's Health. The panels, which consisted of working group members, consumers and researchers, scored the applications for technical merit. The NCI, in conjunction with the PHS Office on Women's Health, established five ad hoc review panels to score the small grant applications for technical merit. The applications were assigned to panels based on the priority issue that they addressed, which allowed the panels to include the judgments of experts and consumers in related areas. Primary and secondary reviewers were used and the scoring procedures were identical to those used at NIH, including the assignment of rank from 1 to 5 and the utilization of a triage system.

Dr. Blumenthal informed members that the review criteria included the proposed project's originality, the scientific and technical significance for the Action Plan's six priority areas, the appropriateness and strength of the approach, the degree of public/private cooperation involved in the approach, the potential for success, and, when considering supplement applications, the appropriateness of the budget and activities in relation to the parent award.

After the grants were scored, they were then distributed to the relevant working group and discussed in the order of the scores they received for technical merit. The members initially ranked the applications "yes," "revisit," or "no." All of the applications that were marked "yes" or "revisit" were then ranked by members of the working group. Dr. Blumenthal reiterated that the working groups were composed of consumers, researchers, and government representatives. She explained that written justification for the Steering Committee was required when any application received a score from the working group that was different from that of the ad hoc review panel. Dr. Blumenthal added that a consensus was required for the scoring of each application and that if it could not be achieved, then a minority report was developed and provided to the Steering Committee.

Several guiding principles were used by the NAPBC Steering Committee to establish final funding recommendations for the Action Plan's grant program. Steering Committee members tried to balance the funding allocated to applications from each of the six priority areas. In addition, only the top 20 to 25 percent of applications from each working group were recommended for funding to ensure that only high-quality applications were selected. The Steering Committee made substantial scientific merit a priority in recommending applications

for funding. Additionally, balance across the various grant mechanisms—small grants, administrative supplements, and approved but unfunded grants—was sought, keeping in mind the number of applications and the corresponding awards that were recommended.

Dr. Blumenthal announced that a total of 610 applications were submitted in response to the grant solicitation, with a majority addressing the etiology priority area. A diverse group of applications was received overall, with the following percentages of applications addressing each priority area: 1) etiology—50 percent; 2) information dissemination—20 percent; 3) hereditary susceptibility—10 percent; 4) clinical trials—7 percent; 5) consumer involvement—6 percent; and 6) biological resources—5 percent. Furthermore, approximately half of the applications were for small grant awards and half were administrative supplements and intramural grant projects. Ten percent of the applications that were received were previously reviewed grants from other federal agencies that had not received funding because the resources did not exist at the time.

Of the 610 applications that were received, 163 were ranked as "yes," and 99 of these were recommended for funding, which is 16.3 percent of the total number of applications. Of those recommended, 31 percent address biological resources, 14 percent are relevant to clinical trials, and 23 percent are related to breast cancer genetic susceptibility. By funding mechanism, $3.6 million will be devoted to small grants, $4 million to supplement awards and intramural grants, and $1.6 million for unfunded grant applications. These figures translate into 39 percent of the funding being allocated to small grants, 43 percent to administrative supplements, and 17.2 percent to unfunded grants. Dr. Blumenthal reminded members that all of the slide information was included in their information packet.

Dr. Blumenthal concluded by thanking the NCAB for their support of the Action Plan. She indicated that she is pleased to see progress being made in its research program and strategic planning process.

Questions and Answers

Dr. Rimer thanked both Ms. Visco and Dr. Blumenthal for their efforts on behalf of the Action Plan and asked for any comments, particularly regarding questions that had arisen at yesterday's closed session. Ms. Visco said that she had some comments regarding tensions that were created because the Action Plan's funding came from within NCI's budget, when the Secretary of Health and Human Services had intended those funds to be for the Action Plan. In this regard, she emphasized that all grants recommended for funding by the steering committee were submitted to a rigorous review process involving government, scientific, and consumer representatives. The final step involved review by the steering committee, whose members were selected by the Secretary for Health and Human Services. Based on this information, she stressed the need to adhere to all final funding recommendations.

Dr. Klausner clarified that one of the grants recommended for funding by the Action Plan steering committee had not been recommended for funding by the NCAB. Ms. Visco asked whether an appeal process exists for grants that are not recommended for funding by the NCAB. Dr. Klausner asked Ms. Visco to clarify what she meant by an appeal process. Ms. Visco stated her belief that the conclusions of the rigorous review process were not honored by the Board in one case and wondered whether there is any recourse for Action Plan participants.

Dr. Blumenthal supported Ms. Visco's comment that further discussion of this case should occur, particularly as the recommended applications have proceeded through many levels of review, that involved numerous individuals from both the private and public sector. She added that this is a new process and its intricacies and flexibility require more discussion. Dr. Kalt reminded members that it is inappropriate to discuss individual research grant applications during an open session. He noted that the issue of an appeal process can be considered, but the entire discussion should occur in another venue. Ms. Visco asked whether the review process in general allows for an appeal to be made. Dr. Klausner replied that applicants can request an appeal in the case of inappropriate review but, generally, once a funding recommendation is made, it is final. Dr. Blumenthal suggested that a meeting between NCI representatives, Ms. Visco, and herself be scheduled to address the matter.

XIII. ROLE OF THE NCAB—DRS. BARBARA RIMER, RICHARD KLAUSNER, AND MARVIN KALT

Dr. Rimer began by expressing her view that Dr. Klausner is a Director with whom the NCAB can have a collaborative relationship and begin to develop a new role for the Board. While the NCAB's legislative mandate is clear, its potential for accomplishment is much broader and more meaningful. Dr. Rimer continued by reminding Board members of the proposed goals that were distributed to them for the next year and suggesting that the Board begin to evaluate itself in terms of meeting such goals. As part of this discussion, Dr. Rimer asked that the Board address upcoming changes in Board membership.

Two overarching goals of the Board, Dr. Rimer stated, are to review the role of the NCAB in developing the NCI budget, since budget priorities impact all other efforts, and second, to work with Dr. Klausner to institute a meaningful role for the Board in the NCI strategic planning process. Specific goals for the coming year include examining managed care issues, exploring what can be done regarding tobacco use, particularly among youth where improvements have not met expectations, and working with the NCI to develop a state-of-the-art cancer genetics program. Clinical investigations should also be a key part of the Board's agenda for the next year.

Dr. Rimer concluded by stating that she would like to see Board members involved in each of the strategic planning groups that Dr. Klausner appoints and a part of the strategic planning processes, whether in the areas of budget, clinical investigations, or divisions. She asked Dr. Klausner to provide his comments before opening full discussion.

Dr. Klausner reminded Board members of his commitment to work with the Board, as outlined in his letter to each of them. He emphasized that the Board must not only understand its statutory requirements, but also define for itself what it would like to accomplish. Dr. Klausner said that the most important point he wanted to make was that the Board can be very useful and helpful, and that it is his desire to work with the Board.

As Dr. Rimer described, the Board can play an important role in planning and review processes and Dr. Klausner concurred that he would like to see the Board involve itself in planning based on its interests and see members participate in review processes. An important planning and review process that is upcoming is the Bypass Budget planning group. A retreat is also scheduled in November 1995 to discuss in more detail the short-term, mid-term, and

long-term planning processes for the NCI. Dr. Klausner invited Board members to attend that meeting. Based on that planning meeting, Dr. Klausner continued, specific planning processes will be reported to the Board, allowing members to distribute themselves into different areas of planning processes. In addition, the BSC and BSA will be reviewing a defined menu of issues. Dr. Klausner encouraged Board members to contact the chairs of the BSC and BSA with any issues that they would like to see addressed in terms of overarching planning and evaluation. These issues should be communicated over the next month as the BSC and BSA develop their priorities and menus.

Aside from planning issues, Dr. Klausner stated that the Board is an effective forum for addressing overarching policy issues regarding the NCI. Examples include looking at the position that the NCI, as an institution, should take on standards of care, regulatory issues, and legislative issues, among others, as well as consensus issues—examining how the NCI relates to other agencies in terms of funding, budget planning, project planning, and project implementation. Dr. Klausner pointed out that the Board can play a very important role in facilitating and implementing interactions between NCI and other institutions.

Another area in which the Board can assist the NCI, Dr. Klausner continued, is the development of an effective information retrieval system to track the information generated by numerous workshops, consensus conferences, and other meetings. Currently, there is no good means for accessing such information. In conclusion, Dr. Klausner restated his opinion that, in order for the Board to function effectively, it should rethink the composition of its agenda to incorporate fewer presentations and more time for discussion. He noted that many topics initiate a much larger discussion and, in fact, bring many issues together. The Board, Dr. Klausner suggested, needs a mechanism for prospectively deciding the issues that it will address, and then ensuring that time is properly allocated to develop and discuss those issues. The interaction between the Board and the NCI will be most effective and satisfying if those choices can be made.

Dr. Becker began the discussion by commenting on both the statutory and inherent powers of the Board. He noted that the statutory authority of the Board is very limited—approving grants—however, through its power of resolution, the Board has great inherent power and can exert its influence to support and oppose programs and policies. The Board can also lend its support to the efforts of the NCI and its Director. Dr. Becker continued by providing his thoughts on the proposed establishment of new advisory structures at the NCI. He recommended to Dr. Klausner that any such advisory boards include at least one representative of the NCAB, past or present, in order to facilitate coordination and avoid duplication of effort in establishing policies. As an example, Dr. Becker pointed out that there was some confusion in one of the subcommittees over the handling of current proposals for comprehensive status—several Board members were under the impression that the NCI Director already had a group looking at the centers, while other members felt it was up to the subcommittee to develop recommendations. This type of confusion could be reduced by having an NCAB member onsite at other advisory group meetings.

Dr. Becker also recommended that the NCAB take a more active role in the process for appointing members to the Board. In the past, this process has not been clear. Dr. Becker noted that in his experience, it is difficult for recommendations of outside organizations (i.e., AACR, ASCO) to gain consideration, and it is not clear where recommendations are to be

provided. Dr. Becker said that the Board needs to be proactive in asking how the process works and to whom recommendations are forwarded, because the future of the Board depends on its membership.

Continuing, Dr. Becker reflected that the Board should act as the custodians of the Bishop-Calabresi report and evaluate, over the next several years, how its recommendations are being implemented. The Director should also be charged with reporting to the Board, on a routine basis, how the Bishop-Calabresi recommendations are being implemented.

In concluding, Dr. Becker suggested that the Board be proactive, attack important issues jointly with the Director and other members of the NCI, and followup on its recommendations and resolutions to ensure they are being heard and/or implemented.

Dr. Rimer thanked Dr. Becker for his comments and asked that some time be reserved at the end of the discussion to discuss the NCAB membership issue. She pointed out that the meeting which Dr. Kessler attended last year was a good example of how the Board can be more proactive. At that meeting, the Board passed a resolution regarding tobacco use, which was followed up by individual letters and action by Drs. Klausner and Varmus, as well as Dr. Rimer.

Dr. Sigal commented that the Board must recognize that it is an advisory board with limited time and ability to enact major change. On the other hand, by focusing on a few strategic issues that are important to the Institute, i.e., the R01 pool, and focusing more directly on those areas in which the Board can effect change, the Board could accomplish more and be most effective in its advisory capacity. Dr. Sigal agreed that it would be helpful for the NCAB and other NCI advisory boards to be connected in some manner.

Dr. Rimer concurred that it is critical for the Board to be involved with the new BSC and BSA and asked Dr. Klausner to work with the Board in addressing this issue.

Ms. Mayer suggested that the summer meeting of the Activities and Agenda Subcommittee be used as a forum for outlining the goals of the Board for the upcoming year. She noted that clarification may be necessary on what "advisory" means, because although advice can be given, it does not have to be heeded. Continuing with this point, Ms. Mayer said she would like a discussion of the process of advice seeking and giving—what happens when advice is given and not followed—in order to clarify the Board's informal power in this capacity.

Dr. Chan offered his opinion that the Board can make a major impact in the area of lung cancer in relation to tobacco. This is an area in which the Board has made advances and can impact cancer statistics as well as improve public health. Dr. Chan recommended maintaining momentum in efforts to reduce smoking and improve youth smoking statistics, especially among women. Ms. Malek concurred with Dr. Chan, noting that in the past 6 months the Board has done much and should continue its efforts to reduce smoking. Ms. Malek also recommended that the Board follow up in tracking the recommendations of the SENCAP report, as well as the objectives of the Healthy People 2000 report.

Dr. Goldson commented generally on the appropriateness of the comments by Board members, noting that key words seem to be prioritization, focus, and team play. He opined that if the Board and NCI staff present a unified front, all efforts that they undertake will succeed.

Dr. Rimer asked if there were any further comments. She encouraged members to agree to work collaboratively and closely with NCI strategic planning efforts. She noted that the Board could have an especially powerful impact on the budget process and budget priority setting, because that is what will determine the course of the Institute over the next several years. She acknowledged that all Board members agreed to follow the implementation of the Bishop-Calabresi report and the SENCAP report over the next year. Dr. Rimer asked for more discussion on particular areas of focus for the Board, mentioning managed care, tobacco, and genetics as examples of some topics.

Ms. Mayer reflected that the agenda of the Board should be kept flexible and open enough so that if new opportunities arise, they can be addressed. Dr. Rimer agreed. Dr. Klausner commented on the issue raised by Dr. Becker regarding establishing a liaison between advisory committees. He noted that it is important to ensure there are no parallel processes taking place. Dr. Klausner said he would be pleased to have a formal liaison between the BSC and BSA and that some Board members will be asked to serve as members of these committees. In addition, he said he would like to see regular presentations to the NCAB by the chairs of these committees. The first such presentations are scheduled for the November meeting.

Dr. Rimer asked to spend a few minutes discussing the Board's membership. She noted that she is disheartened, as the Chair of the NCAB, not to have been asked by the White House for her input or recommendations, noting that six critical membership appointments are set to be made. Dr. Rimer emphasized that top scientists are needed for these appointments.

Dr. Klausner noted that during the process of being appointed as Director, he had an opportunity to raise the issue of Board representation and the need for input from the Board, the NCI Director, and professional societies to members of the White House staff. It was Dr. Klausner's impression that the White House is certainly open to a discussion of these issues. Personally, Dr. Klausner stated, he feels that the issue of the selection criteria and process should be addressed if the Board expects its resolutions to carry the power of moral persuasion.

Dr. Sigal remarked that since Board appointments are made by the President, they are necessarily political. She asked whether it would be viable for someone other than the President, i.e., the NCI Director, to make these appointments. At this point, Dr. Rimer welcomed Dr. Varmus, Director of NIH. Ms. Visco pointed out that NCAB members are appointed by statute and that this cannot be changed without changing the National Cancer Act. She also commented that she has some concern over how comfortable the Institute Director should be with all of the people who are nominated, since diversity of opinion on the Board is part of what makes it effective.

Dr. Rimer emphasized that the concern of the Board is making sure that nationally recognized, accomplished scientists are included on the Board. Otherwise, its impact is greatly

diminished. She expressed doubt that Dr. Klausner expected or desired a lack of disagreement. Dr. Schein stated that it might be appropriate for Drs. Klausner and Rimer to meet with the White House administration and enter into a discussion on the need to identify individuals who enjoy the respect and confidence not only of the NCI management, but also the outside constituencies served by the Board. Without such consideration, the credibility of the Board and confidence in its opinions will be diminished. As part of these discussions, Dr. Schein continued, the Administration may need to be educated about what the Board is attempting to do within the purview of its mandate, and the type of individuals who are needed, representing tremendous expertise in a broad range of disciplines, to fulfill the Board's obligations. Dr. Schein concluded with his opinion that it is important to solicit recommendations—not representatives—from outside professional societies. It is important that appointees come unencumbered by professional affiliation and with an open mind.

Dr. Klausner reiterated that it would be reasonable to describe to the White House the principles of membership that will allow the Board to fulfill its potential and not dwell on the process, since that is mandated.

Ms. Visco asked if there are requirements of members once they are appointed, i.e., to attend a certain percentage of meetings. Dr. Rimer responded that there is nothing in the legislation to this effect and noted that the Board has had excellent participation. She said that the pressing concern is membership, and offered to draft a letter to the White House which will be circulated to Board members for comment. Dr. Sigal observed that while having something in writing is important, a meeting may still be necessary with appropriate Administration officials. Dr. Rimer acknowledged this as a good suggestion. Dr. Becker asked if he is correct in summarizing that the purpose of the communication would be not to recommend specific persons nor in any way direct the appointment process, but to urge the White House to recognize the significance of its actions and the necessity of having a critical mass of expertise in several key areas—basic science, clinical research, clinical oncology, et cetera. Dr. Rimer concurred with this summary. Dr. Becker urged that any such letter or resolution be completed as quickly as possible, since many of the recommendations for the next round of appointees may have already been made.

Ms. Malek pointed out that the legislation clearly states that 12 of the appointed members shall be selected from among the leading representatives of the health and scientific disciplines and that this could be reiterated to the White House.

Turning to the future structure of NCAB program review meetings, Dr. Rimer noted that there had been some discussion of this topic at the July Activities and Agenda Subcommittee meeting. The feeling at the meeting was that program review should be a strategic discussion of the future of the program, rather than a show and tell. She introduced Dr. Alan Rabson, who has been through numerous program reviews, to lead the discussion on how to develop a more effective program review.

XIV. FUTURE STRUCTURE OF NCAB PROGRAM REVIEW MEETINGS—DR. ALAN RABSON

Dr. Rabson stated that although he is listed on the agenda, he thought it would be important for the Board to hear from Dr. Klausner regarding NCAB Program Review meetings. He asked whether Dr. Klausner would share his thoughts and Dr. Klausner gladly agreed. First, Dr. Klausner suggested that for the November Board meeting, an agenda be arranged where the individuals in charge of new NCI program structures present their activities and their vision for the programs. In addition, he suggested that Drs. Fraumeni and Knudsen be invited to present their vision of cancer genetics; that Drs. Harlow and Abeloff present their future activities with the Board of Scientific Counselors and its new program; and that Dr. David Livingston present his approach with the extramural Board of Scientific Advisors. Dr. Klausner stated that he would also like to take time at the November meeting to update members on the ongoing reorganization process, development of the new Bypass Budget, and the status of planning processes. He noted that between now and the November meeting, the NCI will be having its own internal retreat on the intramural program and that it may be very useful for the Division Directors to present in November, in conjunction with the chairs of the BSC, their review of the current status of the intramural program, what is being done now, and what is being planned. This would also provide a good opportunity to solidify the issue of liaisons in each of these different areas of activity between the NCAB and the Institute.

Dr. Rimer said that this sounds appropriate and asked for comments from Board members. Dr. Day asked Dr. Klausner to clarify that what he is proposing is different from what was done in the past for program reviews, which was primarily to assign several Board members the task of reviewing written program materials and then listening to presentations without an opportunity for much discussion. Dr. Klausner confirmed that his proposal is different and would be more future oriented. He noted that it is important for the Board to obtain a broader picture of potential activities in order to have input into those activities. Dr. Day asked whether his assignment with respect to the program reviews still stands. Dr. Rimer said it does not, that it has been overridden by Dr. Klausner's plan, but that she appreciates Dr. Day's willingness to assist. Dr. Rimer also clarified that as future formal program reviews evolve, it is hoped that substantive, thoughtful, strategic discussions will take place about past activity and future directions, and that Board members will be liaisons to those presentations as they are being developed.

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

Dr. Rimer asked if there were any new business items to discuss. There being none, she introduced Drs. Robert Browning and Marvin Kalt to discuss peer review and reinvention. As background, Dr. Rimer noted that the Board recommended that the NCI return to standing committees for the review of program projects and that this has been gradually put into place over the last year. She stated that Dr. Kalt would bring the Board up to date on these activities.

XVI. PEER REVIEW AND REINVENTION UPDATE—DRS. MARVIN KALT AND ROBERT BROWNING

Dr. Kalt began the presentation by noting the NIH-wide interest in the peer review process. Systematic reinvention teams and committees have been formed to look at the fundamental way the government does business. A leadership retreat was recently held by Dr. Varmus to discuss the nature of the relationship between NIH and the academic and research institutions. Included in this self-evaluation is a fundamental review of the way that research is funded.

Noting that these are all ongoing activities and, as such, "works in progress," Dr. Kalt then moved to a focused presentation of NCI's grant review process. NCI reviews approximately 5,000 applications per year, with a substantial amount of fluctuation per round. As an example, he mentioned the 284 small grant applications for the breast cancer initiative that were reviewed during the summer of 1995. Thanking Drs. Wilna Woods, Michael Kerwin, and Lalita Palekar for reviewing those grants in a very short time span, he remarked that this effort is an example of reinvention. In this case, applications that were received in mid-July were reviewed and awarded in September, as opposed to the 9-month period that is usual for the review and award process. He noted that all parts of the application review, award, and management process are under scrutiny for improvement.

Dr. Kalt informed the audience of the new PHS 398 grant application kit, which is now in two parts—instructions and actual application paper. He noted that detailed information about NIH and NCI are now accessible via the World Wide Web (WWW). The address for NIH's home page is www.nih.gov and from there, one can obtain a great deal of information about NIH and NCI. He displayed the second screen of NIH's home page, which lists all the Institutes, Centers, and Divisions. Highlighting NCI, he added that hypertext links are embedded that enable one to explore further information easily. NCI's home page is easily accessible via the NIH home page or directly by typing www.nci.nih.gov. NCI's home page is still under development, but will enable the user to access information from the Division of Research Grants (e.g., advisory committee rosters, information on grants and contracts, and the *NIH Guide to Grants and Contracts*). The CRISP system, which contains information on awarded grants, can be accessed as well as listings of job vacancies. An NCI extramural home page is in the process of development that will allow users to access a variety of grant information.

Dr. Kalt stated that they are now reviewing documents to place on the WWW based on public demand and availability through other Web sites. He added that all the International Cancer Information Clearinghouse documents and documents from the public information office of the NCI are also accessible through the NCI Web site. He then invited members to experiment with using all of the home pages.

Dr. Rimer asked if a Web page could be created for the NCAB to receive feedback on issues from a variety of constituencies. Dr. Kalt responded that a page could be prepared on an experimental basis to test response to such an idea.

Dr. Kalt then introduced Dr. Robert Browning, Chief of the Grants Review Branch, to update the Board on the changes to the peer review committee structure of the NCI.

Dr. Browning stated that he would apprise the Board of progress in implementing their recommendation to review P01 grant applications within the chartered committee structure instead of through ad hoc special review committees. The process, he said, is nearly completed. He noted the difficulty of reinstating and managing a chartered committee, which is a labor- and time-intensive activity, in an era of cost cutting and downsizing. The committee nominees are in the final clearance process.

Dr. Browning reminded the audience of the change to a flexible committee model that includes subcommittees—a model that was adopted last year. This reduced the number of chartered committees from four to three. The model makes it possible to shift reviewers or applications among the subcommittees to meet their needs. The next logical step, he added, is the creation of one large, flexible committee—the National Cancer Institute Initial Review Group. It will serve as an umbrella committee for eight subcommittees, and will allow them the freedom to shift applications to the most appropriate group to review program projects, and will facilitate flexibility by cross-training reviewers to work with different mechanisms and with different subcommittees as needs arise. The final corrections to a charter for this committee are under way.

Focusing on the subcommittees, Dr. Browning noted that Subcommittees C, D, and E are closely aligned with the new extramural divisional structure of the NCI, which should foster communication between review and program staff and among the applicant and reviewer constituencies. He added that they are developing a list of specific liaisons from the Grants Review Branch in each program area to apprise the NCI of anticipated grant receipts and review issues and concerns, thus heading off problems before they become issues for the Board.

Dr. Browning them moved to a discussion of the Extramural Special Emphasis Panel (SEP). This Panel is responsible for all contract reviewing activity as well as the review activity previously held by the special review committee, including RFAs. SEPs are also necessary for reviewing applications in which the key investigators are members of the chartered review committee. A SEP also operates under a charter, but is a one-time panel drawn from the universal pool of scientific experts. SEPs are simpler to operate, Dr. Browning explained, but lack the type of corporate memory that is established with a standing committee.

Dr. Browning then displayed some data on the outcome of the peer review with the new committee structure, which was started in October of 1994. The data are from three rounds of ad hoc or special review committees (prior to October 1994), then four rounds of review under the chartered committee structure. The data show a good spread of scores initially and then some round-to-round variation. The median scores are approximately 20 percent higher after the change in committee structure. The spread of scores—that is, the difference from the best to the worst—has been hard to maintain because of changes in the peer review system that have trended toward not scoring the bottom half or bottom third of applications. This has caused all measures of central tendency to slip back for grants.

The new system has had an impact in the scoring of grants, said Dr. Browning. This has been especially true for site visit team recommendations. The subcommittees have been very effective in limiting the positive spin that a site visit seems to have on reviewers. The

subcommittee structure has also been useful in bringing additional information to the committee's attention prior to the final evaluation.

Dr. Browning then presented data on the most current round of grants, which depict three areas of importance. First, they show the distribution of the work among the three subcommittees. Second, they depict the distribution of scores among the committees. Dr. Browning noted that the distribution of the scores is good, eliminating any need for corrections. The third area of importance depicted is the fate of revised applications. In the round displayed, revised applications composed 10 of the top 11 scores. He indicated that this demonstrates the complexity of the P01 grant application and the requirement of outstanding ratings in all components. Very few make it on the first try. Dr. Browning noted that amended applications are reviewed via teleconference, to ensure better retention of the original review team. He added that there are considerable time and cost savings as well.

Dr. Browning explained that there was also one special review committee because one of the principals on a grant application was on the chartered committee. As an aside, Dr. Browning mentioned that this reviewer was absented from the review of any program project application for that round.

In conclusion, Dr. Browning stated that the finishing touches are being incorporated into the revised Program Project Guidelines to provide instructions consistent with the new application forms. The criteria for scoring individual projects, research projects, and program projects as stand-alone R01 grants have also been eliminated. The revised guidelines will be ready prior to the February 1 receipt date.

Questions and Answers

Dr. Day asked what the payline is for the current round of grants. Dr. Kalt responded that there is no way to tell, because they haven't received the budget yet. Dr. Day then observed that the grants for the three subcommittees will be pooled and all of those below the payline will be funded. This is different from the way the Division of Research Grants (DRG) operates, in which each group would be percentiled and then the payline would be based on those percentiles. Dr. Kalt agreed, but added that because there are so few program project grants, it is difficult to get meaningful statistics in order to percentile rank the grants. He emphasized that the program project funding is done in a very conservative mode, and then a large number of applications are funded by exception after extensive discussion by the Executive Committee. It was observed that the numbers for basic and clinical applications and revised and new applications are about equal. Dr. Kalt again emphasized that the payline is very stringent for these applications and that unless an applicant receives high marks in each component, the application is not likely to fall within the payline. This results in amended applications that are very strong and focused. The exchange between the applicant and the committee produces better science, Dr. Kalt remarked.

Dr. Schein inquired about the composition of the review committees and the process for choosing reviewers. Dr. Kalt replied that the selection of peer reviewers is based on recommendations from program staff, members of the current review committee, applicant pools, grantee pools, and knowledge of the science base. The overriding consideration, he stated, is the science contained in each application and who is needed to review that science.

He added that he feels the correct scientists are being chosen as peer reviewers, noting that those scientists who are funded by program project grants seem to be more willing to serve as reviewers. Dr. Browning then added that one of the reasons the teleconference method was adopted for reviewing revised applications is because it conserves time and, therefore, reviewers are more likely to participate. Dr. Kalt stated that the ultimate test is the rebuttal and complaint rate for program projects, which is very low.

Dr. Schein asked if there is any way to quality control the process to ensure that the correct people are involved in the review process. Dr. Browning responded that the rosters are attached to all summary statements that the NCAB has to review. Dr. Kalt offered that they could print a list of every reviewer used in a given year.

Dr. Chan asked about the small number of reviewers on some of the committees. Dr. Browning replied that the number of reviewers is usually based on the number of applications. He also said that the RFAs generally have fewer reviewers because they are concerned with a very specific area of science and can thus have a tighter review group.

XVII. FUTURE AGENDA ITEMS AND ADJOURNMENT—DR. BARBARA RIMER

In closing, Dr. Rimer asked if there were any final questions, comments, or agenda items to place on the table. There being none, she thanked the Board members and NCI staff for their participation and distributed a summary of responses received by the NCAB to the Bishop-Calabresi report—10 letters and pieces of e-mail in total, which were all positive. There being no further business, Dr. Rimer adjourned the 95th National Cancer Advisory Board meeting at 12:31 p.m.

November 5, 1995
Date

Barbara Rimer
Dr. Barbara Rimer, Chairperson