Department of Health and Human Services
Public Health Service
National Institutes of Health
National Cancer Institute
National Cancer Advisory Board
Summary of Meeting
November 28-29, 1995

The National Cancer Advisory Board (NCAB) convened for its 96th regular meeting at 8:00 a.m., November 28, 1995, in Building 31, C Wing, 6th Floor, Conference Room 10, National Institutes of Health (NIH).

NCAB Members

Dr. Barbara K. Rimer (Chairperson)
Dr. Frederick F. Becker
Dr. J. Michael Bishop (absent)
Dr. Richard J. Boxer (absent)
Mrs. Zora K. Brown
Dr. Kenneth K. Chan
Dr. Pelayo Correa
Dr. Robert W. Day
Dr. Kay Dickersin
Mrs. Barbara P. Gimbel
Dr. Alfred L. Goldson (absent)
Mrs. Marlene A. Malek
Ms. Deborah K. Mayer
Dr. Sydney Salmon
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)
Dr. Paul Calabresi
Ms. Frances M. Visco (absent)

Alternate Ex Officio NCAB Members

Dr. Robert J. Delap, FDA
Dr. Derrick Dunn, NIOSH
Dr. Marilyn A. Fingerhut, NIOSH (absent)
Capt. Bimal C. Ghosh, DOD
Dr. Apina Koppikar, EPA
Ms. Rachel Levinson, OSTP
Dr. Lakisma C. Mishra, CPSC
Dr. Gerald Poje, NIEHS
Dr. Raymond L. Sphar, DVA
Dr. P.C. Srivastava, DOE
Dr. Ralph E. Yodaiken, DOL

Members, Executive Committee, National Cancer Institute, NIH

Dr. Richard Klausner, Director, National Cancer Institute
Dr. Alan Rabson, Deputy Director, National Cancer Institute
Dr. Edward Sondik, Associate Director, Strategic Planning
Mr. Philip D. Amoruso, Associate Director for Extramural Administrative Management
Ms. Maryann Guerra, Associate Director for Intramural Administrative Management
Dr. Faye Austin, Acting Director, Division of Cancer Biology; Chairman, Extramural Advisory Board
Dr. Joseph Fraumeni, Acting Director, Division of Cancer Epidemiology and Genetics
Dr. Peter Greenwald, Director, Division of Cancer Prevention and Control
Dr. Marvin Kalt, Director, Division of Extramural Activities
Dr. Philip Pizzo, Acting Director, Division of Clinical Sciences
Dr. Robert Wittes, Acting Director, Division of Cancer Treatment, Diagnosis, and Centers

Members, Executive Committee, National Cancer Institute, NIH (continued)

Dr. Claude Klee, Chairman, Intramural Advisory Board, Board of Scientific Counselors
Dr. George Vande Woude, External Advisor, Division of Basic Sciences; Director, Advanced BioScience Laboratories, Inc., NCI-Frederick Cancer Research and Development Center
Dr. Martin Abeloff, External Advisor and Co-Chairman Clinical Sciences Subcommittee A of the NCI Intramural Board of Scientific Counselors; Professor and Director, Johns Hopkins Oncology Center
Dr. Edward Harlow, External Advisor and Co-Chairman, Basic Sciences Subcommittee B of the NCI Intramural Board of Scientific Counselors; Member, Massachusetts General Hospital
Dr. David Livingston, External Advisor, Chairman of the NCI Extramural Board of Scientific Advisors; Professor of Medicine, Dana-Farber Cancer Institute
Dr. Alfred Knudson, External Advisor, Special Advisor to the NCI Division of Cancer Epidemiology and Genetics, Acting Director Intramural Genetics Program; Senior Member, The Institute for Cancer Research, Fox Chase Cancer Center
Mrs. Iris Schneider, Executive Secretary, Asst. Director for Program Operations and Planning
Dr. Maureen O. Wilson, Executive Secretary of the President's Cancer Panel

Liaison Representatives

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

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

Dr. Barbara Rimer called to order the 96th meeting of the National Cancer Advisory Board (NCAB). Dr. Rimer introduced guests representing several cancer education and research associations and institutions as well as federal agencies involved in cancer-related issues. Dr. Rimer welcomed the Intracultural Cancer Council, a new liaison group being added to the Board. She welcomed the members of the public and invited them to submit in writing any comments regarding items discussed during the meeting. Comments should be submitted within 10 days of the meeting to Dr. Marvin Kalt, Executive Secretary of the Board.

Dr. Rimer referred to the confirmed meeting dates for 1996 and 1997 and asked Board members to report any conflicts with future meeting dates. She indicated that 3-day meetings have been scheduled, but that the meetings are anticipated to last only 2 days, unless more time is absolutely necessary.

Dr. Rimer called for approval of the minutes of the September 12-13, 1995, meeting. Dr. Dunn stated that although he arrived late, he did participate in the September meeting. Dr. Rimer thanked him for his participation and again called for a motion to approve the minutes. The motion was seconded and the minutes were approved.

Dr. Rimer announced that the meeting agenda was full and requested that presenters adhere to their allotted times for speaking. She also reported that 3 Board members were absent and, consequently, stressed the importance of having the Board members in attendance present at all times. Dr. Rimer announced that this meeting would include discussions on the bypass budget, as well as focus on presentations about both the Intramural Program and the Extramural Program.

Dr. Rimer noted that the meeting of the Planning and Budget Subcommittee to discuss the fiscal year 1998 bypass budget would be held during lunch, and that several other subcommittee meetings would be held from 11:45 a.m. to 2:30 p.m.

Dr. Rimer congratulated Dr. Philip Schein and U.S. Bioscience for being awarded the Technology Transfer of the Year Award and Dr. Joseph Fraumeni for his receipt of the John Snow Award from the American Public Health Association.

Dr. Rimer introduced Dr. Richard Klausner, Director of the National Cancer Institute (NCI), to give a status report on the NCI.

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

Dr. Klausner indicated that over the past 3 months, the NCI has begun carefully reviewing each program, mechanism, and approach of the NCI. He emphasized that the purpose of this meeting was to share information and encourage others to voice their comments about NCI programs.

At the September 1995 meeting, Dr. Klausner spoke to the Board about his future plans for the NCI. He indicated that the NCI has expended great efforts to begin implementation of his plans since that meeting. The reorganization of the NCI was completed on October 1, 1995, and additional

administrative changes continue to be executed within the Divisions' structures. Dr. Klausner indicated that Mr. Philip Amoruso and Ms. Maryann Guerra are in charge of the administrative changes and expressed his hope that, at a future meeting, they would speak about their activities. He stressed that the administrative changes are essential to the goal of having the NCI function intramurally and extramurally to serve science.

Dr. Klausner listed other developments and changes, including: formulation of external advisory structures; initiation of most of the major program reviews (anticipated to be completed within a year from initiation of each review, under the guidance of the external and internal advisory boards); establishment of both an Intramural and Extramural Advisory Board; and commencement of activities of the advisory boards, including delegation of authority and streamlining of functions for the intramural and extramural communities. Dr. Klausner explained that he believes these changes have effectively generated the message that the staff is empowered to speak to administration and the administration is empowered to listen.

Dr. Klausner explained that formal reviews of NCI activities have been initiated, and that the Intramural Research Program would be discussed extensively throughout this NCAB meeting. He indicated that a systematic review has been started of each funding mechanism (e.g., merit grants, Requests for Applications (RFAs), contracts). Dr. Klausner stated that some delays have been experienced in reviewing the normal NCI funding mechanisms due to the temporary government shutdown and changes in funding.

Dr. Klausner emphasized that the restructuring of the Divisions has resulted in an Executive Committee that allows the chairpersons of external and internal advisory boards to discuss funding mechanism issues openly without bias from preconceived notions of specific entitlements of either external special interest groups or special interest groups representing internal structures within the NCI. He explained that this has allowed the NCI to make profound changes regarding decisions and priorities for use of funding mechanisms.

Dr. Klausner listed other areas of new initiatives for the NCI, including: delegations of authority; streamlining; information technology; clinical trials; AIDS; and AIDS-related malignancies. Dr. Klausner explained that Dr. Alan Rabson is chairing the NCI's effort to develop an approach to collaborate with the Office of AIDS Research (OAR) and the National Institute of Allergies and Infectious Diseases (NIAID) on the NCI's AIDS funding mechanisms. This effort has included establishing a formal mechanism for determining what is and what is not AIDS funding, as well as developing a series of mechanisms for coding in conjunction with the strategic planning of the OAR. Dr. Klausner noted that, as a result of reprogramming, money has already been transferred from the Intramural Program to the Extramural Program for addressing the issue of imbalance of distribution of AIDS funding. The NCI has also made a specific commitment to oversee activities in AIDS malignancies through the AIDS Malignancy Consortium and formation of a working group to be chaired by Dr. Ellen Sigal.

Dr. Klausner indicated that the NCI is also striving to strengthen communication initiatives through patient liaison and communication partnerships. He stated that at a future meeting he would like Ms. Susan Hubbard, Mr. Paul Van Nevel, and Ms. Eleanor Nealon to describe some of the planning and initiatives that they have been working on in this area.

Dr. Klausner reported on the current status of the NCI's budget. The NCI, along with other areas of the federal government, is currently operating under a continuing resolution that has been passed only through December 15, 1995. The Department of Health and Human Services (DHHS) bill was passed in the House, but was not approved by the full Senate. He stated that it is currently unclear whether there will be a bill and whether or when the Senate will take action.

Dr. Klausner indicated that the NCI operating level under the continuing resolution is 100 percent of FY95 funds. He explained that until the previous week, the NCI was working with a continuing resolution at 95 percent of the FY95 funds. Consequently, the NCI can only be sure about having 20 percent of its FY95 funding level available for FY96, because the current continuing resolution expires on December 15, 1995. Dr. Klausner presented a slide showing a total of $2,129,000,000 for the FY95 closeout budget, as well as the breakout of this total among the various programs and mechanisms.

Presenting a slide, Dr. Klausner indicated that planning for the FY96 operating budget continues to be difficult because of the uncertainty under which budget the NCI might be operating. As part of the planning for the FY96 budget, all program areas are being reviewed (including contracts; the Research Project Grants (RPG) pool; and the RPG mechanisms). As part of this review, the Executive Committee is examining the implications of changing commitment bases and the success rates for each different type of RPG mechanism. He emphasized that this process was time consuming and, as an example, stated that it took 3 months to pull together previous detailed budget information for the Intramural Program. He recognized the Bishop-Calabresi Committee for their efforts in this activity. He acknowledged that the variations among tracking mechanisms for the various programs have contributed to the difficulties encountered in gathering information. The mechanisms are coded in different ways using different monitoring systems for different programs—the NCI has eight different personnel mechanisms for tracking employees in the different divisions. Dr. Klausner thanked all who have contributed to gathering demographic information.

Dr. Klausner presented several slides describing the budgets for each program. He indicated that the monetary levels shown for each program did not show his proposed changes for reprogramming funds to depict accurately each program area's true funds. He gave several examples of funding that was covered under one program when it should be covered under another. He explained that every program and every mechanism were reviewed, and he anticipated that, based on this review, the budget can be redone to show a more accurate picture of where costs are incurred. Dr. Klausner indicated that although he had already proposed these changes, he was not at liberty to share them with the Board, because the changes had not yet been approved by the National Institutes of Health (NIH), DHHS, or Congress. He said that he was anxious to share the changes with the Board and would do so as soon as approval was received.

Dr. Klausner stated that because the NCI is currently operating at last year's funding level and because of these uncertain financial times, it is necessary to take a conservative planning approach for the future for all program areas, including intramural research and contracts.

Dr. Klausner presented a slide describing the RPG line for 1996. He stated that the NIH decided in a joint policy under the previous continuing resolution, which was 95 percent of the FY95 level (although now it is 100 percent at the FY95 level), that to deal with the 5 percent cut in the budget, the NIH would suspend the cost management principles for noncompeting grants. He further explained that this meant that the 4 percent increase per year for Type 5 grants was suspended and the

current policy is to pay Type 5 grants at the FY95 level. Dr. Klausner explained that this would be revisited in association with the 100 percent continuing resolution, but for now the policy is to pay Type 5 grants without cost management.

Dr. Klausner described potential scenarios that might occur with the 100 percent continuing resolution. He indicated that in the previous year, the R01 percentile's payline was 15 percent, or the 15 percentile. The resultant success rate was 21 percent. With the current continuing resolution and reprogramming that has already been completed for the RPG line (i.e., with respect to RFAs), there will be a significant drop from $40-50M to $11-15M. The resultant funds will become available to investigator-initiated research, primarily in the R01 pool. This, in conjunction with the continuing resolution and suspension of cost management, would allow the NCI to pay at the R01 percentile instead of at the 15 and 21 percentile, with a success rate of 23 percent. Dr. Klausner explained that if fewer RFAs are issued, the NCI does not get as many applications and, consequently, the numbers change, but the percentile still increases.

If the NCI budget is reinstated at the 100 percent continuing resolution with cost management and 4 percent for Type 5 grants, the R01 percentile payline will increase from $15M to $17M and the calculated success rate would be 19 percent even with the current reprogramming. Dr. Klausner reported that he did not know what the status of the NIH would be in terms of cost management if there is a 100 percent continuing resolution. He indicated that there has been no discussion on this issue since the government reopened and, consequently, cost management is still suspended. Dr. Klausner presented a slide depicting where the NCI is trying to go; however, he qualified it with the statement that a better picture would be available once all the reviews and reprogramming have occurred.

Dr. Klausner moved his discussion to contracts. He indicated that all of the numbers should be obtained by this week so that all contracts can be examined and reevaluated as a group to determine if there is duplication within the Division structure. As part of this examination, each contract will have to be justified scientifically. The Executive Committee is extensively involved in this process. Dr. Klausner went on to say that through communications with Dr. Rabson, he has learned that the Executive Committee has changed dramatically because of the opening up of the NCI and its decision-making processes to additional staff other than Division Directors, Institute Directors, and Deputy Directors, and because of the participation of advisors, such as Dr. Claude Klee, Dr. Edward Harlow, Dr. David Livingston, and Dr. Martin Abeloff.

Dr. Klausner added one additional personnel issue by announcing that Dr. Faye Austin is now serving as the Acting Director of the Division of Cancer Biology (DCB); this Division did not have a director at the time of the September meeting.

Dr. Klausner presented several examples of rethinking of the NCI issues. Ms. Susan Hubbard and Mr. Paul Van Nevel of the International Cancer Information Center (ICIC) and the Office of Cancer Communication (OCC) are creating a new strategic plan for partnerships to leverage limited resources for dissemination, education, and communication in the best possible manner and for bringing the larger cancer community into this area. Dr. Klausner expressed his hope that this new strategic plan would be presented at the next NCAB meeting.

Dr. Klausner identified the privatization of the *Journal of the National Cancer Institute* (*JNCI*) as an additional area of rethinking. Currently the *JNCI* is a successful journal wholly owned and

operated by the NCI. Operation of the *JNCI* is at a cost of 16 Full Time Employees (FTEs) and $1.7M per year. The *JNCI* maintains an extremely high citation index with an impact factor of 9.4. Because of its success, the *JNCI* has the potential to be a source of revenue; however, this potential is limited because it is owned by the government, which prevents it from using advertising and other revenue-producing activities. The NCI has developed a plan, through a Cooperative Research and Development Agreement (CRADA), to find a partner (e.g., professional organization, publishing house) to which to transfer the ownership of the *JNCI*, so that it can generate revenue. This CRADA has already been announced. Through the CRADA, the NCI would continue to provide input for the operation of the *JNCI* (e.g., appointment of the Editor-in-Chief). Thus far, this proposal has received a significant positive response from professional organizations, and Dr. Klausner interpreted this as an indication that there would be interest in other partnership proposals for cancer communication, dissemination, and education planned through the ICIC and OCC. Dr. Klausner indicated that Ms. Hubbard will further describe the *JNCI* initiative at a later NCAB meeting.

Dr. Klausner described recent occurrences in several scientific initiatives described at the previous NCAB meeting. The NCI and the National Center for Human Genome Research (NCHGR) have announced the identification of the specific *BRCA1* mutation found in the Ashkenazi Jewish population. Since the announcement, Dr. Margaret Tucker of the new Division of Cancer Epidemiology and Genetics (DCEG), has established and implemented a program and research protocol in the Metropolitan Washington area. The research protocol was designed in cooperation with the local and national Jewish communities, patient representatives, advocates, and activists. In 6 to 9 months, a study of this population will be initiated to study the incidence of this mutation, which is currently estimated at 1 percent of that population. The study will also examine geographic specificity, especially with respect to point of origin of individuals and frequency of this two base-pair deletion in the *BRCA1* gene. The primary element of this study is a questionnaire that will characterize penetrance and expressivity of carrier status for this mutation, based on family history. Most of the patients identified in the literature have come to the attention of researchers because they were in a high penetrance family. Consequently, this is the first opportunity for population-based screening. This screening is possible because of the technical feasibility of using a simple allele-specific oligonucleotide hybridization test for the specific two-base deletion to screen for a potential cancer predisposition mutation. One of the questions to be asked because of the availability of a population that was not selected because of family history (i.e., an unselected population) is what will the study reveal in terms of penetrance (i.e., what can be inferred about the risk of cancer, age, and type of cancer in males and females?). The study is anticipated to be completed by late spring or early summer. Dr. Klausner explained that up to this point the study has moved quickly but, because it includes a questionnaire, the study is now waiting for the Office of Management and Budget's approval.

Dr. Klausner announced that support of the Cancer Genetics Consortium would be expanded. The Consortium consists of 11 institutions that are funded by the NCI and the NCHGR, the National Institute for Nursing Research (NINR), and the National Institute for Mental Health (NIMH), and deals with issues related to counseling for the psychological effects of cancer predisposition diagnoses based upon molecular and genetic tests.

The NCI also needs to expand and be prepared to work on designs for clinical trials in prevention, surveillance, diagnosis, therapy, and stratification studies in terms of response to therapy. The need to think about design of clinical trials arises from the rapidly accruing numbers of accessible cancer predisposition mutations. Dr. Klausner has requested that Dr. Robert Wittes establish a task

force working group within his division to begin collaborating with the Human Genome Center and the Cancer Genetics Consortium on the planning of an infrastructure for using clinical trials based on the described issue.

Dr. Klausner described a special workshop that occurred last month regarding the ataxia-telangiectasia gene (*ATM*) that convened most of the major researchers from throughout the world who are involved with this disease. Ataxia-telangiectasia (A-T) is a rare disease (affecting approximately 1 in 40,000) and is identified as a recessive neurologic disorder. A-T is also a cancer predisposition disorder in the homozygous state. This workshop was convened to consider the issues raised by data in the literature that suggest carrier status and heterozygote frequency may be as high as 1 percent in the population and may predispose to cancer (especially breast cancer). Dr. Klausner indicated the findings are not definitive and he emphasized the importance of developing more definitive answers. He also explained that the heterozygote incidence of mutations in the *ATM* gene is not presently known—1 percent is an extrapolation of how many homozygotes are found in a population. Because A-T is a rare disease, it is believed that there is a large error in the estimate of 1 percent.

Dr. Klausner explained that the articulation of the new bypass budget is anticipated to be ready for spring, and it will describe new and immediate opportunities for investment based on scientific advances. He commented on the responsiveness from the administration and Congress to the proposed bypass budget, and he thanked the many people who contributed their efforts.

Dr. Klausner closed his presentation by stating that this is a difficult and confusing time for the NCI because of the current status of the budget, and he predicted that the NCI will be in an *ad hoc* and reactive mode for how to proceed with 1996 expenditures until the budget issues are resolved. Dr. Rimer thanked Dr. Klausner for his presentation and invited the Board to ask questions.

Questions and Answers

Dr. Sydney Salmon referenced Dr. Klausner's indication that the number of RFAs announced by the NCI would be reduced as part of the budget reprogramming. He asked if a new mechanism would be implemented for funding clinical research because, over the past 5 years, RFAs have been an important mechanism for correcting problems in funding clinical research grants. Dr. Klausner agreed with Dr. Salmon and responded that most of the RFAs being cut were not clinically oriented, and that the budget would be articulated so that RFA mechanisms are used in the context of overall goals. RFAs will continue to be used, but the intent is to use them in a better way.

Dr. Paul Calabresi commented on the findings in Texas, recently reported in *Science*, on *BRCA1* protein localization in the cytoplasm and asked if this was being confirmed or examined. Dr. Klausner responded that he knew of several laboratories that were looking into the findings. He clarified that Dr. Calabresi was referring to a study that found the majority of breast cancer cells demonstrate an apparent abnormality in the *BRCA1* protein, which is the gene product. He explained that the investigators developed polyclonal antibodies against the protein that is found in the nucleus in normal cells, and used it to demonstrate that the protein is found in the cytosol in most breast cancer cells. Dr. Klausner indicated that this was important in the context of the question about whether the *BRCA1* pathway is deranged in most or all breast cancers. Dr. Klausner emphasized that confirmation of these findings was necessary and stated that this was an intriguing area of study.

Dr. Rimer referenced Dr. Klausner's comments about the partnership of the *JNCI* and, citing that the *JNCI* appeals to a variety of professional disciplines, asked how a partnership with one professional society would maintain the appeal to such a broad group. Dr. Klausner responded that the CRADA, which has been published in the *Federal Register*, makes clear the need for the NCI to have strong input so that it can maintain the successful aspects of the *JNCI*. He also indicated that the professional societies that have responded thus far are fairly general in nature. He explained that the intention of the CRADA is to maintain the good features of the *JNCI* and to improve it so that it achieves revenues, saves money for the NCI, and reduces potential perceived conflicts of editorial interests because of its government-operated status. Dr. Klausner emphasized his optimism that the CRADA will be a successful approach.

Dr. Sigal inquired whether Dr. Klausner had any projections on the possible income from the *JNCI* partnership. Dr. Klausner responded that it was too early to tell.

Mrs. Marlene Malek asked whether the NCI would receive any of the profit realized by the *JNCI* partnership. Dr. Klausner indicated that the NCI could specify how the profits are used—that is, stipulate as part of the agreement that a specified amount of revenue would be used to support fellowship programs or educational activities. The NCI would not receive direct revenues from the partnership.

Dr. Robert Day requested that Dr. Klausner give some examples of how other CRADAs are working and indicate whether they are generating revenue in a similar fashion. Dr. Klausner indicated that this is a unique CRADA and explained that current CRADAs provide mechanisms where other entities pick up the costs of programs, projects, and research that would otherwise be covered by the NCI. Dr. Klausner expressed his belief that a CRADA was the best mechanism for the NCI and the *JNCI*.

Dr. Sigal inquired whether there was a specific prohibition against having revenues put into the R01 pool and asked whether this might be a possible solution for the *JNCI*. An NCAB member stated that it was against the appropriations law. Dr. Klausner indicated that the issue of what the NCI can take for revenues and use is dependent on where the revenue originates. He also noted the amount of money that would be saved as a result of not using the NCI's appropriated funds to support the 16 FTEs, as well as the $1.7M a year spent to operate the *JNCI*.

Dr. Day commented that most major research institutions have successful arrangements through licensing that return substantial revenues—citing the biotechnology session to be held at the next NCAB meeting as an example. Dr. Klausner agreed that the NCI has a successful revenue screening from royalties, patents, and technology transfer. He indicated that this would be discussed in greater detail at the next NCAB meeting.

Dr. Rimer asked Dr. Klausner to comment on the controversy about what type of medical surveillance advice should be given to women with the *BRCA1* mutation and asked if the NCI had any recommendations as part of the snapshot study that is being conducted. Dr. Klausner responded that the NCI does not recommend that women be tested for the *BRCA1* mutation other than through a clinical research Institutional Review Board (IRB) approved trial. Dr. Klausner noted that, in this snapshot study, the individuals tested will not receive the results of testing. He indicated that the reason for doing the snapshot study is because the NCI does not currently know what to

tell individuals about what it means to carry the mutation. He strongly stated that this should not be a test that is part of a clinical practice—it is a research issue.

Dr. Rimer thanked Dr. Klausner and introduced Ms. Dorothy Tisevich, the Legislative Liaison for the NCI, to give an update on current legislation.

III. LEGISLATIVE UPDATE—MS. DOROTHY TISEVICH

Ms. Tisevich explained that she would be presenting a brief legislative update at this meeting, which she supplemented with a more detailed handout. She indicated that she would present the usual extended format of the legislative update at the next NCAB meeting.

Ms. Tisevich explained that the NCI is being funded at the FY95 level through a continuing resolution, *Public Law 104-54*, which was signed by the President on November 19, 1995, and funds the federal government until December 15, 1995. She stated that the House has completed its action on the NCI's budget; however, the Senate has not yet taken the bill to the floor. Ms. Tisevich indicated that, in the absence of an appropriation, the NCI will probably operate under a continuing resolution through the remainder of the year, with the funding level currently unpredictable.

Ms. Tisevich explained that the last funding crisis resulted from the compromise about a strategy for reaching a balanced budget by the year 2002. She read an excerpt from this agreement between the President and the 104th Congress regarding a balanced budget. After reading the excerpt, she stated that the first session of the 104th Congress ends on December 31, 1995, and that they have a large task at hand to come to an agreement by the end of December. She explained that if budget issues are not resolved by December 15, there could be another federal government furlough. Ms. Tisevich stated the possibility that another furlough may be longer than the previous one, and that the federal government workers' payroll may be affected this time.

Ms. Tisevich indicated that the *Istook Amendment* was included in the House Labor/HHS bill, but not in the Senate bill. This amendment would prohibit the use of federal funds by grantees for political advocacy. She reminded the Board that this amendment was included in the House-passed version of the Labor/HHS bill, but it is not included in the Senate version, which is a nonlegislative document including only appropriation issues. She explained that efforts to attach the *Istook Amendment* to other spending bills (including the *Treasury/Postal Bill* and the recent continuing resolution) have not succeeded. Ms. Tisevich described a more moderate Senate proposal that was included in the continuing resolution and bars federal funds to 501(c)(4) nonprofit groups with annual budgets over $3M. 501(c)(4) is a tax code designation for certain nonprofit groups that are organized specifically for lobbying purposes. The specific legislative language limits the definition to lobbying and mandates that all groups wishing to receive federal grants would have to limit lobbying expenditures to $1M. Those organizations with budgets in excess of $17M would be able to spend more on lobbying, and those groups receiving less than $125,000 would be exempt. The *Lobbying Disclosure Act of 1995* also addresses lobbying restrictions and is intended to close loopholes in the existing lobbying law and specify who is and is not a lobbyist.

Ms. Tisevich indicated that the Senate has taken the lead on *The Medical Records Confidentiality Act of 1995* that would limit access to medical records. This effort would protect the privacy of personally identifiable health care information, but still allow the effective and safe use of health information systems to facilitate safe and effective exchange and transfer of health information.

Federal rules would govern the disclosure of health information. Senator Robert Bennett and Senator Nancy Kassebaum introduced this bill.

The Genetic Privacy and Nondiscrimination Act of 1995, introduced by Senator Hatfield and Senator Mack, prohibits disclosure of genetic information without written authorization of the individual being investigated. It prohibits employers from using genetic information to discriminate against current or prospective employees, and it prohibits health insurers from using genetic information to determine an individual's coverage. It also requires that the newly appointed National Bioethics Advisory Council develop recommendations on further protections for DNA samples and genetic information in several different settings. This bill incorporates recommendations from the NIH-sponsored Ethical Legal Social Implications (ELSI) working group and the National Breast Cancer Action Plan.

Ms. Tisevich presented a slide depicting the make-up of the 105th Congress. She presented a list of individuals intending to retire from the Congress. She noted that 3 members have resigned and 22 members have announced their intention to retire. She pointed out that a number of the prospective retirees are Democrats. Ms. Tisevich stated that Senator Kassebaum is retiring and noted that the Senator currently chairs the Senate committee that oversees the NIH's authorization. The NIH is up for authorization next year, and Senator Kassebaum will likely hold hearings in the spring.

Ms. Tisevich announced that she had attached, in her handout, several statements commemorating Breast Cancer Awareness Month by members of both the House and the Senate. She noted that Congresswoman Caroline Maloney organized a Special Order of the House and made a statement to call attention to breast cancer.

Ms. Tisevich invited the Board members to comment or ask questions.

Questions and Answers

Ms. Deborah Mayer asked Ms. Tisevich to comment on the likelihood of *The Genetic Privacy and Nondiscrimination Act* getting through Congress. Ms. Tisevich responded that there had been quite a bit of bipartisan support for this issue in the Senate, and she was not aware of its status in the House. Dr. Klausner added that he and Dr. Frances Collins had attended an informal hearing on genetic testing and cancer organized by Senator Mack and Senator Feinstein, and he perceived that they were very receptive to the need to act soon on genetic discrimination issues.

Dr. Sydney Salmon asked Ms. Tisevich to comment on two issues: (1) the NCI's position on the proposal by the Chairman of the House Appropriations Committee to prohibit funding of a Tobacco Education Grant from the NCI that allegedly had an outstanding priority score; and (2) the proposed Medicare limit for reimbursement for uses of antiemetics in the care of cancer patients.

In response to the first issue concerning the work of Dr. Stan Glantz, Ms. Tisevich stated that there was specific language in the House Appropriations Report about prohibiting the NCI from using any funds to support the final year of Dr. Glantz's grant. She also explained that following the appearance of this language, Mr. Porter indicated to Dr. Klausner and Dr. Varmus that his concern was with a specific portion of that grant linking tobacco industry campaign contributions to voting patterns by elected officials who received the campaign contributions and examining how they voted on tobacco legislation. Ms. Tisevich stated that the NCI is evaluating the issue and identifying how

much of the grant is related to that particular activity. Dr. Klausner added that the NCI had looked into whether it had a legal commitment to fund Dr. Glantz's work and found that there was not a commitment from year to year—it is dependent upon the appropriation. Dr. Klausner also explained that he has had further discussions with Mr. Porter regarding the significant contributions that Dr. Glantz has made to the NCI, and they are attempting to find other nongovernment sources of funding for Dr. Glantz.

Regarding the second issue—the proposed Medicare limitation on reimbursement for the use of antiemetics in cancer patient care—Ms. Tisevich responded that she has been attempting, with difficulty, to get clarification on this issue. She indicated that she hoped to provide information on this issue at the next NCAB meeting.

Dr. Sigal asked Ms. Tisevich to provide comment on who is sponsoring, as well as the feasibility of, the proposed legislation for an excise tax on tobacco that would go to cancer centers. She also asked Ms. Tisevich to comment on the status of the Harkin-Hatfield legislation. Ms. Tisevich indicated that she did not know of the tobacco excise tax linked to cancer centers and welcomed anyone who was aware of it to comment. Dr. Sigal indicated that she would try tc get more information on it. In response to Dr. Sigal's question about Harkin-Hatfield, Ms. Tisevich stated that the Harkin-Hatfield legislation was still in draft form.

Dr. Rimer asked if the NCAB members could receive a copy of the proposals when the continuing resolution comes up again so that they would be able to comment accurately on the implications of the budget and how it would affect the NIH and the NCI. Ms. Tisevich indicated that, to the extent that information is available regarding the issues being discussed, she would try to accommodate the NCAB. She indicated that this task would be complicated by another furlough or if discussions were to take place in closed sessions.

Dr. Kay Dickersin inquired about Food and Drug Administration (FDA) legislation introduced by Senator Kassebaum regarding off-label use of certain drugs that would preclude the drug companies from having to produce evidence of the effectiveness of these treatments if there is general use in the clinical community. Ms. Tisevich reported that the FDA reform legislation contains language that will help accelerate the drug approval process and limit the amount of data required for the process. Ms. Tisevich indicated that she is following that bill, and she will provide additional information on it at the next NCAB meeting.

Dr. Rimer asked Dr. Klausner to comment about his statement to Congress regarding mammography and mammography recommendations. Dr. Klausner responded that he had prepared a statement for Breast Cancer Awareness Month that was issued on Mammography Awareness Day to clarify his stance on that issue. He agreed to make the statement available to the NCAB members later during the meeting so that they could comment if they wished.

Dr. Rimer thanked Ms. Tisevich for her important update. She introduced Dr. Harold Freeman, Chairman of the President's Cancer Panel, to provide a report of the Panel.

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

Dr. Freeman reported recent activities of the President's Cancer Panel. He stated that he would be providing an overview of the Panel's exploration of the "Information Superhighway," in a

meeting hosted by the University of Maryland-Baltimore Campus. Dr. Freeman explained that the need for the meeting stemmed from the Panel's awareness that the cancer research community must strengthen its attempts to educate the public, patients, community physicians, and lawmakers about the value of clinical research. He emphasized that advances in knowledge are futile unless they can be effectively communicated and applied for public benefit. The Internet presents an opportunity to communicate these technological developments; however, at the same time, it isolates underprivileged Americans who do not have access to phones and intercity physicians who cannot afford the time or money required to use the Internet.

The speakers at the University of Maryland-Baltimore meeting discussed several issues involving the technological and intellectual information transmission process, including the clinical research infrastructure for collecting and encoding medical information, and disparate data systems with little guidance regarding ownership or confidentiality of the data. Dr. Freeman emphasized that the clinical research effort must be strengthened through standardization, quality control, and ethical protection of appropriate release of data. In addition, he noted that because the patient data infrastructure forms the basis for insurance evaluation of patient populations, it is important that improved algorithms be established to distinguish among populations and evaluate their needs.

Dr. Freeman indicated that the Internet offers opportunities for these types of standardization, as well as communication opportunities such as mail, file transfer, list servers, news groups, and global penetration. He also described potential drawbacks including the Internet's lack of quality control and security—which limits its usefulness for transmission of patient data—and its predominantly more-affluent user group. Dr. Freeman predicted that improvements in these areas, coupled with the readily available data on the Internet, will change the balance-of-power relationship between doctor and patient. This modification of doctor and patient roles will result in patients having a bigger impact on the selection of their own treatment options. Consequently, it will be up to medical professionals to reengineer the research information process to increase efficiency and productivity. During these activities, the medical professionals must take care not to isolate underserved populations further. They must consider the needs of all information users, the access requirements for the Internet, and the information users' ability and desire to access the Internet. Dr. Freeman pointed out that, in low-income families, cable television has a lower disconnect rate than telephone service.

Dr. Freeman identified the NCI's ICIC as an information source that makes use of computer technology. World Wide Web Home Pages are currently being developed for the NIH, as well as around the world, to facilitate multilingual information access to federal databases. Graphic and multimedia objects are being incorporated into clinical statements to make them more user friendly. In addition, public access is being considered for several systems, including Physician's Data Query (PDQ)—through the SAILOR system, which is available through Maryland Public Libraries. Government agencies are collaborating to encourage private industry to include protocols in PDQ. Links with other cancer resources such as the Cancer Centers and advocacy groups are also being developed. Dr. Freeman stated that private organizations such as the Cochrane Organization have collaborated internationally to build a database of all randomized trials completed in all areas of medicine for the use of scientists and consumers.

Dr. Freeman identified the greatest problem associated with the rapidly developing communication process to be that the patients' access and ability to self-determine medical treatment are increasing more rapidly than the patients' ability to financially access protocols. In this context,

insurers and legislators must be viewed as targets for education (using survival statistics, cost effectiveness information, or outcomes analysis) so that third party payors and controlling lawmakers have an understanding of the value of clinical trials. They must also be made aware that health education is leading to preventive health behaviors that may be the most cost-effective for the future. Efforts must be made to bring health education to geographically or financially restricted sites.

Dr. Freeman also discussed the need for support of medical informatics, which is the union of information computer science, disciplinary sciences, and the service of health care delivery research, education, and management. The Panel believes that teleradiology, telepsychiatry, and telepathology will be part of future medical practice.

Dr. Freeman concluded his presentation and welcomed the Board to ask questions.

Questions and Answers

Dr. Philip Schein directed a question to either Dr. Freeman or Dr. Klausner regarding the *BRCA1* information release and the initial belief that this information release might create some hysteria. He asked how this type of information release would be managed in the future, and how the NCI would decide how much data is required before a research statement can become a policy statement, followup mammography, or the application of a new technology. Dr. Klausner responded that in the case of *BRCA1*, the NCI prepared for the information release by addressing the issue of communication. This issue was addressed by working with a task force on genetic testing, set up by Secretary Shalala, who will report on a policy regarding genetic testing within a year. The NCI also worked closely with the Jewish community and women with breast cancer. The communities were monitored carefully following information releases and, thus far, the predicted hysteria has not been observed. He stated the Jewish communities have responded very positively to the research approach even though it includes not receiving the results of the study. Dr. Klausner and Dr. Francis Collins have discussed guidelines with various companies for not introducing this type of test into the clinical arena too rapidly, and the companies have been receptive. The NCI is doing as much as possible to maintain an information system.

Dr. Schein asked Dr. Klausner what the perceived timeframe is for work in this area to actually become a practical, providable new diagnostic aid for women. Dr. Klausner stated that it depends on the pace of the research. He has met with Dr. John Glick, the President of the American Society of Clinical Oncology (ASCO), and is requesting a meeting with ASCO's Subcommittee on Genetic Testing to approach jointly the issue of guidelines on genetic testing that would be aimed at oncologists by ASCO. Dr. Schein emphasized the need for a defined strategy for making statements. Dr. Klausner was in agreement with this suggestion.

Dr. Day inquired whether the PDQ is available on the Internet. Both Dr. Klausner and Dr. Rimer confirmed that it is. Ms. Hubbard added that PDQ statements, state-of-the-art statements, and patient information statements are available via e-mail free of charge. The entire PDQ database is also available to members of the Information Associates Program as an interactive application on the Internet. Ms. Hubbard also indicated that PDQ is freely available to the general public through the Cancer Information Service and to physicians who do not have computer access through a toll-free telephone number.

Dr. Day referenced the tremendous response to the newly available Salk vaccine in 1955 and predicted that the same degree of demand will be seen for breast cancer tests. Dr. Klausner stated he agreed with Dr. Day, and that data emerging from the breast cancer test showed a positive response when individuals were told they could take a test to determine if they would get breast cancer. However, the response was mixed when individuals were given more detailed information about what the test did and did not mean. Dr. Rimer announced that this issue could be further considered in future discussions about the Epidemiology and Genetics Program.

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

Dr. Rimer opened the floor for identification of new business to be discussed during the second new business session on the following day. Dr. Dickersin expressed frustration about the short length of NCAB meetings and proposed to discuss whether the subcommittee meetings could be longer. Dr. Rimer requested that NCAB members think about whether they would be willing to travel to the NCAB meetings earlier to allow for extra time for the subcommittee meetings. Dr. Dickersin also indicated the need to discuss having a closed session at every NCAB meeting. She emphasized that this was an important mechanism to make NCAB members aware of certain issues prior to the information being released to the press, so that the NCAB could be prepared to respond to questions from the press. Dr. Klausner indicated that NCAB members should send information that they wish to be discussed in a closed session to either himself or Dr. Rimer.

Dr. Salmon requested an update on the tamoxifen Breast Cancer Prevention Trial including information on accrual, dropout rate, and the ability to achieve its objectives.

Dr. Chan noted that, for the benefit of new and existing NCAB members, it would be helpful to have summaries of ongoing business that was introduced at previous meetings but has not been resolved.

Dr. Rimer introduced Dr. Klausner to provide a brief introduction to the new structure of the Intramural Program.

VI. INTRODUCTION TO INTRAMURAL PROGRAM—DR. RICHARD KLAUSNER

Dr. Klausner explained that in the last 3 months, the NCI has been moving toward restructuring and reforming its Intramural Research Program. This has included discussions to establish detailed operational principles, as well as analysis of the demographics of the previous Intramural and Extramural Division structures.

Dr. Klausner stated that the Intramural Program spends approximately 18.7 percent of the NCI's budget. During the past 3 months, the NCI has attempted to establish the complete costs of the Intramural Program.

Dr. Klausner announced that individuals involved with the Intramural Program recently attended a retreat to establish an operating plan for the Intramural Program. He explained that additional presentations would be given later in the meeting by Dr. George Vande Woude, Division of Basic Sciences (DBS); Dr. Philip Pizzo, Division of Clinical Sciences (DCS); and Dr. Joseph Fraumeni, DCEG—representing the three Intramural Programs. Dr. Klausner also reported that

Dr. Martin Abeloff, Dr. Edward Harlow, and Dr. Alfred Knudson, also highly involved in this process, would be speaking later.

Dr. Klausner continued his presentation by describing the decisions and changes that were made for the operating plan (the operating plan is currently in draft form and cannot be distributed). The fundamental guiding principle of the Intramural Research Program is that the scientific organization of that program is based on the independent principal investigators (PIs) and not the laboratory chiefs. The allocation and accountability for resources rests with the PIs. The operating plan provides the definition of a PI, defines how to build a PI program (i.e., it explains the resources, opportunities, and specific types of individuals and positions that are available), defines tenure and nontenure, defines tenure track, defines how to establish and disband a PI laboratory, and explains the overall promotion and resource allocation process. Formerly, some PIs were not aware of the limits of their resources and budgets. Under the new operating plan, PIs will know and be responsible and accountable for their zero-based budget (i.e., funding starts at zero), including space and personnel. The level of support will be negotiated annually between each PI and their laboratory and branch chiefs. The laboratory and branch chiefs will serve as mediators and advocates for the PI with the division director.

Dr. Klausner indicated that the allocations and expenditures of all laboratories and PIs were carefully reviewed and cost management principles have been developed and initiated as guidelines for Pis to use in their negotiations for funding. Under these cost management principles, when a PI leaves a laboratory, the laboratory does not automatically keep the resources that were previously allocated to that PI; the laboratory must renegotiate with the division director or the Director of the NCI. Similarly, when a laboratory branch chief leaves a laboratory, the continued existence of the laboratory is an administrative or organizational structure issue to be decided by the Director of the NCI.

Dr. Klausner explained that the operating plan defines a laboratory branch as an organizational entity consisting of one or more PIs. An interactive scientific environment will be maintained by the branch chiefs within each laboratory branch to enhance the independent research programs of the Pis in their laboratories. The laboratory and branch chiefs will function as an administrative supervisor instead of a scientific supervisor to the PIs. Each laboratory branch will have an administrative budget and additional resources to be used to support core functions benefiting all of the PIs within that laboratory; however, the laboratory and branch budgets will consist of the sum of the negotiated budgets for each PI and any additional budget, which is a major change from previous budget operations.

Dr. Klausner outlined additional areas covered by the operating plan including processes for open searches; establishment of the prerogatives of the division for development of core facilities; and guidelines for development of new science initiatives. Dr. Klausner predicted that the operating plan should be finished within the next week; it will be distributed to the NCAB and everyone in the Intramural Program.

Dr. Klausner also described other activities that occurred at the retreat. Detailed guidelines were established for an internal review process, including review of PIs, laboratory chiefs, and division directors. These guidelines emphasize the need to review excellence of science and resources, career development, and mentorship, and not just scientific success. In an effort to attain consistency among reviewers, these guidelines clearly describe the goals of the process, define what

the reviewers are being asked to rate, and explain to the reviewers how to perform a rating. The review process will be advisory to the division director and the Director of the NCI.

Dr. Klausner announced that one of the most extraordinary changes related to the Intramural Program was the new intensity of interaction between the NCAB and the Intramural Program. Dr. Klausner concluded his presentation by recognizing Dr. Harlow, Dr. Livingston, Dr. Abeloff, and Dr. Knudson for their efforts.

Dr. Rimer introduced Dr. George Vande Woude to give an overview of the Division of Basic Sciences.

VII. DIVISION OF BASIC SCIENCES (DBS) OVERVIEW: CURRENT STATUS AND PLANS FOR THE FUTURE—DR. GEORGE VANDE WOUDE

Dr. Vande Woude explained that for the past several months he has been acting as a special advisor to the Director for basic sciences and has assisted with the establishment of the new DBS.

Dr. Vande Woude began his presentation by identifying previous problems associated with the way in which the four divisions ran independently and competitively: the program was not cohesive; the divisions used different tracking procedures, making them hard to compare; and the divisions were not aware of the makeup of their staff. The reorganization united the individual divisions into a single program with the goal of improving the quality of basic science at the NCI. The budget review process will be uniform across the program.

Dr. Vande Woude identified the reorganization process, the budget process, and the review process as being the key areas to be addressed in the establishment of the DBS. He explained that he would be focusing primarily on the reorganization process, because Dr. Klausner addressed the budget process, and Dr. Harlow would be explaining the review process.

Dr. Vande Woude presented a slide depicting the current structure of DBS and its new logo and recognized Mike Varmolinsky for creating the logo.

Presenting a slide showing the organization of the DBS laboratories, Dr. Vande Woude explained that there are 33 laboratories in the new division that cover a variety of research disciplines. He indicated that currently five laboratories have acting laboratory chiefs (Dr. Albert Fornace—Laboratory of Biological Chemistry; Dr. James Lautenberger—Laboratory of Molecular Oncology; Dr. Edward Tabor—Laboratory of Molecular Virology; Dr. Carl Baker—Laboratory of Tumor Virus Biology; and Dr. Marvin Reitz—Laboratory of Tumor Cell Biology) and the next step will be determining whether they continue as they are or be integrated into other laboratory programs.

Dr. Vande Woude presented a slide describing existing staff in DBS. Currently, there are approximately 1,400 research staff, including 147 tenured PIs and 34 tenure-track investigators. Dr. Vande Woude referred to a handout containing a descriptive list of each laboratory, as well as the name and telephone numbers of associated PIs. For purposes of his discussion, Dr. Vande Woude explained that a PI is an independent investigator responsible for justifying his/her science through a review process.

Dr. Vande Woude emphasized the wide range of research represented by the staff and program areas, including immunology, immunotherapy, molecular genetics, molecular biology, biochemistry, biological and chemical carcinogenesis, virology, retrovirology, medicinal chemistry, cell biology, and mathematical biology. He also indicated that some deficiencies existed with respect to what should be in an intramural program, and that plans were being made to fill those gaps (e.g., plans for a developmental biology area).

Dr. Vande Woude explained that the DBS is establishing a more coherent review process. He presented a slide describing all of the laboratories that have been reviewed this year. Dr. Vande Woude indicated that the last several laboratories were reviewed using newly established criteria, including direct recommendations for the budget. He stated that the materials and recommendations generated as a result of these reviews will be examined on January 8, 1996, by the Interim Board of Scientific Counselors. Then, the reviews will be examined by Dr. Vande Woude before being released to the Intramural Review Board and the Steering Committee.

Dr. Vande Woude referred briefly to a handout showing scientific highlights of the intramural research program. He indicated that this was the first time a summary for the entire intramural basic sciences had been prepared.

Describing the budget process, Dr. Vande Woude explained that each laboratory director was asked to submit a budget, which Dr. Vande Woude will review in conjunction with each laboratory director within the next few months. He indicated that personnel services (i.e., salaries and fringe benefits) are now being categorized as fixed costs. Animal costs will now be split out among the laboratories. Dr. Vande Woude estimated that a good first draft of the Intramural Program budget will be ready by mid-January 1996.

Dr. Vande Woude continued his presentation by describing the administration of the DBS. Showing a slide, he stated a steering committee had been established that is responsible for overseeing hiring and tenure-track positions. This committee will also be responsible for overseeing the annual laboratory budgets and funding requests, reviewing the laboratory branch management practices as they affect the NCI, evaluating allocation of division resources, and reviewing and approving laboratory responses to site visits. Dr. Vande Woude acknowledged the members of the steering committee, including Dr. Douglas Lowy, Dr. Alfred Singer, Dr. Stuart Yuspa, Dr. Harold Varmus, Dr. John Ashwell, and Dr. Jacalyn Pierce.

Dr. Vande Woude described the Intramural Advisory Board as a body that will make recommendations on the scientific processes of the Intramural Program to enhance the performance of science at the NCI. Dr. Vande Woude also indicated that the Resource Teams, guided by Ms. Maryann Guerra, would be interactive in all of the basic science locations where they are represented.

Dr. Vande Woude then identified new DBS initiatives. The first program 2-day retreat will be held on the Monday and Tuesday following this NCAB meeting. By the next NCAB meeting, Dr. Vande Woude hopes to have prepared a DBS Annual Research Directory that will include accomplishments, lists of recent publications, and photographs of each PI. He predicted that the annual research directory could be used in the future as a recruiting tool, and noted that it will provide a readily accessible overview of the entire program.

Dr. Rimer thanked Dr. Vande Woude for taking on such a big effort. Dr. Vande Woude introduced Dr. Edward Harlow to describe the role of Subcommittee B of the Intramural Board of Scientific Counselors (BSC).

VIII. ROLE OF INTRAMURAL BOARD OF SCIENTIFIC COUNSELORS (BSC), SUBCOMMITTEE B-BASIC—DR. GEORGE VANDE WOUDE AND DR. EDWARD HARLOW

Dr. Harlow explained that Subcommittee B interacts with the Intramural BSC in two key areas: (1) the review procedure and (2) planning.

Dr. Harlow presented a slide showing the elements of the previous review process and referred to its complexities.

Showing a slide, Dr. Harlow listed the nine different laboratories that are currently under review. He explained that an Interim Board will handle the site visit reports and recommendations. He cautioned that the review process is still being developed and should be viewed as a working model. The objective of the review is explained to the laboratory at the onset, and a rationale for the rating is provided at the conclusion of the review.

Dr. Harlow explained that in developing the review process, Subcommittee B considered what elements the review should cover. This resulted in two models. The first model resulted from a suggestion in the Bishop/Calabresi report that all reviews should be retrospective, written, and offsite. The second model incorporated a prospective review—looking at the future plans of the laboratory, including needed resources. The subcommittee determined that reviews will be based on past performance and future plans; the review will include a site visit, a written report, and periodic review checks. The reviews will be scheduled during a 4-year period.

Dr. Harlow indicated that the basic unit of the review is the PI. He noted three aspects of this review: (1) contributions made since the last review; (2) whether current research is on the cutting edge; and (3) scientific plans for the future. Laboratory and branch chiefs must exhibit leadership ability and organizational skills. The review will concentrate on how well resources have been used. Dr. Harlow pointed out that important aspects of the review process are its mechanism for rebuttal, and that the Intramural BSC's review comments and recommendations are advisory.

Dr. Harlow presented a slide showing an outline of the new review process. Each PI will be reviewed separately from the branch. The review will consist of a narrative description of the projects and will characterize positives and negatives, as well as analyze future plans. Both the laboratory and branch will be reviewed for organizational structure, administrative skill, and scientific leadership, using the same review procedures as for PIs. Dr. Harlow emphasized that this review process is commonly used for reviewing grants in the extramural community. The narrative review will also include resource recommendations. Dr. Harlow outlined the possible research recommendations that could result from a review: (1) suggested expansion—recommended significant change in resources; (2) recommended continuation—shows exceptional performance; (3) reevaluation required in 1 year—review identified a serious, but repairable problem; (4) resource reduction—review revealed a need to get budgets in line with the amount and quality of science being performed; and (5) closure of a PI's group or laboratory—review identified a severe problem.

Dr. Harlow described the planning element of the Intramural BSC—which will be cross-organizational including clinical, genetic, and epidemiology aspects—as well as the roles of other major planning organizations like the NCAB and the extramural community. Subcommittee B is currently developing or planning *ad hoc* working groups or workshops for four major projects. The Preclinical Models of Cancer *ad hoc* working group has been tasked with determining how to ensure the use of mouse genetics to develop models of human cancer (i.e., how to make sure this resource gets used and disseminated to carry out the next round of cancer biology). The Developmental Diagnostics *ad hoc* working group has been formed to determine how to move forward in the area of developmental diagnostics. The two workshops include the Tumor Immunology Workshop and the "Nonnatural and Natural Products" Workshop. The "Nonnatural and Natural Products" Workshop addresses the possibility of moving genes and enzymes that are involved in polyketone synthesis into microorganisms and then using these microorganisms to develop chemicals that could be used in drug testing.

Dr. Harlow concluded his presentation and invited questions from the NCAB. Dr. Rimer thanked Dr. Harlow for his presentation.

Questions and Answers

Dr. Calabresi thanked and complimented Dr. Klausner, Dr. Vande Woude, and Dr. Harlow for their presentations. He emphasized his interest in the retrospective and prospective review, and wondered if the previous confusion experienced among the reviewees regarding how they were being evaluated will be resolved with the new process. Dr. Harlow agreed with the importance of making the reviewees aware of expected productivity goals, as well as the relationship between the results of the review and future funding. Dr. Klausner emphasized the importance of making the review document a working manual that is available to everyone.

Dr. Frederick Becker described former criticisms that have been encountered, including excess or perceived excess of resources and staffing in the laboratories, the lack of critical review, and response by the reviewee to review recommendations. He indicated that it is important that the division head's actions, as related to recommendations, are tracked and reviewed by the committee. When recommendations are not heeded, the division head should have to provide justification.

Dr. Day asked for clarification on the definition of the terms "tenure," "principal investigator," "lab," and "branch." Dr. Klausner responded that a PI is a tenured or tenure-track scientist who has been appointed through the NIH tenure-track or tenure-review procedures. A PI develops and determines the direction of an independent research program using allocated independent resources (i.e., personnel, operating budget, and space). He indicated that the other terms were defined in the review document, which would be provided to everyone as soon as possible.

Dr. Day asked if the distribution of the DBS over different locations and buildings is a problem. Dr. Klausner explained that it is an issue that is in the process of being addressed.

Dr. Day asked what the relationship of the Intramural Program is to the Extramural Program. Dr. Rimer indicated that this relationship would be discussed at a later session.

Dr. Day asked how the issue of core resources being shared among scientists at different locations is being addressed. Speaking as an intramural scientist, Dr. Klausner explained that core

resources have always been a problem because of the way they are controlled, and that this is an issue that needs to be revisited.

Dr. Sigal directed a question to Dr. Vande Woude regarding whether he had an exact target date in mind for the estimated completion of the budget by mid-January 1996. Dr. Vande Woude stated that the meeting with the last laboratory chief is on January 14, 1996, and that he hopes to have a draft budget prepared within a week from that date. He also added that, with regard to communication, five laboratories are currently on the World Wide Web, and five more are scheduled to go on in the near future.

Dr. Day asked, considering the size of DBS, how basic science results find their way into clinical activities. Dr. Klausner stated that, for basic science research, he does not believe that projects should be chosen as intramural or extramural. He identified the unique opportunity found in attempting to integrate clinical, basic, and population-based research at the NCI. He emphasized that movement toward this goal is evidenced by a single BSC with two co-chairs, the Intramural Advisory Board, and other mechanisms intended to prevent basic science, clinical science, and population-based research from being separate activities.

Dr. Salmon asked if the review of the administrative activities of laboratory chiefs occurs separately from the review of their research activities as PIs. Dr. Klausner responded that every laboratory chief is a PI, and their role as a laboratory chief is evaluated separately from their role as a PI. Dr. Salmon suggested that the review of the laboratory chief in a particular laboratory should not occur until after the PIs in that laboratory have been reviewed. Dr. Klausner responded that this is already being considered in the development of the review document.

Dr. Dickersin asked whether the laboratory chiefs are new. Dr. Klausner indicated that the current laboratory chiefs are existing. Dr. Dickersin also commented that because most of the PIs are male, she would recommend not publishing a picture book (i.e., the annual research directory) of PIs. Dr. Klausner agreed that most of the PIs are male, but believed that the annual research directory would help to identify existing inequities.

Dr. Rimer indicated that Dr. Harlow mentioned the relationship between NCAB and the Intramural Board in terms of planning, and that it was important to continue working in that area. Dr. Harlow agreed.

Dr. Rimer thanked Dr. Harlow for his efforts at the NCI and introduced Dr. Philip Pizzo, Acting Director, Division of Clinical Sciences.

IX. DIVISION OF CLINICAL SCIENCES (DCS) OVERVIEW: CURRENT STATUS AND PLANS FOR THE FUTURE—DR. PHILIP PIZZO

Dr. Philip Pizzo, Acting Director of the DCS, began his presentation by referring to copies of his slides in the Board book. He stated that his discussion of the DCS would provide some answers to the questions: (1) How did we get here? (2) What do we look like? (3) What do we want to look like? and (4) How will we get there? Dr. Pizzo explained that, 20 years ago, the NCI's Intramural Program was recognized as one of the premier programs of its kind in the Nation. Since then, numerous changes have occurred along with the emergence of programs in the extramural community (e.g., medical oncology). Some of the problems that emerged in the clinical component of the

Intramural Program stem from the loss of leaders in clinical investigation and structural problems that have prevented collaboration among smaller programs. These problems were compounded by different established priorities.

Dr. Pizzo indicated that prior to the reorganization, a number of the branches in the clinical programs had been undergoing structural changes, although some had remained stable. Dr. Pizzo stated that as a result of the reorganization completed October 1, 1995, there is now an Intramural Program and an Extramural Program. DCS is encompassed under the Intramural Program and is aligned closely with the DBS and the DCEG.

Dr. Pizzo presented a slide showing the six branches of the DCS—Adult Oncology (containing seven Branches), Pediatrics, Radiation, Surgery, Pathology, and Biostatistics.

Dr. Pizzo explained that DCS now consists of 880 individuals, including both FTE and non-FTE positions, and 127,000 square feet of space. He stated that approximately half of the individuals and space are spread out over adult oncology, and the remainder is distributed among pediatrics, surgery, pathology, radiation and biostatistics. The $84M allocated spending for FY95 was similarly distributed over the programs.

Describing the current composition of PIs, Dr. Pizzo explained that the Adult Oncology Program includes both tenured and tenure-track PIs. The clinical programs also include staff physicians with clinical tenure who are not formally recognized in the new nomenclature as PIs. Dr. Pizzo indicated that there is currently a relative paucity of individuals on tenure track.

Dr. Pizzo described the fellows-in-training program, which allows PIs to train at a number of Accredited Council of Graduate and Medical Education (ACGME) accredited programs in medical oncology, pediatric pathology, radiation, and pathology. The number of fellows entering the Adult Oncology Program in the past has been 10 to 17 individuals, each making a 3-year commitment.

Dr. Pizzo indicated that, in reference to patient care resources, approximately 127 adult inpatient and 20 pediatric beds are distributed throughout the Clinical Center, the Naval Medical Center, and the Frederick campus. Outpatient services are also available at the Clinical Center, Navy hospital, and the Frederick campus. In the past year at the Clinical Center, there were approximately 30,000 outpatient events and 20,000 inpatient hospitalizations.

Dr. Pizzo presented a slide showing the current profile of clinical protocols by disease, covering a spectrum of malignancies. He listed the categories in which the studies were focused, including natural history, studies where samples or observations are collected on patients, pilot or Phase I/II studies, and Phase III studies. At the time of the review, there were 299 operative protocols. There were 48 Phase III studies (16 percent), which Dr. Pizzo emphasized was a questionable category of studies to be conducted in the Intramural Program.

Dr. Pizzo emphasized that the primary goal for the future is having a seamless interface between population-based research, patient-oriented translational research, and basic science research. Other specific goals include: (1) to conduct pioneering clinical and scientific research that improves the understanding of cancer and its diagnosis, treatment, and prevention; and (2) to be poised to pursue clinical research issues that either promote the NCI's unique strengths or are not achievable in the extramural community. Dr. Pizzo stated that research must be both investigator-initiated as well

as interdisciplinary problem-oriented, including team-based research that uses the efforts of both the NCI's basic and clinical investigative communities. He also explained that the values that will be needed to achieve this mission include excellence in scientific and clinical research, excellence in patient care, support for career development, and support for the professional and personal demands of individuals.

Dr. Pizzo described issues being considered that are related to patient care. These include determining who should provide patient care, the value of expert clinicians, and where patients should be treated. He indicated that interactions will continue with the National Naval Medical Center, and that the continued role of the Frederick Cancer Center is being examined. Dr. Pizzo suggested that the Adult Oncology Program might be a good place to consider a different approach for a clinical program—that is, making the beds a national resource accessible to the extramural and intramural communities. He indicated that, in the past, the beds and clinical operations have been controlled by existing branches and staffed by fellows under the guidance of supervising physicians. As a result, a large number of fellows must be accepted into the program each year to cover outpatient care activities adequately. Dr. Pizzo suggested reevaluating this situation. He provided a recommendation to centralize the clinical services under the division instead of the branches, which would consolidate inpatient and outpatient resources. Within this consolidated group, a team of primary care providers led by excellent clinicians and physician extenders would be developed. This change would remove the dependency of clinical services on the fellows. This clinical service would work cooperatively with a research team for clinical research and would include protocol and data management systems that would be organized to provide centralized, orchestrated, standardized support for clinical research activities. Dr. Pizzo indicated that consolidation and resource control would provide cost savings and quality control for clinical care and clinically related research. He announced that Dr. Greg Curt is chairing a task force to consider these restructuring options and their associated costs. He estimated that the plans for this will be completed by December and will potentially encompass patient care being provided by a multidisciplinary team of physician leaders, nurse practitioners, and physician extenders. In tandem, the research team activities would include data management, tissue and sample procurement, sample processing, and the development of a central protocol office having regulatory relations with the Cancer Therapy Evaluation Program (CTEP) and providing a resource for clinical programs.

Dr. Pizzo explained that they are examining these methods to develop the mechanisms for translational research as a step toward achieving a unified approach to data collection, management, and analysis. Development of these methods would better assure quality performance and the formation of a comprehensive tissue data bank. Activities have already begun in this area in conjunction with the Pathology Department and involve cooperative interactions with the CTEP that will lead to improved relationships with the FDA and industry, as well as improved technology development. Dr. Brigitta Mueller is heading a task force to coordinate development and consistency with representatives from other clinical branches and the Clinical Center Informatics Group. A subcommittee has been established within this task force to address development of resources for a central tissue bank. A protocol office is also being developed to help with implementation of protocols, especially for difficult issues related to the regulatory interface.

Dr. Pizzo indicated that the area of clinical outreach is also being examined. He emphasized the importance of developing comprehensive interactive programs that reach out to the extramural community in a bidirectional manner. Potential mechanisms for these outreach activities include newsletters, electronic communication, and newly evolving telemedicine technology. He explained

that operating in conjunction with cancer communication and information systems will help identify the Intramural Program as a vital participant in the National Cancer Program and its continuing education programs.

Dr. Pizzo moved his discussion to the area of training and mentoring. He indicated that there are 12 fellows in the Adult Oncology Program who have the opportunity to stay on for 3 years. He emphasized the importance of having committed investigators, but cautioned the NCAB that not all fellows fulfill the NCI's research goals. He also indicated that, in the past, the numbers selected have been guided by the need to support patient care obligations rather than on the NCI's or the Nation's training needs. Dr. Pizzo went on to explain that the Pediatrics Program selects five new fellows per year. Dr. Pizzo suggested that, at a minimum, the size of the medical and pediatrics fellowship programs should be driven by the need to train outstanding clinical investigators and improve the conduct of the Clinical Care Program rather than by patient care needs per se. He described some options in the area of training that might include continuing with accredited fellowship programs, but training fewer numbers of individuals; or, bringing on individuals who have already completed a clinical fellowship program elsewhere to function as clinical scholars in the areas of clinical research. The ultimate goal would be to develop an outstanding program for training investigators in cancer research and redirect the resources that are saved by these activities to improve the Clinical Care Program.

In addition to reducing the number of fellows, Dr. Pizzo emphasized the importance of examining the quality of training and mentoring that fellows receive. In this respect, a workgroup has been formed, and Dr. Carol Thiele is serving as its interim chairperson. This workgroup is also considering mechanisms that will appropriately promote tenure for qualified investigators.

Dr. Pizzo presented activities regarding quality of investigations in both clinical and laboratory research. A Protocol Review and Monitoring Group has been formed and is charged with prospective responsibilities, as well as reviewing all current active protocols to determine whether they should be continued. There are approximately 300 current protocols to be reviewed. Once the active protocols are reviewed, the group will examine protocols that represent new directions of research, that will consume resources, or that have been identified as needing further scientific review. This multidisciplinary group is chaired by Dr. Frank Balis from the Pediatric Branch. The goals of this group include increased emphasis on translational research, especially interactions between clinical and basic research.

Dr. Pizzo indicated that evaluation of ongoing protocols is based on scientific merit, design of the trial, progress of the trial, and resource consumption. As part of this evaluation, each PI and Protocol Chair was asked to complete a description of all of their active protocols. Investigators have been granted the authority to close protocols as they see appropriate. An initial period of closing protocols has occurred, and the active review has begun. A standard protocol format will be developed that will be utilized throughout the DCS so that the components of protocols will be consistent, regardless of their origin. Each protocol will be prereviewed by the laboratory or branch before it undergoes scientific review or is released to the IRB.

Dr. Pizzo explained that a Clinical Research Advisory Group is being chaired by Dr. Ronald Gress. Its function is to look at future activities in terms of interdisciplinary and basic research within the DCS. This group is currently assisting with creating an agenda for clinical research topics

or problems that would benefit from interdisciplinary research efforts and that would facilitate collaboration and interaction within the DCS, the DBS, and the DCEG.

Dr. Pizzo explained that every branch and PI have been reviewed during the last 2 months. The reviews have included presentations by all tenure-track PIs, an evaluation of their work, prior site-visit reports, and overall assessments of program strengths and weaknesses. Dr. Pizzo presented several slides depicting the recommended review schedule for 1996, 1997, and 1998. He indicated that adult programs are being evaluated first because of the timing of their last review, as well as specific questions that relate to these programs.

Dr. Pizzo described structural changes that might be required to achieve current and future goals, which in the short-term include improved communication and in the long-term include the recruitment of new senior scientific and clinical staff.

Dr. Pizzo explained that one of the options presented by the Bishop-Calabresi Committee for accomplishing the mission for adult oncology is to combine the various adult programs into one large branch. Another option that is being considered would include interfacing according to disease-oriented research laboratories and mechanism-oriented research laboratories. This option would divide the current adult program into smaller unit laboratories with disease-specific areas of knowledge and investigation supplemented with mechanism-oriented areas of investigation. With this option, depending on the topic being investigated, interaction could occur among working groups in these individual areas that would allow investigators with specific areas of interest to work together. This would enhance communication and discussion. Potential areas for development include assessing and developing a mechanism for flexibility, and finding areas for interdisciplinary collaboration based upon mutual needs and benefit of the overall program development. Implementation of these ideas could create enhanced interaction and cooperation among investigators and mechanism- and disease-oriented laboratories that would be smaller than traditional clinical branches, but would have more flexibility. Oversight and coordination will be very important factors in implementation of these ideas—the governance of the division will have to be expanded to allow more comprehensive oversight. These activities are currently being overseen by the Deputy Director for Clinical Affairs, but Dr. Pizzo envisioned a need to have a Deputy Director for Clinical Research in the future who would help with oversight for the mechanism- and disease-oriented laboratories and working groups. This would be done in conjunction with the Board of Scientific Advisors (BSA).

Dr. Pizzo concluded his presentation by stating that the future is a challenging and exciting time for the NCI's Intramural Program. He also emphasized the importance of taking advantage of the opportunity to make the NCI intramural community a center of excellence that will help to define the future of clinical research.

Dr. Rimer thanked Dr. Pizzo for his presentation and indicated that questions would be taken following the presentation by Dr. Martin Abeloff, Co-Chairman of the Intramural BSC Subcommittee A-Clinical.

X. ROLE OF INTRAMURAL BOARD OF SCIENTIFIC COUNSELORS (BSC), SUBCOMMITTEE A-CLINICAL—DR. PHILIP PIZZO AND DR. MARTIN ABLEOFF

Dr. Abeloff is the nominated chair for the Intramural BSC Clinical Science Subcommittee. He expressed his pleasure with working with Dr. Klausner, the leadership team, Dr. Pizzo, Dr. Harlow, and Dr. Livingston.

Dr. Abeloff summarized the activities of the Clinical Science Subcommittee. He indicated that a search committee has been formed and will soon begin seeking a head of the DCS. Official announcements soliciting potential candidates are being sent out. A plan of action has been outlined along with a timeline.

There are 18 individuals on the BSC for the DCS, who represent a wide variety of disciplines, with an emphasis on translational research. The BSC will regularly review the research program by evaluating research activities and contributing to decisions made on resource allocations and spending. The Board will also participate in reviewing the fellowship program and patient care activities. The Board will identify potential for exploration of unique opportunities. An effective Board will serve to facilitate interactions within the Division, as well as extramural activities. The Board will also perform scientific reviews—a schedule for scientific reviews has already been developed. The Board is working on issues integral to the success of the reorganization. The Board will interact with Dr. Pizzo and his task forces regarding organizational restructuring, patient care and education, and interdisciplinary research.

Dr. Abeloff concluded his presentation by stating that he thinks this is an exciting time at the NCI and looks forward to working with Dr. Pizzo and others. Dr. Rimer invited questions from the NCAB members.

Questions and Answers

Dr. Becker commented on the number of changes to be made. He asked if the Pediatric Program added five new fellows per year. Dr. Pizzo indicated that this was true. Dr. Becker asked how, with 20 beds and 15 outpatient rooms, the Pediatrics Program justified five new fellows per year. Dr. Pizzo indicated the fellows work intensively in the clinical area only during the first year of the fellowship and have multiple rotations during the first year of training, at other Medical Centers in the greater Washington area, permitting them to achieve training in both hematology and oncology; subsequent years focus on building clinical investigators (laboratory-based training). As a result, because the fellows are actually providing primary care in the first year (there are no interns or residents), additional fellows are needed each year to keep up with primary care. Dr. Pizzo indicated that it is important to examine who is being trained and how that relates to national needs. Dr. Pizzo explained that needs for new scientists in pediatric oncology are declining because of decreased funding and the program has to balance that along with patient needs. Dr. Becker suggested that the recruitment of new senior clinicians should be based on their ability to fulfill preselected areas of focus where the DCS can make a difference. Dr. Pizzo agreed, but added that there should also be clinicians who are outstanding doctors who will help with providing excellent care. Dr. Becker commented that the best clinicians the DCS has are the clinician researchers. Dr. Salmon agreed—he did not see a reason to recruit physician researchers. Dr. Abeloff commented that there is agreement concerning focusing on and taking advantage of unique research that can be performed only at the

NCI. He raised the issue that how one achieves enough depth in medical staff coverage is important, but indicated that it is a separate issue to be raised in the future.

Dr. Schein commented that conducting clinical research involves a serious commitment to excellent patient care because of the ethical issues and responsibilities associated with introduction of new therapies. Therefore, to train clinical investigators, they must be immersed in clinical care and extremely knowledgeable about diseases. It is important for them to witness what happens to a patient once a new therapy is introduced to that patient. They need to have experience; if they are sent outside the program without appropriate clinical experience, their own credibility as well as the NCI's will be damaged. Dr. Schein indicated that bypassing clinical care by delegating it to primary care physicians should be discouraged. Dr. Pizzo responded that it was not the intent to bypass clinical care and delegate the responsibility to primary care physicians. He emphasized that NCI would be seeking outstanding clinical oncologists and aimed to encourage, nurture, and support the participation of these individuals in the clinical arena. Also, they will look at training outstanding clinical investigators.

Dr. Day commented that the NCI is an organization very focused on cancer research and asked what the criteria for success was in translational research. What should the NCAB be looking for in the future to determine how well translational research has been conducted? Dr. Pizzo indicated that the evaluation criteria should be driven by science rather than empiricism. He stated that clinical studies should be configured to address the fundamental issues in the natural history or diagnosis of disease that employ the best scientific technology possible. He indicated that he would not predefine the size and scope of studies, because they are determined by the nature of the research. He discouraged the conduct of large clinical trials or Phase III type studies and emphasized that the NCI should be a center where developmental studies are driven by science.

Dr. Rimer suggested the multidisciplinary team should include a representative from epidemiology. Dr. Pizzo agreed. She also suggested that cancer prevention fellows should have the opportunity to participate in the Intramural Clinical Program. Dr. Greenwald responded to Dr. Rimer's comment, indicating that this had happened in the past and that senior staff physicians also had participated in the Clinical Oncology Programs.

Dr. Chan commented that there are currently about 300 protocols and inquired about which section would have the responsibility for compliance, accrual, contracting, quota control, and other activities. Dr. Pizzo indicated that the number of protocols will be significantly reduced by the end of December. He added that a number of the protocols exist as followup studies and are not actively accruing patients (i.e., in order for patients to return for followup visits once enrollment is completed in a protocol, the protocol must remain open). Dr. Pizzo predicted that he should be able to give an overview of these protocols at the next NCAB meeting. Dr. Chan asked which branch will be responsible for protocol compliance and quota controls. Dr. Pizzo indicated that, through the Clinical Center and the Clinical Trials Monitoring System for Phase I studies, there are quality control mechanisms in place as data management systems utilized by the branches for accrual and monitoring of patients.

Dr. Sigal inquired about the relationship between the clinical centers and Phase I activities and asked whether there was any amount of funding or reimbursement that could be obtained for Phase I work. Dr. Pizzo indicated that critical assessments in the past have opposed the NIH's being involved in third-party billing. Dr. Sigal suggested that, rather than have negotiations for coverage, a

certain preset fee per person be charged. Dr. Salmon indicated that the accrual of patients to the Clinical Center is declining even in the absence of reimbursement and discouraged implementation of additional obstacles. He emphasized the importance of having a Phase I center where bills will be paid. Dr. Klausner added that other ways of cutting costs may be through the reduction of expenditures of clinical centers rather than third-party billing. The efficiency of the Clinical Center is currently being evaluated by the Smits' Committee for areas where costs could be decreased.

Dr. Rimer concluded the discussion session and introduced Dr. Joseph Fraumeni, Acting Director, Division of Cancer Epidemiology and Genetics. She also indicated that Dr. Alfred Knudson, Special Advisor to the Division, would give a presentation following Dr. Fraumeni.

XI. DIVISION OF CANCER EPIDEMIOLOGY AND GENETICS (DCEG) OVERVIEW: CURRENT STATUS AND PLANS FOR THE FUTURE—DR. JOSEPH FRAUMENI AND DR. ALFRED KNUDSON

Dr. Fraumeni presented a slide showing the organization of the DCEG, which was created from the Epidemiology and Biostatistics Program, formerly in the Division of Cancer Etiology. The new division was formed to ensure that the pulse of recent and current discoveries in molecular genetics and cancer biology is broadened through population-based etiologic studies. Dr. Fraumeni indicated that he would summarize the organizational and functional aspects of the DCEG.

Presenting several slides, Dr. Fraumeni defined the mission of the DCEG as follows: (1) conduct epidemiologic, genetic, and biostatistical research with a population-based and interdisciplinary orientation aimed at identifying environmental and host determinants of cancer, leading to prevention strategies; (2) identify natural experiments and cancer variations in areas lacking regional expertise or resources to investigate unusual patterns or exposure; (3) undertake studies that cannot be done easily in extramural settings because of their high-risk nature and requirements for extensive methodologic development; and (4) develop epidemiologic, genetic, and biostatistical resources for the intramural and extramural communities, provide pre- and postdoctoral training in interdisciplinary population-based cancer research, and advise on topics related to cancer causation and prevention.

Dr. Fraumeni emphasized the DCEG's interdisciplinary approach toward epidemiologic research into the causes of cancer in both the Intramural and Extramural Programs. Population-based studies are conducted whenever possible at the interface of clinical and basic sciences in order to derive insights that might not be achieved by using only one discipline. The DCEG has a broadly-based research program in which a wide range of environmental and host factors and their interactions in the etiology of cancer are investigated.

Dr. Fraumeni explained that the DCEG also focuses on the identification of unusual exposures and variations in cancer occurrence, especially with respect to geographic areas that may require epidemiologic assistance from the NCI. As an example, Dr. Fraumeni explained that the U.S. cancer mortality maps published by the DCEG are used for identifying and targeting areas of the country with elevated cancer rates for more intense epidemiologic study.

Dr. Fraumeni explained that the Intramural Program often conducts studies that are risky or speculative in nature, or that may require extensive national and international collaboration or coordination.

Dr. Fraumeni indicated that the DCEG staff members also develop epidemiologic and statistical resources that may be important to the epidemiology community at large. Training activities are developed and encouraged within DCEG, as well as extramurally, including the Cancer Epidemiology and Biostatistics Fellowship Program and a new program under development to train investigators in the interdisciplinary approach to cancer genetics.

Dr. Fraumeni depicted the current organization of the DCEG. There are five intramural branches and one extramural branch. The intramural chiefs include Dr. Margaret Tucker—Genetic Epidemiology, Dr. James Goedert—Viral Epidemiology, Dr. Robert Hoover—Environmental Epidemiology, Dr. Mitchell Gail—Biostatistics, and Dr. John Boice—Radiation Epidemiology. Dr. Iris Obrams heads the Extramural Programs Branch.

Presenting a slide, Dr. Fraumeni described the staffing for FY95. The Intermural Program had 31 tenured investigators, 5 staff scientists, 11 tenure-track investigators, 10 staff fellows or medical officers in temporary positions, 8 fellows in the Epidemiology and Biostatistics Training Program, and 2 visiting fellows. The Extramural Program had five program directors at the doctoral level.

Dr. Fraumeni presented a slide that summarized the FY95 budget. In-house costs totaled $15.8M and contracts totaled approximately $26M, with a total figure for the DCEG of $42M. In addition to the in-house costs, there were 282 grants in the portfolio of the Extramural Program, totaling more than $80M.

Dr. Fraumeni explained the rationale for resource and research contracts. Approximately 70 percent of the contracts are resource contracts that provide the support necessary for the conduct of epidemiologic studies. This mechanism permits rapid expansion and contraction of the workforce to accommodate changing staffing needs. Support for resource contracts includes development of questionnaires, operation of biospecimen repositories, tracing of subjects, data editing and processing, and field work (i.e., interviewing, record abstracting, and environmental measurements). Approximately 30 percent of the contracts are research or R&D contracts that serve as a mechanism for collaborative epidemiologic studies with universities, cancer centers, cancer registries, and other government agencies. Dr. Fraumeni showed a series of slides describing several recent scientific highlights from the DCEG. He then presented several slides outlining the RFAs and Program Announcements (PA) funded in FY95.

Dr. Fraumeni indicated that to implement its expanded scientific mandate, the DCEG is proposing to reorganize. The new structure will include three program areas—two intramural and one extramural. Dr. Knudson is serving as the Acting Director of the Intramural Human Genetics Program. The Epidemiology and Biostatistics Program, headed by Dr. Robert Hoover and Dr. Patricia Hartge, is the other intramural program. The Extramural Program is headed by Dr. Iris Obrams and consists of several units: a Genetics Group headed by Dr. Daniella Seminara, an Epidemiology Group led by Dr. Kumiko Iwamoto, a Biometry Group headed by Dr. Gina Day, and a Special Projects Group led by Dr. Iris Obrams. Presenting a slide, Dr. Fraumeni further described the proposed organization of the Epidemiology and Biostatistics Program, which will have six Intramural Branches: the Biostatistics Branch, and the Radiation, Viral, Environmental, Occupational, and Nutritional Epidemiology Branches.

Dr. Fraumeni used another slide to depict the organization of the Human Genetics Program, which will consist of the Genetic Epidemiology Branch, as well as a new Clinical Genetics Branch, and a new Laboratory of Human Genetics. In search of susceptibility genes and gene-environment interactions, the Genetic Epidemiology Branch conducts epidemiologic and interdisciplinary studies of individuals, families, and populations that run a high risk of cancer. The Clinical Genetics Branch will integrate clinical observations and genetic counseling into an interdisciplinary approach to investigate ways to expedite appropriate clinical applications and interventions once a susceptibility gene is mapped and cloned. The Laboratory of Human Genetics will serve as the critical laboratory component for collaborative research to investigate genetic predisposition in the context of population-based studies.

Using a slide, Dr. Fraumeni described the Cancer Genetics Training Program, which is to be a major initiative of the Human Genetics Program. This will be created as a postdoctoral training program that integrates epidemiologic, clinical, and laboratory research.

Dr. Fraumeni stated that a working group has been formed within the DCEG to help coordinate the expanding initiatives in cancer genetics. The group will identify opportunities for collaborative studies in genetic epidemiology, resource development, and training activities. The group will also examine ways to improve interactions and collaboration in cancer genetics across the NCI and the NIH.

Dr. Fraumeni indicated that the Extramural Program in DCEG is planning a series of workshops to identify obstacles and gaps in population-based genetics research. The workshops will focus on a number of topics, including the need for specialized resources such as cancer-prone family registries, laboratories for DNA isolation and genetic assays, specimen banks, and information record-linkage systems. Guidance will be sought from the Board of Scientific Advisors in developing these workshops.

A cycle of site visits was completed this past year. Dr. Fraumeni showed a slide listing the 1995 site visits, culminating in reviews of the Viral Epidemiology Branch in April 1995 and the Genetic Epidemiology Branch in June 1995.

Presenting a slide, Dr. Fraumeni described several oversight and advisory groups that have been created within DCEG, including the Senior Advisory Group, the Protocol Review Committee, the Contract Utilization Committee, the Promotion and Tenure Review Panel, and several working groups. The Senior Advisory Group, consisting of branch chiefs and senior staff, advises on policies and priorities. The Protocol Review Committee conducts an extensive scientific and technical evaluation of every protocol before a study is launched. The Contract Utilization Committee includes representatives from other divisions and will serve to review every contract for need, appropriate usage, productivity, quality control, and cost efficiency. The Promotion and Tenure Review Panel also includes staff from other divisions and conducts rigorous evaluations of candidates for promotion and tenure. Several working groups have been formed to focus on specific tumor sites, risk factors, approaches, and resources used.

Challenges for the future, as described by Dr. Fraumeni, include retaining a balanced research program, maintaining flexibility while expanding work in genetics, providing rapid response, promoting interactions between laboratory and clinical scientists, accelerating the transition from etiologic discoveries to preventive measures by closely interacting with cancer control programs,

training new investigators to provide them with multidisciplinary skills, and identifying and developing resources to facilitate population-based research.

Dr. Fraumeni concluded his portion of the DCEG overview and introduced Dr. Alfred Knudson, a Special Advisor to DCEG. Dr. Knudson thanked Dr. Rimer and the Board members for the opportunity to speak at this NCAB meeting.

Dr. Knudson presented a slide listing cancer-causing agents that have a serious impact on genes. Assuming that cancer is a somatic genetic disease, Dr. Knudson described four groups of individuals that could be associated with any particular cancer and indicated that he had coined the term "oncodeme" to describe these groups. These groups include spontaneous, hereditary, environmental, and interactive oncodemes. Estimates have been made that approximately 15 percent of cancers worldwide originate from spontaneous mutations. If genetic changes are of importance in somatic cells, then inheriting such a change would put an individual at increased risk of hereditary cancer. Environmentally-induced cancer includes two groups—one caused solely by the environment and the other caused by genetic predisposition to environmental damage. Dr. Knudson indicated that little is known about how these two groups are divided.

Showing another slide, Dr. Knudson explained that if it is true—based on migrant studies and variations of incidences of cancer around the world—that approximately 80 percent of cancer is environmental, 5 percent or less is caused by a dominant hereditary gene, and 15 percent is spontaneous, then even though cancer could not be eradicated by prevention, great progress would be made if environmentally-induced cancers were eliminated.

Showing a series of slides, Dr. Knudson discussed Burkitt's lymphoma. This cancer results from activation of an oncogene by chromosomal translocation. It demonstrates that cancer can be caused by a nonviral mechanism, but involves a gene that was originally discovered in viruses.

Dr. Knudson showed a slide with an example of hereditary cancer. The example consisted of a dominantly inherited pedigree where penetrance is high. For this example, Dr. Knudson described high penetrance as meaning that a person who has the gene nearly always gets the cancer. Other pedigrees have low penetrance. Dr. Knudson indicated that there are families of this type for essentially all types of human cancer, and further information is needed on what is actually being inherited and on the relationship between the hereditary form of the cancer and the nonhereditary form of the same cancer. Dr. Knudson explained that since 1971 and the creation of the National Cancer Program, some answers to these types of questions have been found.

Using a slide, Dr. Knudson showed an example of retinoblastoma tumors in children. He indicated that approximately one in every 20,000 children worldwide has this condition and that spontaneous mutations may account for some of the cases. He explained that approximately 40 percent of these tumors are due to inheritance of one mutant copy of the retinoblastoma gene. Using another slide, Dr. Knudson illustrated the relative risk that a dominant gene imparts to a normal child and a gene carrier child. Dr. Knudson stated that two events are necessary to develop a tumor. If a child born with the cancer gene loses the protective gene, then cancer develops. A normal child must lose both copies of the gene. These two examples show the relationship between hereditary and nonhereditary cancer. They also suggest a second type of gene that is different from the oncogene. A superactivated oncogene causes division and the production of more DNA, but the other type of gene does not promote division and suppresses tumorigenicity. This type of gene is called a tumor

suppressor gene, which Dr. Knudson indicated he had termed an "antioncogene" to contrast it with an oncogene. He explained that it is now known that there are examples of both genes in the origin of human cancer. Showing a series of slides, Dr. Knudson also described the cancer-initiating events for adult cancer. He explained that, in adult cancers, the antioncogene appeared to have great importance.

Using another slide, Dr. Knudson explained that cytogenetics helped to determine that, with retinoblastoma, some individuals who are born with the defect have a partially deleted chromosome 13, which is the location of the gene for retinoblastoma and led to its cloning. Dr. Knudson presented a slide of the cloned familial cancer genes and noted that the first one cloned, in 1986, was the retinoblastoma gene; the remainder have been cloned in the 1990s. He emphasized the great progress that has occurred, and noted that scientists are considering whether this new information is being capitalized on appropriately.

Dr. Knudson presented a slide describing the *p53* tumor suppressor gene. He indicated that recent findings have suggested that genes that control the activity of the *p53* gene are mutated in cancer. Showing another slide, he indicated that certain DNA viruses manufacture proteins that immobilize both the retinoblastoma and the *p53* genes. Other cancers have been found to have abnormalities of both *p53* and *Rb* (the retinoblastoma gene). It is believed that these two genes are integral to the origin of many cancers. Future goals include proving that this is true for more cancers and that other genes exist that have equivalent effects in carcinomas.

Showing a slide, Dr. Knudson discussed the familial polyposis coli gene that increases risk of colon cancer. Individuals with this gene develop thousands of colon polyps. These polyps are precursors of cancer, but not inevitable precursors. The presence of these polyps gives the medical profession the opportunity to implement secondary prevention—that is, intervene in the transformation of the polyp into carcinoma. This information has confirmed the importance of individuals with hereditary cancers in preventive research. Because of the extremely high risk of cancer in these individuals, new means for preventing this transition can be evaluated and implemented. If the new methods are successful, then it is possible that the use of these methods for normal people could be considered. He indicated that this possibility seems probable because the known genes that are mutated in colon cancer (the polyposis gene, the *ras* gene, the deleted in colon cancer gene) are mutated in both the polyposis coli individual's cancer and in the normal individual's cancer of the colon. Dr. Knudson pointed out that these individuals differ from each other because the familial polyposis coli group has inherited one of the steps. Therefore, any measure implemented to help the polyposis individual would be anticipated to help the normal colon cancer individual.

Dr. Knudson presented a series of slides inferring how the area of genetics has undergone a large revolution over the lifetimes of many of the NCI scientists. He explained that in children's cancers, the number of events appears to be very small, which means that prevention may not be very feasible for children's cancers. However, children's tumors are quite homogeneous and somewhat responsive to treatment. The cure rates for pediatric cancer as a whole are approximately 70 percent. In adult cancers, the same success rate is not evident, but the feasibility of prevention is greater.

Dr. Knudson concluded his presentation by stating that knowledge about the genetic defects in cancers is being developed at a tremendous rate, which presents new opportunities in cancer prevention and treatment. He expressed his hope that Dr. Fraumeni's plan would capitalize on these opportunities. He also indicated that a laboratory component was very important to the Division.

Dr. Rimer thanked Dr. Knudson and opened the floor for discussion.

Questions and Answers

Dr. Klausner reiterated that the NCI's view of research, in which the care and approach to patients is transformed by science, is not limited to the relationship between basic science and therapeutics, but also should include population- and epidemiologic-based research, which have been ignored in the past. Dr. Klausner indicated that the three Divisions are collaborating to integrate these components. He explained that the NCI's approach to translational research will include development of a training program to ensure that individuals with a certain area of expertise also gain expertise in other areas, such as statistical genetics, molecular genetics, or clinical genetics.

Dr. Correa asked what will happen to the epidemiology discipline, given the tremendous change it has undergone. He inquired whether epidemiology will be taught to the molecular biologists or molecular biology will be taught to the epidemiologists. Dr. Knudson responded that their hope is to develop answers to that question. He indicated that it is anticipated that if there is a training program in which genetics, laboratory research, clinical work, and epidemiology are brought together, then individuals can enter the program from any of the areas. To enter the program, an individual would have to have a well developed background in one of the areas and an interest in developing the others. He indicated that because these areas have progressed in different directions, the areas are not able to communicate with each other. Dr. Knudson feels that, at the NCI and Cancer Centers nationally, these areas can be joined back together.

Dr. Correa asked about the function of the laboratory. Dr. Knudson responded that an enormous amount of work is already occurring in the Division and that rapid progress has occurred in genetics—the genetics of viral cancer, genetic changes involving viral cancers, and genetic susceptibility associated with radiation damage represent some examples. He indicated that this was strong evidence of the need for an Intramural Laboratory Program to develop this progress further. He expressed the importance of following through with an Intramural Laboratory Program to fulfill the promise of DCEG for the future.

Dr. Dickersin expressed her concern with trying to maintain the up-to-dateness of epidemiology at the risk of eliminating breadth. She asked if the marriage of the different components will do away with good research. She indicated, for example, that some of the funded research is very innovative and involves cancer, but has nothing to do with genetics. She questioned what is being done in the DCEG to ensure that good ideas coming in from other areas are not lost. Dr. Knudson agreed that these issues are dangers. He did indicate, however, that the intention is not to make molecular geneticists out of epidemiologists—it is to make them aware of what is happening in the area of molecular genetics. The laboratory would provide an environment to learn about molecular biology and the areas where it is useful. The goal is to foster a familiarity with different disciplines. Dr. Dickersin added that the presentation was confusing because of its focus on genetics and led her to believe that the entire Division would focus on genetics. Dr. Rimer added that Dr. Knudson was summarizing new initiatives for the Division and that these new initiatives would be in addition to the old initiatives. Dr. Fraumeni added that, in his presentation, he tried to illustrate the future challenges as maintaining the current strengths in environmental epidemiology and related areas, while differentially expanding genetics.

Dr. Salmon indicated that he sees as more important the bridging of the entire Human Genome Center on campus because of its large interest in cancer and asked if that was part of the plan. Dr. Fraumeni indicated that they are working closely with the Center. Dr. Salmon asked why they would need a laboratory when they already have an Institute (the Center). Dr. Klausner responded that it is not really an Institute. He indicated that the Center has a very strong Intramural Program, but cannot operate a cancer genetics program. The Center has an interest, but does not have the resources to develop cancer genetics. Dr. Klausner explained that, with respect to the Intramural and Extramural needs, it is not unreasonable to have the goal of being able to identify all high penetrance tumors of the cancer susceptibility genes. He explained that the NCI currently does not have all of the facilities necessary to achieve this goal. He raised several issues that the National Cancer Program as a whole should think about, including the ability to act on and recognize the identification of potentially informative families; to have an infrastructure (which is currently not available) to allow the high proof of genotyping for mapping; and, once the mapping is available, to allow individuals to find the genes. He predicted that mapping will remain a difficult problem and indicated that it was one of the items in the bypass budget that is being dealt with as necessary infrastructure. He indicated that once high penetrance genes are identified, additional issues such as the identification of low penetrance genes, gene environment interactions, modifier genes, and others will require new infrastructure on a national scale.

Dr. Day, referring to Dr. Knudson's mention of the SV40—presumably as a transforming virus with a genetic effect—and explaining that a lot of the polio vaccine was contaminated with SV40, asked whether there was any indication that specific portions of the genome are so transformed. Dr. Knudson responded that SV40 T antigen interacts with both Rb and p53, as well as some other proteins that have not been characterized. Dr. Day inquired as to whether there was any indication that it has carcinogenic potential in populations. Dr. Knudson and Dr. Fraumeni indicated a preliminary examination gave no evidence of that. Dr. Fraumeni also indicated that the exposure was significant—six or seven million people.

Dr. Rimer commented that the training program is exciting and suggested that partnerships with the Cancer Centers should be explored. Dr. Knudson and Dr. Fraumeni agreed with this suggestion.

Dr. Klausner introduced Dr. Claude Klee as the Chair of the Intramural Advisory Board and the Chief of the Laboratory of Biochemistry and commended her for being one of the best biochemists at the NIH and in the world.

XII. ROLE OF THE INTRAMURAL ADVISORY BOARD—DR. RICHARD KLAUSNER AND DR. CLAUDE KLEE

Dr. Klee indicated that the establishment of the Intramural Advisory Board created a mechanism for the internal staff to communicate their concerns and needs on issues pertinent to the mission of the Intramural Program to the NCI Director, the Scientific Director, and the Associate Director for Intramural Management. This mechanism allows for effective, efficient, and prompt reviews for the Research Program.

Dr. Klee explained that there are 17 members on the Intramural Advisory Board represented by 8 Basic Research representatives, 7 DCS representatives, and 2 DCEG representatives. The members represent both senior and junior investigators, including 11 laboratory chiefs, 5 section

chiefs, and 1 staff physician. The members serve for 2 years. In addition, the NCI Director, the Scientific Director, and Ms. Maryann Guerra participate in the meetings as ex officio members and, thus, provide regular direct access for communication.

Dr. Klee described the duty of the Intramural Advisory Board as the evaluation of existing and proposed policy and regulation to assure that it will have a positive impact on the Intramural Research Program. The Intramural Advisory Board can propose changes and suggestions to the Director and, if they are approved, these proposals can be submitted to the Executive Committee for consideration. She suggested that the most important role of the Intramural Advisory Board is to collect information from the scientific staff to present to the NCI Director and Scientific Director. Dr. Klee indicated that, because members of the Intramural Advisory Board only serve for 2 years, there will be opportunities for scientific staff on the Board to participate in decisionmaking.

Dr. Klee announced that, to date, there have been three meetings of the Intramural Advisory Board, each of which Dr. Klausner has attended. Ms. Maryann Guerra and Dr. Pizzo have also provided input at the meetings. Dr. Klausner has identified six issues on which he would like the Intramural Advisory Board to report to him by the year's end: (1) distribution of resources by the Scientific Director; (2) the fairness and uniformity of the review process by the BSC; (3) whether the review recommendations of the Board are implemented fairly by the Director; (4) the new administrative infrastructure, as well as the research facility, cost of contracts, need for core and shared facilities, associated costs, and especially the transgenic animal core facility; (5) recruitment of young investigators at both the postdoctoral and tenure-track level; and (6) the employee performance management plan.

Dr. Klee stated that, overall, she believes that the Intramural Advisory Board will have an impact on decisionmaking. Dr. Klee concluded her presentation and was thanked by Dr. Rimer.

XIII. GENERAL DISCUSSION OF INTRAMURAL PROGRAM INTEGRATION—DR. BARBARA RIMER, DR. RICHARD KLAUSNER, AND BOARD MEMBERS

Dr. Rimer invited the NCAB members to raise questions or comment on the integration of the programs. She also invited the presenters to add any information that they were not able to include in their earlier presentations.

Regarding the structural and procedural changes, Ms. Deborah Mayer asked Dr. Klausner to explain his vision on all the changes that are being planned (i.e., How will the changes make a real difference in the work performed?). Dr. Klausner responded that the NCI needs to improve its research quality, use of resources, and contributions to the scientific enterprise. He explained that the purpose of the infrastructural mechanisms is to create a spectacular scientific institution. Dr. Klausner indicated that the first step in making these improvements is to determine the available resources. He predicted that activities are going to become more rigorous and demanding; however, the Intramural Program will not grow in terms of its funding percentage of the NCI. He explained that at the same time the Intramural Program is shrinking as a percentage of the total NCI, individuals will have to be recruited to serve the purpose of reinvigorating the Intramural Program.

Dr. Klausner reiterated predictions that there will be an elaborate process of shifting resources. He stressed that the outcome of these changes at the NCI ought to result in a world-class research institution and, to achieve this, the structures have to be in place and the will and energy

have to be mustered to reach the goals. Dr. Klausner explained that this will be a very open, clear process. He stated that although the process will be straightforward, it will also be a lot of work. For example, exactly how to create a great clinical research entity is one of the obstacles that Dr. Klausner noted. He explained that if steps are made toward having a smaller fellowship program, there will be a need for some clinical infrastructure support; however, it will not be the normal clinical infrastructure support with house staff and staff physicians. He indicated that changes to the Clinical Center will include new recruitments and integration among the different divisions. He restated that he and the NCI would be open to criticism.

Dr. Salmon commented that he believes the NCI's plans for the Intramural Clinical Research Program are reasonable. He explained that the plans were similar to those for a number of outside Clinical Centers. He commented that he did not think anyone was criticizing the need for support resources such as nurse practitioners and physician assistants to replace a portion of the fellow group. He added that he believed that the issue of staff physicians is an area of concern because, if the staff physicians are there specifically to see patients, research initiatives may erode and physicians may be carrying out the practice of medicine instead of clinical research. In light of this, he reemphasized the need for dynamic clinical investigators who are not staff physicians. Dr. Klausner agreed and added that one of the structural issues related to this is the ownership of beds (independent from the issue of who is taking care of the patients)—whether the beds belong to individual branches or to the Division. He explained that the idea of central quality control overlooking protocols and providing central clinical resources available to everyone spurs certain issues. One of the issues that it drives is the estimated bill to the Clinical Center. Dr. Klausner explained that last year the NCI used only a fraction of what had been estimated for bed use and, as a result, was drastically overcharged.

Dr. Salmon asked what the charge per patient was if the total charge for last year was $120M. Dr. Klausner responded that the $120M covers more than just clinical costs—it is the total management fund. He explained that the clinical costs covered a large portion of the $120M, but he was not sure of the exact breakdown.

Dr. Becker commented that there is an additional large task in the future, and that is to alleviate the "we" versus "they." He expressed his belief that it would be a great accomplishment to open up the interior of the NCI for all to view—constituencies, legal scientists, researchers, and clinicians—and think in terms of the common task, which is alleviation of cancer. He commended Dr. Klausner for the progress made thus far on that issue.

Dr. Rimer announced that the Subcommittee on Information and Cancer Control would be meeting that evening and then adjourned the first day of the full NCAB meeting.

XIV. INNOVATIVE USE OF INTRAMURAL MECHANISMS TO STUDY CELL CYCLE CHECKPOINTS—DR. RICHARD KLAUSNER

Dr. Klausner explained that his presentation focused on a new experimental project that uses an exciting approach to study cell cycle checkpoints and noted that the intramural mechanism being used for this project is also innovative. Although this project is essentially a developmental therapeutics project, it aims to capture our evolving understanding of the fundamental nature and mechanisms of cancer by exploiting the universality of biologic mechanisms over time and evolution. The recognition that fundamental and accurate insights into the mechanisms of human biology can be achieved by studying simple organisms, such as prokaryotes and eukaryotes, is an amazing

revolution. The solutions that developed billions of years ago for fundamental biologic problems have changed very little. In fact, some biologic mechanisms have changed so little that gene products of simple organisms will actually function in Baker's yeast and human cells.

The first slide depicted the fundamental cycle of life, defined about 100 years ago. Dr. Klausner stated that this basic cell cycle was preserved morphologically over time. Organisms transfer genetic information—that is, DNA—from one cell to two cells through this cycle. Dr. Klausner explained that we have come to understand this cell cycle better and our understanding has progressed from a morphologic level to molecular and regulatory levels. Some of the fundamental molecular issues of cancer are beginning to be understood within the context of the constraints and the needs of fulfilling this cycle. Dr. Klausner does not view carcinogenesis as simply a disregulated movement through the cycle, but rather as a violation of some of the fundamental principles of moving through the cycle that emerged with simple organisms, and that have remained. The cell cycle must incorporate fidelity; fidelity of transfer of genetic information as it is duplicated and distributed to daughter cells is critical. In many ways, it is extremely appropriate and useful to consider cancer not as a disease of proliferation, but as a disease of the infidelity of transmission of the genome—that is, a disease of genomic and genetic instability. And, we can understand the issues of genomic and genetic instability by putting them in the context of the emerging understanding of how fidelity is dealt with in the cell cycle.

Using a series of slides, Dr. Klausner discussed how a morphologic description of the cell cycle can be converted into a description of different biochemical phases of the cell cycle. In the 1950s, the "beautiful perfection" of DNA as the carrier of genetic information was recognized by the scientific community; however, there was little interest in the question of fidelity. Over the past 20 to 30 years, a whole field of cell biology relates to the fact that DNA is enormously vulnerable and an unstable molecule. In a normal cell that goes through a cell division, perhaps 10,000 mistakes and structural changes are made. The issue of fidelity and how cells recognize whether genetic information is successfully and accurately copied and then distributed between daughter cells has now taken center stage and is fundamentally part of the issue of cancer as a disease of genetic instability.

One of the great advances of biology (driven by Dr. Leland Hartwell of Seattle) was use of the simple, genetically trackable haploid organism—Baker's yeast—to investigate development of conditional mutants by blocking the cell cycle at various points. This was facilitated by being able to readily identify cell cycle phases under a microscope. The observations resulting from this genetic dissection have transformed understanding of the cell cycle. Dr. Klausner stated that there is now increased understanding of the biochemistry that describes the transitions from one phase of the cell cycle to the next one. In these different phases of the cell cycle, growth and other factors initiate the duplication of DNA, which takes place in S-phase—the synthesis phase of DNA—in preparation for the separation of the chromosomes and the division of the cell.

Dr. Klausner depicted the different cell phases, as defined by discreet transitions. A universal biochemistry underlies these transitions—that is, a somewhat complex family of kinases, which are enzymes that transfer phosphate to proteins, and that are regulated by a variety of other proteins and events. He stated that it is now known that each of the cell phase transitions are driven by the activation and inactivation of this conserved family of kinases called cycline dependent kinases (CDKs).

Using another slide, Dr. Klausner discussed the multiple cycles that occur in a cell cycle to complete the process of the duplication of DNA and the distribution of that duplicated genomic information to the two daughter cells. The three major cycles are: (1) DNA replication; (2) spindle pole body or central cell duplication; and (3) correct alignment and separation of the chromosomes, by means of the spindle apparatus. A "cytokinesis" cycle, which is the structural cycle of dividing the cell in two, could be considered a fourth cycle. These different processes are potentially independent processes that all have to take place at the right time and in the right spatial orientation to complete the cell cycle.

Dr. Klausner stated that it is now known that if any of the major cycles are carried out incorrectly, problems develop with the genetic composition—the genomic composition of the daughter cells. Presenting a slide, he pointed out that defects in DNA replication result in a variety of chromosomal aberrations, including deletions, mutations, amplifications, and translocations. Spindle errors will result in chromosomal abnormalities of the monosome or disome; spindle pole errors can result in hyperploidy, tetraploidy, and so forth. These are, in fact, characteristics of cancer cells.

Dr. Klausner noted that, during yesterday's meeting, Dr. Knudson stated that certain cancers look as if very minimal chromosomal changes occur, from a karyotypic viewpoint. Dr. Klausner believes that as more refined and precise techniques (e.g., comparative genomic hybridization) are used to look at the genome in these cancers, the level of aberration observed will be more striking in most—if not all—cancers, in terms of the genomic integrity.

Using a slide, Dr. Klausner described how the multiple cycles that occur during the cell cycle are linked together through fidelity. The spindle pole body duplication process senses issues related to spindle movement and DNA replication. DNA replication—the ability to proceed through S-phase—is able to sense spindle pole body and spindle phenomena. The spindle itself is able to sense the fidelity of the DNA replication. Thus, built into this system is a series of internal and external signal transduction mechanisms that can monitor the fidelity of each of these processes and respond to the results of this monitoring through a system of controls that are called checkpoints. The checkpoint pathway is defined as the signal transduction mechanism that allows the cell to sense damage.

Dr. Klausner, presenting a slide, explained that checkpoints respond to the cell's ability to constantly survey the molecular progress through the cell cycle in ways that are still not clearly understood. When mistakes in any of the cell cycle processes are sensed, the transitions from one part of the cell cycle to another are altered. If previous processes in the cell cycle do not occur with the fidelity that the cell's mechanisms demand, the cell is not allowed to pass through the next transition. The transition contains a checkpoint that basically stops the cell from proceeding.

There are then three options. First, the cell may stop and initiate repair mechanisms to repair the errors if it can. There is an enormous amount of data and information on the ability to repair sequence and small-level DNA structural errors in replication; less is known about the ability to repair spindle and spindle pole body abnormalities. If the repair does not work, there are two other options. The checkpoint may adapt and go ahead. This is problematic, because the errors will be propagated. The other option is that the checkpoint recognizes that repairs have not been made, and the cell commits suicide through a variety of mechanisms and programmed cell death, some of which fall under the pathologist's description of apoptosis. Apoptosis is one manifestation of programmed cell death.

Dr. Klausner indicated that much of what is seen in the death of cancer cells in response to chemotherapy may be pushing these checkpoints to the induction of programmed cell death. He commented that we are beginning to lose the distinction between damage-induced death and programmed cell death because much of what stimulates programmed suicides is whether or not the damage can be sensed and repaired.

Dr. Klausner stated that the checkpoint pathways in yeast will be completely identified and fully characterized very soon; 70 percent of the *Saccharomyces cerevisiae* genome is already sequenced and the full sequence of the entire genome should be completed within the year. He indicated there is every reason to believe that each of these pathways and perhaps others exist in human cells. As more is learned about cancer susceptibility genes, it appears that some—or possibly all of them—exist on these checkpoint pathways.

Using a slide for illustration, Dr. Klausner showed how the cell cycle could be drawn as a series of transitions. He stated that more is becoming understood about the biochemistry of these transitions, including transitions that are controlled and governed by checkpoints that have very important and interesting properties directly related to cancer. These checkpoints are being defined in terms of the questions asked at the checkpoint. For example, the G1 checkpoint asks whether enough nutrients are present to begin replication. Another checkpoint asks whether the DNA has been replicated with fidelity. It is not known how many checkpoint pathways there will be—possibly 10 but not more than 15. Dr. Klausner noted that, in the past, the NCI has not always funded this type of basic research in yeast because the potential connection to cancer was not readily apparent, and he emphasized that the NCI should view such research with a more open mind in the future.

Dr. Klausner used his next slide to summarize the properties of the checkpoint controls. They act to inhibit the downstream events of the cell cycle. They are signal transduction systems, and are linked to the CDK transitions that are the biochemical basis for the cell cycle transitions. The checkpoints are not essential components. Cells will survive if a checkpoint is eliminated; however, the cells will accumulate genetic instability, as cancer cells do. The checkpoints function to increase the fidelity of the mitotic cell cycle process. One problem is that checkpoints exhibit adaptation. That is, if the cell cannot initiate repair mechanisms to repair errors, the checkpoint may adapt and the cell cycle will proceed, with a resultant loss of fidelity.

Dr. Klausner explained that for the last couple of years a group of individuals, many in the cell biology community, have been involved in discussions to rethink the approach to cancer therapeutics, based upon the reconceptualization of cancer as a disease of genomic instability, rather than of proliferation. If cancer is a disease of genomic instability, then it can be understood as the failure of checkpoint pathways—perhaps, the failure of multiple checkpoint pathways. Dr. Leland Hartwell and Dr. Stephen Friend have proposed a developmental therapeutics approach based upon the issue of checkpoints. The basis for this approach is that if each cancer can be defined by a pattern of specific breakdowns of specific checkpoint pathways, each of these checkpoint pathways can be thought of as being placed within damaged response pathways. Many of these damaged response pathways are genomic damaged response pathways, but there are also protein, organellar, and cellular damaged response pathways. Each failure of the checkpoint system represents a fundamental failure of specific pathways that protect the cell against damage and, thus, may be a potential target to induce cell death by agents with specific mechanisms of action.

Dr. Klausner emphasized that pathways for protecting a cell against damage are varied, and quite specific. Using a slide, he explained that the number of genetically distinct damaged responses in checkpoint pathways in yeast is growing. These include mismatch repair, nucleotide excision repair, base excision repair, double-strand break repair, G1 and G2 arrest by DNA damage, S-phase control by DNA damage, M-phase arrest by spindle damage, integration of G2 arrest, postreplication repair problems, base modification repair pathways, and various topological processes that relate to cytokinesis, spindle orientation, and so forth. In each of these pathways, a prototypic gene allows genetic access into the pathway; it is then possible to define the other genes in the pathway.

In terms of cancer susceptibility genes, Dr. Klausner suggested that there is not as much interest in the particular tumor suppressor genes or oncogenes that might be found in these pathways as in the pathways themselves. Dr. Klausner postulated that, as a more molecular picture of cancer is developed, the pattern of molecular characterizations of cancer will be the pattern of pathways that are knocked out, such as the *BRCA1* pathway, or the *Rb* pathway, or the *p53* pathway. Different cancers may knock out different genes in those pathways. It may not matter which gene is knocked out, because only one point in the pathway will have to be hit to knock out the pathway.

Dr. Klausner explained the importance of defining these pathways. He stated that the hypothesis is that if a lesion exists in a mismatch repair pathway, a double-strand break pathway, or a spindle damage pathway, those cells will be specifically and selectively damaged, hopefully to the point of death, by agents whose mechanisms of action target the specific pathway. A large variety of genotoxic and cytotoxic agents are available that are now administered as global genotoxic or cytotoxic agents. In fact, some cause double-strand breaks, some cause mismatch, some cause specific spindle effects, and so forth. Therefore, if the abnormal damage response pathway can be identified, it may be possible to define, in each particular cell, the specific type of damage to which the cell ought to be specifically sensitive. This could be a more effective approach than using a mechanistically random attempt to kill cells by genotoxicity or cytotoxicity.

Dr. Klausner further explained that one objective of the Seattle Project—which will be led by Dr. Hartwell and Dr. Friend and carried out in Seattle—is to define yeast genetically, resulting in a complete library of defects in all specific damage response and checkpoint pathways. Then, the question is whether therapeutic agents already known to be effective in some cancers are also effective at killing yeast cells. By using a precisely isogeneic strain with only a single known genetic defect in a pathway, it is possible to screen drugs. He stated that Drs. Hartwell and Friend are trying to define the efficacy of particular drugs by their molecular mechanisms of damage and to predict whether that damage results in cell death based upon the specific pathways. About 150 drugs given by the Developmental Therapeutics Program (DTP) have been screened.

Dr. Klausner showed a slide with isogeneic lines having different damaged response pathways and different checkpoint pathways. He noted that there were significant and reproducible differences in the ability to kill the cell—up to three orders of magnitude—as a function of the specific agent and the specific mechanism of action. He explained that multiple agents that have the same mechanism of action are used to test the hypothesis. He further noted that data indicate a knockout of any one of several different genes in a genetic pathway results in the same selectivity, as predicted by the hypothesis.

Using a slide, Dr. Klausner discussed the use of camptothecin and a camptothecin derivative. Camptothecin had shown some promise in screening, but its specific effect on cells was difficult to

interpret. In the Seattle Project, this drug has been found to have significant selectivity for the *mec-2* pathway, which happens to be the *ATM* gene pathway. This agent has since been used in a selective knockout of the *ATM* gene in mammalian cells that either have or are homozygous for a deletion of the *ATM* gene. He further stated that such results suggest it might be possible to do pathway diagnostics of damaged response pathways as reflective of a fundamental molecular characteristic of cancer, rather than using the characteristic of proliferative ability. As we begin to understand the potential selectivity of drugs, we may find that multiple drugs are needed for effective therapies, because of the existence of backup pathways.

Dr. Klausner stated that this project will be funded as an intramural program in the DBS. It will begin as a field station in Seattle for the first year to year-and-a-half. Dr. Hartwell and Dr. Friend have joined the Intramural Program, on a part-time basis. Their detailed proposal for this project went through a rigorous review. Clear preliminary data will be available within the year that will allow a decision as to whether to proceed with the project. If this project succeeds, it will be integrated with the DTP in terms of testing new compounds and will actually be moved to the NIH campus.

Dr. Rimer thanked Dr. Klausner and opened the floor for discussion.

Questions and Answers

Dr. Philip Schein commented that not everything exciting needs to be moved back to the NIH campus. He thinks that the investigators are capable of establishing and maintaining their programs. His understanding is that there are clinical trials already in progress that are attempting to exploit some of these concepts, such as Dr. John Mendelsohn's work with specific growth factors such as epidermal growth factor (EGF). Dr. Klausner responded that he had reviewed the work being done with the EGF receptor. He commented that the new study is very different from the other types of studies being done.

Dr. Sydney Salmon commented that this work might be important for prevention. However, by the time there is a clinically diagnosable cancer, the stochastic events and the multiple mutations have accumulated so that there are many pathways and genes that are altered. Therefore, detecting the approximate cause may not yield a unique treatment. It may tell where a given drug acts, but it would not address the underlying hypermutability that is a characteristic of cancer, because there are so many genes altered by the time the clinical diagnosis is made. Dr. Klausner responded that the idea is that specific genomic instability remains as a fixed genetic aspect of that cancer independent of the additional phenotypic changes that then accrue because of it. If we knew in each of those cancers, regardless of the added phenotypic and genotypic changes, that there was an underlying sensitivity because of a particular lost damage response pathway, then what would remain would be a specific susceptibility to targeted therapy regardless of the progression and the accumulation of other phenotypic changes.

Dr. Salmon asked whether there was evidence in mammalian cells that the other checkpoint control pathways (not other steps in the same pathway) are not also damaged and the cause of this stochastic progressive mutational serial event. Dr. Klausner responded that the question could not be answered until all of the pathways are defined and pathway assays are developed.

Dr. Frederick Becker commented that most of these agents that will be tested do not cure cancer, and they will not do any better even if their target is identified. However, it may provide some molecular beginning towards synthesizing an agent that would act more specifically. In addition, the heterogeneity of a tumor even in its incipient presentation makes it possible for some cells to have independent and separate aberrations of these mechanisms. It is possible that you could select out the population that is a target for your specific agent but leave behind the residual that has gone a completely different route. Therefore, you may end up targeting the 99 percent, which have a mismatch repair problem, and not the 1 percent residual that will eventually kill the patient. Dr. Klausner agreed with Dr. Becker's comments and added that one aspect of developmental therapeutics is that much is learned from it.

Dr. Rimer thanked Dr. Klausner and introduced Dr. Robert Wittes, Director, Division of Cancer Treatment, Diagnosis and Centers.

XV. DIVISION OF CANCER TREATMENT, DIAGNOSIS AND CENTERS (DCTDC) OVERVIEW: CURRENT STATUS AND PLANS FOR THE FUTURE—DR. ROBERT WITTES

Dr. Wittes used a series of slides to report on the organization of the Division of Cancer Treatment, Diagnosis and Centers (DCTDC). The division represents an amalgamation of the Extramural Units of the old Division of Cancer Treatment and the units that used to be in the Division of Cancer Biology, namely, the Cancer Diagnosis Branch, and the Centers Training and Resources Program (CTRP). The Division is organized into four Programs: the Centers Program, the DTP, the CTEP, and the Radiation Research Program. The Division has two freestanding branches: the Cancer Diagnosis Branch and the Biological Resources Branch. The Biological Resources Branch used to be the Extramural Unit of the Biomedical Response Modifiers Program (BRMP) at Frederick.

Dr. Wittes reported that future directions for the DCTDC include developmental therapeutics, molecular diagnostics, diagnostic imaging, clinical trials, cancer centers, and the promotion of patient-oriented research. As one of the first activities of the new Extramural BSA, chaired by Dr. David Livingston, there will be formal reviews of developmental therapeutics, the clinical trials, and the cancer centers. These reviews will be completed over several months and will provide information on the future directions to be taken by the programs.

Dr. Wittes stated that the role of the NCI in new drug development included discovery, development, and clinical trials. He briefly discussed the history of commercial anticancer drugs before 1979 and pointed out that both the pharmaceutical industry and the NCI were major players. The NCI's involvement in the drug discovery and development effort covers a uniquely broad spectrum. It includes collaboration with academia and industry, ties to basic research, ties to a development network, and ties to a Clinical Trials Network.

Dr. Wittes posed a series of questions. Does the Nation still need a cancer drug discovery and development effort operating in the public sector with the public interest as the only relevant bottom line? If the answer is yes, what should be the justification of such an enterprise? He stated the answer could be that the science being done in this program is more innovative, or that industry is not willing to assume higher levels of risk.

Another question posed by Dr. Wittes was: How should we be screening? He explained that results of cytotoxicity assays are now used to decide initially whether a compound or extract might be useful or not. The advantage of this approach is that it allows for the serendipitous discovery of mechanisms that are not anticipated, biochemical targets, or, as the Seattle Initiative exemplifies, pathways. In addition, how do you generate structural diversity? Dr. Wittes explained that a traditional method has been to acquire compounds from natural sources, but the area of combinatorial chemistry has increased the ability to generate great structural diversity in chemistry laboratories.

Dr. Wittes indicated that the criteria for making decisions as to what substances go or do not go to clinical trials should be reexamined. He stated that a real strength of the program is the ability of the NCI to take compounds with low probabilities of success to clinical trials. As an example, he explained that the DTP has been criticized for years because of the balance between lead discovery versus lead improvement. The question that needs to be looked at is whether you take lead compounds to clinical trials quickly or whether you invest substantial effort on lead improvement before you take them to clinical trials.

Dr. Wittes briefly described the National Cooperative Drug Discovery Program established about 10 years ago by the DTP. This is an investigator-initiated program that attempts to use hypothesis-based drug discovery, based mainly in academia, but with government and industry participants built into the awards. A number of the compounds that have been developed under these awards have already or will shortly come to clinical trial. The total amount of awards for fiscal year 1994 was about $14.5M.

Continuing his presentation, Dr. Wittes turned to the topic of molecular diagnostics. An inquiry concerning appropriate NCI initiatives in developmental diagnostics will be conducted by the Intramural BSC, chaired by Dr. Edward Harlow. The review will focus on what the field now requires. Dr. Wittes stated that a number of questions need to be addressed. Frequently, biological observations made on tumor cells end up being potential markers or predictors of outcome. One clinical problem is that there is not always a reasonable infrastructure to allow for the conversion of these putative markers into something resembling a high throughput, low-cost test that could be used in a clinical setting along with a test to validate the marker. Another related problem is that the histologically similar tumors arising in different genetic backgrounds may behave differently with respect to susceptibility to early detection or response to therapy.

As a final example, Dr. Wittes posed the question as to whether the expression (or absence) of particular genes or pathways determine response or nonresponse to a new drug. Currently, this is a very laborious task, and there is a need to expand the ability to access human tissue and test it with available reagents. This is connected to the work that will be done under the Seattle Initiative. When those genes become known and those pathways become defined, it will be of interest to try to determine if the expression or nonexpression of defects in those pathways correspond to certain therapeutic outcomes in therapeutic trials. One cannot even begin to approach this question unless one has access to a tissue resource. Dr. Wittes stated that the tissue bank should be an open national resource available not only to academic investigators, but also to the biotechnology and pharmaceutical firms.

Dr. Wittes reported that the Cancer Diagnosis Branch created the Cooperative Human Tissue Network, which is a cooperative national effort for tissue-procurement-on-demand service. Since its creation in 1987, it has shipped 100,000 samples around the country to investigators requesting

samples for various purposes. Although this is a start, Dr. Wittes stated that unmet needs for tissue archiving still exists.

Dr. Wittes stated four components of a possible molecular diagnostic infrastructure: (1) repositories of archive tissue; (2) informatic support that links tissue to patient information; (3) consortia for the development of diagnostics; and (4) center(s) for developmental diagnostics.

Dr. Wittes briefly listed the imaging techniques currently relevant to cancer. These included metabolic and physiologic imaging, pattern recognition and image enhancement, and integration of imaging and therapy. He pointed out that this was currently a fairly small program, with much of the work being conducted by physicists and engineers in academic departments of engineering or imaging.

Dr. Wittes briefly described the cooperative part of the Clinical Trials Program, which comprises nine multicenter groups and has been in existence for about 35 years. He stated that it was not reasonable to expect industry or private foundations to fund a cooperative clinical trials effort that is not linked to product development. The Cooperative Clinical Trials Program involves over 6,600 investigators in 1,500 institutions and follows about 100,000 patients. The question of what is happening to accrual into the NCI-supported clinical trials has become an issue of concern in recent years. There is no substantial evidence of a trend as yet; however, there was a drop-off in 1994. Dr. Wittes stated that the other issues include the configuration of the program, the optimal funding structure, the coordination of the program by the NCI, relations with industry, the site monitoring system, and an outdated informatics system. He stated that there was an important question of how to integrate the Treatment Trials Group with the need for increasing trials in imaging and in molecular diagnostics. There is also the issue of the right balance between pilot innovative studies at the interface between lab and clinic versus the large Phase III studies.

Dr. Wittes reported that there is also the question of incentives and disincentives for participation in the program. Discussions are being held with the Pentagon regarding the possibility of offering access to the NCI-supported clinical trials to people in the direct care system of the Defense Department.

Dr. Wittes reported that recently, at Dr. Broder's request, the Cancer Centers Branch—in collaboration with the Cancer Center Directors—established and revised the Cancer Center Support Grant Guidelines. The guidelines now emphasize the criteria for review, which fall into six well-defined areas. The Cancer Centers are fairly well distributed geographically. Roughly 50 percent of the budget supports the administrative functions and the core shared resources that are not easily funded under other mechanisms. He posed the following questions: What should the chief purpose of the Cancer Centers be in coming years? Which of these purposes should be the focus of attention in decisions about the NCI Cancer Center designation? How do you decide whether or not something should be an NCI Cancer Center? How should Cancer Center Support Grants (CCSG) be structured so that they support the essential functions of the Center? What Cancer Center activity should be directly supported by CCSG funds? Should there be a cap on the size of individual CCSGs? Is the notion of an NCI-designated center somehow separable from the question of funding?

Dr. Wittes next commented on clinical research. He stated that the issue is whether clinical research is at a selective disadvantage in the review process. He further questioned whether the established Division of Research Grants (DRG) procedures do the job they are supposed to do in

ensuring that the clinical trials proposals or proposals for patient-oriented research get fair review. He stated that the figures suggest that clinical trials are a relatively small part of the budget. Clinical trials in the Research Project Grants category represent somewhere between 2 and 3 percent of the total budget; clinical trials as part of all mechanisms represent 16 percent of the total budget. The Clinical Investigators Subcommittee will be looking for new approaches to clinical trials grants. Dr. Wittes reported that a meeting was being requested with the DRG to propose the creation of a study section that will pay attention to clinical research in cancer.

Dr. Rimer thanked Dr. Wittes and opened the floor for questions and answers.

Questions and Answers

Dr. Day asked how much of the dip in the accruals to the Cooperative Groups was due to the issues with National Surgical Adjuvant Breast and Bowel Program (NSABP). Dr. Wittes responded that most of it was attributed to NSABP issues.

Dr. Rimer asked that comments be limited to the scope of the review of the Clinical Trials Program. Is a part of the possible agenda going to be the reevaluation of the entire program? Is there a redundancy? Are there too many clinical trials? Are they anachronistic in some ways? Dr. Wittes answered yes to all of the questions and added that a committee, composed of persons within and outside the Cooperative Group Program, will be looking at these questions. In response to a further question by Dr. Rimer, Dr. Wittes answered that not all existing cooperative groups would be represented on the committee; they were interested in having people who really understand the system and will approach it knowledgeably.

Dr. Salmon commented that the problem of clinical trials review through the study section mechanism was not a new problem, and that it has existed for more than a decade. He pointed out that it could be fixed if the Institute was willing to decide on a proportion of the budget that it chooses to have for meritorious clinical trials and not have them compete head-to-head within a study section. He referred to a presentation by Dr. Green a year ago who said every Institute has the ability to decide percentiles separately for given targeted areas. Dr. Salmon recommended that this be done because all other mechanisms have been tried. He stated that the RFAs and exceptions are temporary mechanisms. The exception mechanism shifts the burden of selection from peer review to the Executive Committee of the NCI. He thinks that it is easier to review, approve, and prioritize a basic science laboratory grant than a clinical one.

Dr. Klausner stated that he did not think that the mechanism would work for a variety of reasons. The study sections know that there is bias and they are determining scores based upon their anticipation of how the Institute is going to actually fund them; they may lower the scores and percentiles because they do not want them funded. He stated that there was also the issue of the difference between the success on the first submission and the success on amendments. He stated that the difference disappears on amendments, but that the clinical and patient-oriented researchers are not submitting amendments. In addition, the likelihood of a new investigator getting funded without amendments was 8 percent last year; the percentage increased with amendments. Dr. Klausner questioned whether the process of peer review that results in amendments and changing the submission was useful. He stated that the problem was complicated, and he was not sure whether giving a separate payline would not be immediately undermined in the study section.

Dr. Day requested that copies of the slides used by Dr. Wittes be made available. Dr. Wittes agreed to provide members with copies within a few days after the meeting.

Dr. Philip Schein commented that clinical investigation is dying and that all the exciting research on checkpoints and other things may not have an outlet in the near future to determine if there is actual clinical applicability. There is an unfilled need to train well-qualified clinical investigators who are prepared to pick up these research leads and move forward. The Clinical Investigations Subcommittee will be studying this issue. He stated that the DRG Therapeutics II Study Section, which reviews R01 grants in the therapeutic area, has been quite constant over the last couple of years, making about 13 awards. He stated that clinical investigators are very discouraged and they do not resubmit, because they do not feel they will get a fair break. Dr. Schein reported that ASCO will soon have a position paper published in the *Journal of Clinical Oncology* dealing with the subject of support for clinical investigations. He stated that patient-oriented clinical research received 1 percent ($21.5M) of the total NCI budget of $2B. Approximately $300,000 supported clinical investigation, of which Cooperative Groups received close to 50 percent. Investigator-initiated research support is very meager at present and needs some attention.

Dr. Schein stated that the clinical development process was a 10-year or longer process. He questioned whether the process could be shortened—while still maintaining an ethical standard—by moving discoveries into very focused small clinical trails more quickly, getting the relevant information, and perhaps using surrogate endpoints that are thought to be predictive of the types of endpoints of interest. The information could be fed back to the laboratory to tell them whether they are on track or whether some modification of their program has to take place. Under the current system, by the time something goes to clinical trial, it has already been superseded by technological programs in the large basic research programs.

Dr. Paul Calabresi commented that a Senate Appropriation Committee Bill stated that 1 percent of funding would be directed towards clinical investigation. He asked Dr. Klausner whether Dr. Varmus was considering this money. Dr. Klausner responded that he did not know. Dr. Rimer stated that it was not on the last Director's Committee list he presented.

Dr. Klausner stated that he has met with the ASCO Board. He has asked Dr. Glick and other members of the board to make a presentation to the Executive Committee and to work with them in considering ways of implementing approaches to increase the support of patient-oriented research. Dr. Rimer stated that Dr. Schein would provide specific committee recommendations at the February meeting, and that Dr. Glick was on the agenda.

Dr. Ellen Sigal asked whether there were some short-term resolutions that could be tried on an experimental basis. Dr. Wittes replied that there were things, such as the removal of disincentives, that could be implemented with clinical trials while the review was occurring. Discussions have already been held with the Office for Protection from Research Risks and the FDA regarding how to simplify the informed-consent process. He added that another area being looked at was protocol simplification.

Dr. Calabresi commented that if clinical investigation was not supported in a better way, it was going to disappear. A faculty member either does basic research and has a chance of getting NIH grants or goes into clinical practice or practice in a hospital setting. He stated that it is hard to do clinical investigation, because managed care does not allow the patient to be kept in the hospital.

Also, investigators do not have the time to reapply through two or three cycles in the hopes of getting grants funded. He questioned whether investigators who were not awarded grants would be lost as they turned to other pathways.

Dr. Rimer introduced Dr. Faye Austin, Acting Director of the DCB and permanent Deputy Director of the DCB.

XVI. DIVISION OF CANCER BIOLOGY (DCB) OVERVIEW: CURRENT STATUS AND PLANS FOR THE FUTURE—DR. FAYE AUSTIN

Dr. Austin stated that the DCB supports basic research on all aspects of cancer biology, from initiating events through development of neoplasia to metastases. As primarily an Extramural Program, the goal is to support the highest quality science and balance an integrated program to acquire new knowledge in support of the NCI's mission.

Dr. Austin stated that the DCB is composed of five Extramural Program Branches: Biological Carcinogenesis Branch—Dr. Jack Gruber, Chief; Chemical and Physical Carcinogenesis Branch—Dr. David Longfellow, Chief; Cancer Immunology Branch—Dr. John Sogn, Chief; Cancer Biology Branch—Dr. Colette Freeman, Chief; and Radiation Effects Branch—Dr. Bruce Wachholz, Chief. She explained that Biological Carcinogenesis and Chemical and Physical Carcinogenesis Branches have the same names as the NCI programs. The Radiation Effects Branch is part of the Chemical and Physical Carcinogenesis Program, and is indicated on many documents by its former name, Low-Level Radiation. The Cancer Immunology Branch is indicated as the Immunology Program. The Cancer Biology Branch is called the Tumor Biology Program. This Division also includes the Frederick Cancer Research and Development Center Management Branch, which oversees the administration of the contracts that support the program activities at Frederick. Dr. Joseph Mayo is the Acting Associate Director and Chief of the Branch.

Dr. Austin stated that she would focus her presentation on Extramural Programs. Showing a slide presenting a summary of the grants by mechanism within the Division, she pointed out that the DCB supports research by individual investigator-initiated grants primarily by using R01s. The Division supports over 1,600 individual investigator-initiated grants including Method to Extend Research in Time (MERIT) awards (that were peer reviewed as R01s) and R29s (considered to be junior R01s). The Outstanding Investigator Grants of the NCI are being phased out over the next several years, and these investigators may start applying for replacement grants through the R01 pool.

Dr. Austin explained that the Division had a significant number of P01s, which have been very useful for basic research. The Division will be looking at the need and usefulness of P01 grants at the current level for support of basic research. Dr. Austin described the DCB as a small division in terms of the actual number of branches and number of professional personnel. However, she stressed that it is not a small division in terms of the total number of grants that are supported and the total amount of money that is expended in support of basic research. Approximately $427M is expended in basic research. She directed the audience to the tables in their Board book that provided a listing of the major areas of research supported by each branch, an analysis of the grant portfolios by subcategories of research, and a total listing of all active grants supported by the Division. She explained that although the summary table was correct, there were several replacement pages for

some of the branches that indicate the differences in reporting under the new Division. The actual breakdowns of grants by subcategory in some branches include grants that were active during the year, but did not necessarily receive funds.

Dr. Austin briefly summarized the major research areas of the branches. The Cancer Biology Branch supports a broad spectrum of basic research in the biology of malignant cells. Much of the biology of normal cells that is relevant to their mission is supported in the National Institute of General Medical Sciences (NIGMS), and the National Institute of Child Health and Human Development (NICHD) supports considerable research in developmental biology. The major areas of research supported by the Cancer Biology Branch include growth signals and transduction of information in cells; cell division and cell death; controls for cellular proliferation; malignant transformation by oncogenes and tumor suppressor genes; gene disregulation in neoplastic transformation; tumor cell interactions with the host environment (including the role of surrounding stroma in promoting or inhibiting tumor cell growth); and the mechanisms of progression of tumors to metastases. There is a large research emphasis in angiogenesis, which is a very specialized area of interaction with the host.

Dr. Austin described the Cancer Immunology Branch, which supports research in a broad area of immune response to tumors, including *in vitro* studies and *in vivo* studies in animals and in humans. The Branch supports studies of the biology of cells of the immune system that play a role in the antitumor immune response and studies of humoral factors and cytokines that are relevant to antitumor immunity. These areas together form much of the basic information that is important to the rational development of cancer vaccines. This branch also supports studies of the immune mechanisms in bone marrow transplantation for cancer, including studies of graft versus host disease and graft versus leukemia effects; studies of the biology of malignancies of the immune system, the leukemias and lymphomas, including AIDS lymphomas; studies of oncogenes; and studies of the mechanisms of differentiation and gene regulation in hematopoietic malignancies.

Dr. Austin stated that the Biological Carcinogenesis Branch supports studies of the roles of human and animal viruses and other infectious agents in the causation of cancer. This includes molecular interactions of viruses, viral oncogenes, and cells in the induction of transformation. In this area they support research that is very closely aligned with research supported by the Cancer Biology Branch. Supported research includes studies of the kinetics of viral infection, virus and viral receptor interaction, induction of new cell products, viral latency and early events in transformation, and basic studies in the development of viral vaccines for prevention and/or control of caner.

Dr. Austin next discussed the Chemical and Physical Carcinogenesis Branch, which supports studies of the characterization of metabolism, toxicity, activation and physiological disposition of carcinogens, and their molecular structure and activity relationships. The studies include identification of carcinogens, mechanisms of action of inhibitors, identification of natural inhibitors present in the human environment, and the development of synthetic inhibitors. The Branch also supports studies of the genetics and mechanisms of induction of cell transformation, including the analysis of changes in cellular components and cellular functions by carcinogens and mutagens; studies on the analysis of the repair of DNA damage in carcinogenesis, including the consequences of defective repair; and studies of the role of oxygen radicals, tumor promoters, hormones, and other co-factors in carcinogenesis.

Dr. Austin stated that the Radiation Effects Branch supports studies of molecular mechanisms of ionizing and nonionizing radiation-induced DNA repair, mutagenesis and neoplastic transformation, radiation-induced gene induction, signal transduction, and regulation of cell response. They are also interested in the identification of biomarkers for radiation exposure and for radiosensitivity of biological systems, including population subsets; studies of improved models to describe radiation and radionuclide dose-effect relationships and to project future risks; and studies of the influence of modifying factors on biological response and dose-effect relationships.

Dr. Austin briefly discussed the scientific highlights of each of the branches. The highlights identified this year by the Cancer Biology Branch include the concept that mutations in the Type II receptor for transforming growth factor beta (TGF-β) may represent one mechanism through which a cancer cell can subvert normal growth-suppressing signals. TGF-β inhibits the growth of many cells, but cancer cells are frequently refractory to this growth suppression. It has been found that in one-third of colon tumor cells that are examined, the Type II receptor for TGF-β is mutated or inactive. This may be one mechanism by which replication error phenotypes affect this receptor and allow it to escape from growth suppression. It has recently been shown that adding back this receptor by transfection reverses the tumorigenicity of some cell lines.

Dr. Austin explained that the cyclin D1 story is an example of how overexpression of normal cell cycle components can act as potential oncogenes. Cyclin D1 is required for the normal mammary epithelial proliferation associated with pregnancy, and its overexpression can lead to mammary hyperplasia and eventually to adenocarcinoma.

Dr. Austin stated that gene silencing by methylation has emerged as a prominent mechanism in the development of colon, breast, and other epithelial cancers. Methylation prevents transcription by blocking the binding of transcription factors. This has been shown to play a role in altering the gene for p16 and in the Von Hippel-Lindau gene.

Dr. Austin stated that *ras* oncogenes may contribute directly to the growth of solid tumors by stimulating tumor cell proliferation and by facilitating tumor angiogenesis. The release of angiogenic factors by tumor cells gives them a growth advantage by providing neovascularization for the tumor. It has been shown that mutant *ras* oncogenes in transformed epithelial cells are associated with an up-regulation of the production of angiogenesis factors. It is possible that targeting of *ras* oncogenes could be used to inhibit tumor angiogenesis.

Dr. Austin explained that the Cancer Biology Branch, functioning primarily by investigator-initiated grants, encourages new investigators and emphasizes the use of First Independent Research Support and Transition (FIRST) Awards (R29) as well as Shannon Awards, which have been very useful in helping investigators who miss getting funded with R01 grants to develop preliminary data and then return with improved R01 grant applications. This Branch has developed a program initiative to encourage investigators to come into the field of cancer metastases. There is a current program announcement for small development grants (R21 grants) on the molecular and cell biology of metastatic tumor cells.

Dr. Austin reported that the highlights for the Cancer Immunology Branch include the studies of the Jak-Stat pathway of cytokine signalling that have shown implications for the use of cytokinesin immunotherapy. The discovery about 3 years ago of these families of molecules provide a better

understanding of how signaling is controlled by cytokine receptors and some new insights into the specificity of cytokine receptor signalling.

Dr. Austin stated that research in the area of specific transcription factors that control the development of normal and malignant B cells and Tlymphocytes will be aided by the availability of knockout mice that allow for adding back genes for specific transcription factors, in a sequential fashion, to gain more information about how the development of B cells is regulated.

Dr. Austin explained that Tlymphocytes in cancer patients and tumor-bearing mice fail to respond to normal activating stimuli, reducing the ability of the immune system to kill tumor cells. This is a very important finding, because although earlier studies have shown that cancer patients have intact immune systems until very late in the course of their disease, some of the initial studies of immune-based therapies have not been as promising in patients as the model systems would have led us to expect. It may be that immune cells infiltrating the tumors—or, in some cases, the peripheral immune cells—have defects in their T-cell receptor recognition sites and signalling molecules that lead to the loss of their ability to recognize and respond to tumor cells. Further research in how tumor cells actually inactivate host T cells and how this defect could possibly be reversed will have very important implications to the future development of cancer vaccines and other immune-based therapies.

Dr. Austin explained that the deletion of a specific subset of Bcells in HIV-infected individuals may allow for progression to AIDS and the development of B-cell lymphomas. Studies have shown that the gp120 of HIV may be acting as a B-cell superantigen analogous to the way that T-cell superantigens function to activate and then cause the deletion of specific cell subsets.

Dr. Austin stated that the Cancer Immunology Branch also supports primarily investigator-initiated research, but they have current program announcements out for basic studies of the immunologic recognition and control of tumors, to expand the research base for development of cancer vaccines, as well as a program announcement for studies of the immunobiology of AIDS lymphomas. There is a lot to be learned about why lymphomas develop in AIDS patients and, as AIDS patients are living longer, this is becoming a significant problem. The Branch also supports a plenary lecture each year at the American Association of Immunologists' annual meeting (which includes sessions on tumor immunology) to encourage basic immunologists to turn their attention towards some of the more difficult problems of cancer.

Dr. Austin reported that the scientific highlights of the Biological Carcinogenesis Branch include a new human herpes virus, HHV-8—which appears to be an etiologic factor or cofactor in AIDS-associated Kaposi's sarcoma—and body-cavity AIDS B-cell lymphomas. She also reported that the E6 oncoprotein of the human papilloma virus, Type 16—which is a high oncogenic strain of HPV—may contribute to the accumulation of genetic alterations responsible for HPV-associated cervical cancers. It had been shown that E6 binds to *p53* and abrogates growth arrest by that tumor suppressor. The E7 oncoprotein interacts with *Rb* and also plays a role in disrupting control of cell growth.

Dr. Austin stated that new tumor suppressor genes have been identified using genome-wide scans for loss of heterozygosity in transgenic mice expressing the SV40 large-T antigen. These genes are called *Loh-1* and *Loh-2*, and more research will be conducted in this area. This Branch is looking for animal models to study the viral causation of cancer and is also interested in viral vaccine

development, since viruses may play a role for cervical cancers, hepatocellular carcinoma, and lymphomas. There is also increasing emphasis on *Heliobacter* research.

Dr. Austin reported in the highlights for the Chemical and Physical Carcinogenesis Branch that it has been shown by mutational analysis that CDKN2 may play a role in the control of cell immortalization or *in vivo* adaptation of human breast cells. These are nontumor derived cell lines. Studies are under way to determine specifically if loss of CDKN2 is sufficient for immortalization and whether restoration of this gene expression in cell lines will induce senescence.

Dr. Austin reported that a very important finding with the studies of polycyclic aromatic hydrocarbons have shown that depurinating adducts may contribute more to the tumorigenicity of dibenzo[a,l]pyrene than do stable adducts. Most DNA adduct work to date has focused on looking at stable adducts and their role in leading to mutation by misrepair of replication errors. However, new studies are showing that some adducts may not stay attached to DNA, and at the time of leaving DNA, may take purine residues with them. This may be a new mechanism contributing to carcinogenic effects of various compounds.

Dr. Austin stated that the intensity and duration of exercise has been linked to reduction in chemically induced breast cancer. These studies are the kind that do not fare well in regular DRG study sections; they are not molecularly based, and there is difficulty in getting grants funded. These studies were done in rats; they show that both the duration and intensity of exercise affect the promotion stage of chemical carcinogenesis, and that this effect is sustained even after cessation of exercise. Excessive exercise, however, was not shown to be beneficial.

Dr. Austin reported that the treatment of young virgin rats with placental hormone chorionic gonadotropin, which mimics the effects of pregnancy, prevents tumor initiation and progression of breast cancer. This is the first report that this can be done in young virgin rats and supports the epidemiologic evidence in breast cancer that full-term pregnancy, through induction of complete glandular differentiation, is the most effective physiologic mechanism for inhibiting initiation of neoplastic processes in the mammary gland.

Dr. Austin stated that there are several ongoing program announcements for the Chemical and Physical Carcinogenesis Branch in the areas of etiology and prevention of breast cancer; they also have a PA for the molecular epidemiology of prostrate cancer that is jointly issued with the DCEG. A PA for studies of DNA damage in genomic instability will be issued jointly with the Radiation Effects Branch in 1996. The concept was approved in June 1995 for a PA for studies of the role of dietary phytoestrogens in carcinogenesis and anticarcinogenesis.

Dr. Austin reported that the scientific highlights of the Radiation Effects Branch include the finding that recombination or mismatched DNA repair genes may play a role in large-scale chromosomal events observed in mammalian cells that are exposed to ionizing radiation. *p53* has been shown to be mutated in some of the earliest clinical lesions following UV-induced carcinogenesis. She also reported that nuclear matrix-associated DNA sequences are a radiation-hypersensitive fraction of nuclear DNA.

In addition to the jointly issued PAs for this Branch, Dr. Austin reported that there will be an RFA issued jointly with the National Aeronautics and Space Administration (NASA) in 1996 for

studies of transmissible (or heritable) genomic instability from exposure of mammalian cells to ionizing radiation.

Dr. Austin stated that the Division staff work very hard to identify, assist, and encourage promising investigators who have novel ideas. Several of these investigators have been given Shannon Awards, which have helped them to obtain subsequent R01 funding. She commented that there is a movement away from the use of RFAs for basic research, even though there may be times when their use is justified. The Division is relying more on program announcements to encourage research in areas of interest to the NCI and would like to be able to use exception funding for novel investigator-initiated research grants in the areas of opportunity.

Dr. Austin reported that the future activities of the Division include promoting closer interactions of the programs, looking at how to build bridges to other divisions, and identifying ways to facilitate the application of basic research findings to clinical and population studies for the improved diagnosis, treatment, and especially prevention of cancer.

Dr. Rimer thanked Dr. Austin for her presentation. There were no comments or questions.

Dr. Rimer introduced the next topic for discussion and commented that it was a very important one because it dealt with the functioning of the NCAB. She announced that the February agenda would have fewer presentations. Dr. Rimer has received feedback from a number of Board members regarding a number of areas, including the amount of information contained in the Board books and the difficulty in assimilating the information during the NCAB meetings. She has also received feedback, especially from newer members, regarding the frustration of trying to review the grants fairly within the short period given for the review and the lack of criteria to determine what to focus on during the review session. There were also concerns expressed that 1-hour subcommittee meetings were not long enough given the important business that is being conducted in the subcommittees. Dr. Rimer stated that these concerns would be addressed following the presentations. She introduced Dr. Salmon, who gave a historical overview of the grant review process.

XVII. GRANT APPLICATION INFORMATION AND FORMAT OF REVIEW PRESENTATIONS: PROCEDURES—DR. BARBARA RIMER, DR. SYDNEY SALMON, AND DR. MARVIN KALT

Dr. Salmon stated that the primary responsibility for the NCAB is the final approval of grant applications of $50,000 or more before they are funded. It is a very daunting task because of the volume of material that is provided. The basic problem is that the NCI receives such a large number of grant applications; the study section reviews, the printing of those reviews, the collation of the scores, the percentiling, etc., take time and are often completed very close to the NCAB meeting. There have been several actions taken over the last 5 years by the Board and the NCI to reduce the volume of material to be reviewed by the Board members and to simplify the task. These have included identification of topic preferences of Board members so that members would review areas that they are more familiar with; exclusion of very low-scoring applications that were not recommended for further consideration; and the development of tables of contents organized in several different formats. Areas for special consideration have been organized in separate folders, including the review of proposed MERIT awards, proposed extensions, foreign applications, large budget proposals of more than $1M, problem grants for human or animal subject issues, biohazards, minority issues, and other special considerations. Despite these improvements, some NCAB members

still feel there should be more material that is better organized, whereas other members feel there should be less material that is better organized.

Dr. Salmon reviewed a number of examples of alternative application review paradigms that have been proposed by Board members for consideration. One example was a closed subcommittee review of segments. This would involve breaking up the Board into subcommittees that would deal with special areas and then meet together for a plenary closed session, including the *en bloc* vote of grants. Dr. Salmon posed the following questions: Do we need more or less staff presentation on RFAs, P01s, or other areas? Should we organize the discussion of the grants and also the tables of contents and the books of summary statements by generic interest of the Board members? (For example, breast cancer, P01s, clinical research, etc., so that certain areas can be tracked.) Can applications be indexed by funding pool? Could we use electronic transmission of information to either all of the Board members or a subset of the members?

Dr. Salmon stated that other suggestions included providing more or fewer full summary statements to all or a subset of the Board, and organization of applications by study section and percentiles. The issue of organizing applications by percentiles was raised as a way of trying to address those applications that are close to the payline and may be the ones that the Board members would be most interested in giving close attention. The current organization of the review packages does not permit these applications to be segregated. The counter argument for not organizing applications by payline is that the Board should review all of the materials provided, not just a subset of applications.

Dr. Salmon stated that the last issue was that the timing of the meetings influences the review process, and early meetings, relative to the time of completion of the study section and summary statement generation process, makes the review more difficult. In addition, meeting timing is related to the availability of conference room space. There are high costs and logistic issues for off-campus meetings. Currently, the NIH does not give preference to any Institute to use a given room even if it has a small number of applications to review. Dr. Salmon questioned whether a motion would be useful to ask the NIH to give the NCI preference over other Institutes with more flexible space requirements.

Dr. Salmon suggested that NCAB meetings be scheduled as late as possible after the review cycle to give the Division of Extramural Activities (DEA) staff more time to prepare the materials in a way that would be more digestible by the Board members.

Dr. Rimer thanked Dr. Salmon for his presentation.

Ms. Deborah Mayer commented that there was a need to pay more attention to the orientation of new Board members because it takes a year to understand the process. Even if new Board members are experienced grant writers or reviewers, the sheer volume and the obligations and responsibilities as a Board member are different.

Dr. Austin stated that she would discuss the role of the Extramural Advisory Board later, but that this Board is investigating how it can streamline parts of the review process from its own perspective as well as to meet the needs of the NCAB. She suggested that consideration might be

given to having a subcommittee of the NCAB work with the Extramural Advisory Board. She also suggested that it would be useful to look at what other Institutes are doing to streamline their processes.

Dr. Frederick Becker stated that he agreed with Ms. Mayer that there should be mentoring of new Board members regardless of their background. He also stated that the impression should not be left that NCAB members would focus on borderline grants.

Dr. Ellen Sigal commented that it was impossible to provide a serious and thoughtful review of a grant package in only a few days before a meeting.

Dr. Kenneth Chan stated that it was his understanding that their primary role is not just to look at a small segment of borderline cases, but to review all grant applications if at all possible. He suggested that NCAB members be given the opportunity to look at all grant applications. He also stated that he was in favor of some type of mentoring for new NCAB members.

Dr. Rimer stated that the suggestion about mentoring new people was one that could easily by implemented. She introduced Dr. Marvin Kalt, who discussed issues related to meeting schedules.

Dr. Kalt stated that two parameters dictate when summary statements become available and when the NCAB meetings can be held. The first is the schedule of study section meetings and when the summary statements become available. The second relates to the first date to pay an award as a result of actions taken by the NCAB. He stated that the NCI is the largest generator of applications to be reviewed, resulting in approximately 1,500 to 1,800 summary statements generated from the DRG and the DEA. The applications are collated and sent to NCAB members in two or three mailings.

Dr. Kalt addressed the issues involved in scheduling meetings. Space for Board meetings is treated at NIH on a first-come, first-serve basis. Relatively limited facilities are available to the NCI for Board meetings because of the size of the Institute staff, the need to have overflow rooms, and the need to televise the meetings to other staff at other locations. NIH meeting space is free, whereas off-site space is expensive and logistically complex; the cost for hotel space and logistical support is between $30,000 to $40,000. Bidding for meeting dates takes place 2 years in advance. Dr. Kalt explained that the Natcher Facility, a new conference facility, does not have a single meeting room equivalent in square feet to what is currently being used by the NCAB; it is questionable whether that facility could provide enough space for a Board meeting. Dr. Kalt stated that the transcript should show an expression of interest by the NCAB to maximize the length of time available between the preparation of summary statements and the NCAB meeting dates to provide more time to reserve meeting space.

Dr. Klausner commented that there has always been a problem getting a conference room; however, he has found that often the rooms are reserved but not being used.

Dr. Rimer commented that it seemed that people are willing to put in the time and are committed to doing a careful review, but problems are created by the lateness of the packages.

Dr. Day asked whether it was possible to have approximate inside/outside dates for the three meetings each year. Dr. Kalt responded that typically the meetings are set at the latest date possible.

For example, the meeting scheduled in February is close to the last possible time that an NCAB meeting can be held in order to make the awards. He suggested an alternative, which would be to discuss preapproval of applications using subsets of the Board before an NCAB meeting. This would be for those applications that are absolutely clean and extraordinarily within paylines. It would allow the grants management staff and the program staff to develop award notices that would be ready to be issued and might allow for moving the NCAB meetings closer to grants management meetings.

Dr. Kalt explained the timing of the Board meetings. The September Board meeting is held the beginning of the third week of the month. The meeting is held at this time because of the need to pay last-minute applications that go to the NCAB for the current fiscal year that ends on September 30th. The May Board meeting typically has to occur before Memorial Day; it cannot be held in June because the awards are issued on July 1st. The date for the January Board meeting is the only one with any flexibility; it can be pushed back into February.

Dr. Correa commented that it would be helpful to receive summary statements by discipline. Dr. Kalt responded that a common method was chosen to print the summary statements, but any index can be customized and sorted accordingly. The summary statements will still be split, however, as there will be two or three mailings. He further explained that Board members receive summary statements across a fiscal year. For example, in the September Board package, there are applications for the next fiscal year and the current fiscal year. In addition, applications that are reviewed by the Board, but are not paid, are still a funding possibility for three council rounds. Dr. Kalt stated that if a list was prepared of all the applications received in 1 year, it would be a 300-page printout.

Ms. Mayer suggested that consideration should be given to more general discussion, not on individual grants, but on clusters such as RFAs or P01s to see the broader themes or issues that are arising. She asked whether it was appropriate to discuss the use of contracts in relation to the budget. Dr. Kalt responded that there was no statutory requirement for the Board to approve contract awards. Once a year, Board members are provided with the contract information when each of the divisions report their portfolio. The concepts are publicized and, if there are large contracts that the Board has an interest in, generic discussions can be held before the competition takes place, based on what is published and what is public knowledge. This does not have to occur in closed session and can be discussed as long as value judgments are not being made in public sessions.

Dr. Becker requested that Board members be informed in advance of proposed trials and contracts. Dr. Greenwald responded that Dr. Livingston is planning a group to look at prevention and early detection trials. In FY95, the total amount spent on large trials (i.e., over $1M per year) within DCPC was $86M, including $25M for the American Stop Smoking Intervention Study (ASSIST) program. Of that amount, $23M were for 10 investigator-initiated projects. There were debates as to how to deal with such large trials initiated from the outside. Nine large trials, counting ASSIST, came through a process that involved the Division BSC. Trials included the Prostate, Lung, Colorectal and Ovary (PLCO) screening trial, a management trial related to cervix cancer, and four smaller trials. Two trials went through the Community Clinical Oncology Programs (CCOPs) process, including the tamoxifen Breast Cancer Prevention Trial. In the past, the review of such grants included an open session held with the Division BSC and a clinical trials review in the closed session with the BSC to discuss pending applications of individual grants. Dr. Greenwald stated that there was a need for a review of the process for dealing with outside grants.

Dr. Dickersin suggested that an agenda item for the next meeting be a full discussion of the process for review and funding of grant applications that come through the DRG and though the NCI via the DEA, as well as contracts and intramural research.

Ms. Mayer raised a series of contract questions, including whether RFAs were a response to what has happened in the R01 pool; whether contracts have been utilized in the R01 pool; and whether there has been overutilization of a mechanism to accommodate for these issues in other areas. Dr. Klausner responded that a mechanism-by-mechanism review is being conducted to determine how decisions are made in this Institute. Dr. David Livingston is doing a major review on clinical trials and prevention trials.

Dr. Rimer summarized the suggestions made during this presentation. She stated there was a need to have a better means of orienting new members on how to review grants and to look into the meeting room issues to see if scheduling can be changed to provide more time to review grants. There is also a need to streamline the grants process and to look at the contract review process. Dr. Salmon suggested that looking at what other Institutes are doing should also be included. Dr. Chan suggested that there was a need for a better mechanism for tracking the results of discussions.

Dr. Rimer commented that a number of people had suggested that the Monday session start earlier, as more time was needed so that discussions were not cut off prematurely. Dr. Salmon stated that West Coast participants could arrive by 4:00 p.m. Dr. Kalt commented that concurrent subcommittee meetings were not being held because Board members were appointed to more than one subcommittee. Dr. Day suggested that the meetings could run from either 6:00 to 8:00 p.m. and 8:00 to 10:00 p.m. or from 5:00 to 7:00 p.m. and 7:00 to 9:00 p.m. Dr. Sigal commented that 2 hours per meeting in most cases should be sufficient unless there is a special agenda item that requires a special meeting. Dr. Day suggested that a portion of the Tuesday meeting could be set aside for subcommittees. Dr. Rimer stated that the Monday session would end by 10:00 p.m., and more subcommittee meetings would be scheduled on Tuesday.

Dr. Rimer introduced Dr. Robert Day to present the subcommittee report on the Cancer Centers.

XVIII. SUBCOMMITTEE REPORTS

Cancer Centers Subcommittee

Dr. Day presented the report of the Cancer Centers Subcommittee. The Subcommittee addressed two issues: (1) major changes in the financing and delivery of health care; and (2) the comprehensive guidelines requirement.

Ms. Mary McCabe from DCTDC provided a presentation on changes in the financing and delivery of health care, particularly managed care.

Regarding the comprehensiveness guidelines, the Subcommittee discussed the review issues that surfaced at their last closed session. At that time, all of the reviews for comprehensiveness were deferred and will be taken up at the next closed session in February. Dr. Day reported that the Subcommittee had identified two viewpoints. One was that the conduct of the review was the issue and that it could be changed with suggested wording by Subcommittee members. The alternative

viewpoint was that the guidelines themselves were the issue. The elements in the guidelines that are not reviewed as part of the Cancer Center Core Grant Application (i.e., the information, education, and training of outreach service components of Cancer Centers) seem to be the source of the problems in the reviews that were set aside or deferred at the last meeting. Subcommittee members agreed that the definition of those elements in the review criteria should be reviewed and rewritten. Draft language will be prepared and circulated to members before the next meeting in February.

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

Clinical Investigations Subcommittee

Dr. Schein reported to the Board that the Subcommittee focused on the issue of support for clinical research. A concern was expressed about the state of the clinical research and the fact that it is rapidly decaying. The issue is that well-trained clinical investigators who can translate the discoveries coming out of basic research may not be available. As a result, there may be delays in seeing the full impact of recent research on the final bottom line, that is, cancer incidence and survival statistics. Ms. Diane Bronzert made a presentation on the current mechanisms, such as small grants, R21s, exploratory grants, and RFAs, that are in place to help alleviate this problem. Dr. Schein reported that there had been several discussions regarding the barriers and the possible mechanisms to be considered in dealing with what is being recognized as a crisis situation. Additional data were requested from Dr. Wittes, and the Subcommittee plans to identify specific proposals to bring to the Board at the February meeting. Dr. Schein reported that ASCO has a similar initiative in place and will be meeting with the Executive Committee to discuss this issue. According to Dr. Schein, if there is a new initiative presented by the NCI, it is expected that clinical investigators and their mentors will respond to the initiatives. There is also a need to rebuild the infrastructure to take advantage of the advances that are coming out of basic science research laboratories and to encourage people to seek and maintain a career in clinical investigation.

The minutes were revised to include Dr. Chan on the list of attendees. The Board passed a motion to approve the minutes of the Subcommittee meeting.

Special Priorities Subcommittee

Ms. Mayer reported to the Board that the Special Priorities Subcommittee discussed the plans for the conference on recruitment and retention of minority participants in clinical research. The conference will be held on January 26 and 27, 1996, at the Omni Shoreham Hotel in Washington, D.C., and the proceedings will be published. The Subcommittee reviewed plans for speakers and presentations. The Subcommittee discussed meeting in February as a followup to the conference and to discuss an RFA concept for regional workshops.

Ms. Mayer reported that the remainder of the meeting involved a discussion of the future plans of this Subcommittee and an attempt to identify high-priority, well-defined initiatives that the Subcommittee could address. In February, the Subcommittee will discuss how minority programs are organized, planned, and managed within the NCI, and the results of this meeting will be presented to the Board in May.

Dr. Dickersin said that she had heard criticisms from some consumers that the Surveillance, Epidemiology and End Results (SEER) Program does not sample minorities adequately and asked if

the Subcommittee could look into this. Ms. Mayer agreed to include Dr. Dickersin's request as a February agenda item for discussion.

The Board passed a motion to approve the Subcommittee minutes.

Planning and Budget Subcommittee

Dr. Sigal reported to the Board for the Planning and Budget Subcommittee. She thanked Dr. Klausner and others for being very receptive to new ideas. Dr. Sigal reported that the Bypass Budget will be reformatted and will no longer be *pro forma*. The Subcommittee discussed a number of items including the need to identify specific advances each year for presentation to congressional committees, the need for continuity of funding, the yields from additional funding, and the impact of managed care.

The Board passed a motion to approve the Subcommittee minutes.

Information and Cancer Control Subcommittee

Ms. Marlene Malek reported to the Board that the Subcommittee met to discuss a Healthy People 2000 Conference on Women and Tobacco, as well as the Behavioral Research Workshop Report.

Ms. Malek reported that the Subcommittee and Dr. Susan Blumenthal's office at DHHS, Office of Women's Health, are planning to co-sponsor a 1-day conference in Spring 1996 on women and tobacco, focusing on young women. The conference will be held on Capitol Hill and will target government officials, business leaders, community leaders, and health care providers. The conference will focus on state-of-the-art information on smoking and women, such as health consequences, addiction, and how tobacco control efforts can be expanded to reach underserved and multiethnic communities. She reported that the White House is very supportive of this conference and plans to play a significant role. Other organizations, such as the Robert Wood Johnson Foundation, the American Lung Association, and Bristol-Myers Oncology Division, are interested in co-sponsoring the event. Dr. Greenwald has agreed that DCPC staff will help with the conference in collaboration with Dr. Blumenthal's office. If this conference is successful, it could be expanded to communities, similar to the regional Breast Cancer Education Summits that were held in 1993 and 1995.

Ms. Malek provided background information on the Behavioral Research Workshop Report. On July 6 and 7, 1995, the NCI and the NCAB sponsored a meeting to identify behavioral research contributions and needs in cancer prevention and control. At the September NCAB meeting, Dr. Greenwald proposed that a working group be assembled to develop a plan for behavioral research at the NCI and to develop a strong research agenda. The NCI Executive Committee agreed to the development of the working group, and Dr. Livingston and the BSA agreed to evaluate the concepts that originated in the working group. At the Subcommittee meeting, Dr. Thomas Glynn of DCPC reported on the July meeting and the research needs identified by the workshop participants. The group identified numerous research needs within five main areas: diet and nutrition; cancer screening; postdiagnosis quality of life; genetics and behavior; and tobacco use, prevention and control. There were over 400 recommendations ranging from basic behavioral research to communications research. Ms. Malek stated that the NCI now needs to review these recommendations and develop a strategic plan for a strong NCI behavioral research agenda. As part

of developing the strategic plan, DCPC is forming the Behavioral Science Research Working Group to be chaired by Dr. Caryn Lerman of the Lombardi Cancer Center. This Working Group will meet in December 1995 and develop a draft strategic plan by February 1996.

Ms. Malek reported that DCPC is preparing a summary portfolio of current NCI behavioral research and will also publish last July's conference papers in a summary of the recommendations, to be completed by August 1996. The NCI will present the finalized strategic plan and RFA concepts to the BSA in October 1996.

Ms. Malek reported that the Subcommittee unanimously approved a motion to endorse both the implementation plan and the formation of the Behavioral Research Working Group. The Subcommittee would like to receive an endorsement by the full NCAB for the implementation plan and the working group. Dr. Rimer commented that a discussion had been held with Dr. Livingston regarding his willingness to review the recommendations as part of the extramural advisory process.

The Board passed a motion to approve the behavioral research planning process and the working group as presented by the Subcommittee.

XIX. NEW BUSINESS-SESSION II—DR. BARBARA RIMER

Dr. Rimer opened the new business session by stating that certain new business items have already been discussed in other sessions. Dr. Rimer indicated that Dr. Correa will be representing the NCAB at the NIH Director's meeting next week, and that it is an opportunity to bring all of the Board chairpeople together to meet with Dr. Varmus. One of the topics of that meeting will be the Nathan Report on clinical research. Dr. Correa will report on this meeting at the February Board meeting.

Dr. Rimer suggested and it was agreed that the January 30, 1996, meeting would be a conference call rather than have participants travel to Chicago.

Dr. Rimer stated that a suggestion had been made to reiterate the importance of having a closed session at every meeting. Dr. Kalt stated that all agendas for closed sessions must be approved by the Office of General Counsel and notice must be published in the *Federal Register*. Agenda items must have a real requirement as stated in the Federal Advisory Committee Act and the Sunshine in Government Act. These requirements include information of a personal and confidential nature, information that is embargoed from release because of legislation, or proprietary information. Dr. Salmon suggested, and Dr. Rimer agreed, that a regular agenda item should be a scheduled slot for the NCI Director to address some of the embargoed or otherwise closed issues. This was recommended by the Agenda Planning Committee last year.

Dr. Sigal raised a concern regarding the purpose and format of the presentations to the Board. Dr. Rimer responded that staff were under particular duress because of the recent furlough and that she has requested of Dr. Klausner that all slides be readable in the future. Dr. Salmon suggested that it would be more useful if presenters would include a few bullets on each slide and provide more detail in written handouts to Board members for later review.

Dr. Day expressed concern over the Breast Cancer Prevention Trial (BCPT), specifically relating to the way it was conducted, the potential dropout rate, the selective bias, the change in

informed consent, and the issues relating to endometrial cancer. He stated that the BCPT may provide lessons for the conduct of clinical trials. Dr. Day requested an update on the BCPT to answer the following question: Will there be an appropriate sample size without bias in the period suggested with enough observations to be able to come to a statistically valid conclusion? Dr. Rimer commented that a number of Board members had been raising the same questions, and that it was an important enough issue within the NCI that a review of large trials is being conducted.

Dr. Greenwald commented that there were fundamental issues related to strategic planning; for example, the medical field did not do a trial for Premarin and estrogen. Also, a major issue in large prevention trials is that many of them have multiple endpoints that occur at different intervals, which could be relevant to the BCPT. There have been 11,700 women randomized to the BCPT with a target of 16,000. The overall noncompliance rate is about 13 percent per year, as opposed to the initial expected noncompliance rate of 10 percent. This includes women leaving the trial for reasons of protocol. In the last 8 to 10 months, the noncompliance rate dropped to about 2 percent per year. Dr. Greenwald stated that the working relationship with the leaders of the trial and the NSABP is very good, and that this is a tremendously important trial. He added that the Data Safety Monitoring Board has discussed these issues and feels that the trial should continue.

Dr. Rimer agreed to have a presentation on the BCPT at the February meeting. There also will be a discussion with Dr. Livingston about how the Board can be part of the larger process of looking at prevention trials. Dr. Salmon suggested that the discussion of the tamoxifen trial be extended to include other prevention trials being conducted around the world to identify the similarities and differences.

Dr. Klausner commented that the intention is to involve the Board in the functioning of the NCI and thanked members for their involvement in the different committees and groups. Dr. Klausner reported on *BRCA2*, which has been identified by linkage analysis to a region of chromosome 13. The 900 kb region that includes both *BRCA2* and probably a pancreatic cancer susceptibility gene has been completely cloned through the large-scale human genome sequencing project. The sequencing of the entire 900 kb has been completed over the past 4 weeks and the sequence will be entered directly into the Internet database.

Dr. Rabson introduced Dr. David Livingston, Chairman of the NCI Extramural Board of Scientific Advisors.

XX. ROLE OF THE EXTRAMURAL BOARD OF SCIENTIFIC ADVISORS (BSA)—DR. ALAN RABSON AND DR. DAVID LIVINGSTON

Dr. Livingston stated that the fundamental responsibility of the BSA is to maintain oversight of the extramural activities of the NCI. The specific functions of the Board include: monitoring and providing advice and commentary to the Director of the NCI on the ongoing state of extramural activities; regularly monitoring the ongoing state of funding of investigator-initiated research grants; and advocating, when appropriate, enhanced levels of support for these applications. The BSA will regularly survey the state of the Nation's clinical cancer research activities and help to ensure that all segments of the population participate equally in the NCI-sponsored clinical trials. The BSA will also review the annual NCI budget, commenting actively on the proposed allocations to the extramural research units; review the state of health of each extramural division based on annual reports; serve as a sounding board for the views of the NCI grant holders on NCI policies and actions through public

hearings; provide advice and commentary to the NCI planning unit, the Extramural Division Directors, and the Director of the Institute regarding the Institute's long range plan; contribute to the annual bypass budget planning process; perform regular reviews of proposed concepts for future RFAs and other support programs; perform leadership reviews of the NCI Extramural Division Directors; communicate regularly with the NCAB to inform them of BSA activities; and maintain a close liaison with both Subcommittees of the Intramural BSC.

Questions and Answers

At the request of Dr. Klausner, Dr. Livingston described the first four reviews that the BSA will be undertaking. The first review will be of the NCI Cancer Centers Program, which comprises 52 cancer centers in the United States and is a $158M program. The second review will be of the Clinical Trials Program to ensure that it provides the best in clinical trials science over the next 5 to 10 years. The other reviews will include cancer prevention and drug development efforts at the NCI.

Ms. Brown expressed appreciation for the commitment Dr. Livingston has made to include minorities in clinical trials. Dr. Klausner announced that Ms. Brown will be one of the liaisons between the NCAB and the BSA.

Dr. Greenwald commented that two RFAs have February receipt dates. One is to identify research related to building better participation and accrual in ongoing trials, and the other is for small grants for creative work and developmental ideas focused on minorities and underserved populations in relation to clinical trials.

Dr. Livingston stated that, as large trials are brought for consideration, the question will be asked as to how a representative population will be engaged.

Ms. Mayer asked how many and what types of people will be appointed to the BSA and how the appointments will occur. Dr. Livingston responded that potential BSA members were still being identified. The BSA will have a large membership composed of representatives of all of the extramural NCI constituencies. There will also be two subcommittees, one representing clinical science and cancer prevention, the other representing cancer biology, epidemiology, and genetics.

Dr. Sigal asked if the BSA will be looking at the entire extramural program and then make specific recommendations on cost shifting or just other mechanisms of funding. Dr. Livingston responded that a major trigger for BSA action will be the level of hope in the cancer research community, which is currently low, because of chronically low paylines. The BSA will receive a factsheet to identify the paylines for grants. The BSA would like to see that paylines increase to a point at which people who have ideas which could result in discoveries of real substance are getting their chance to test them.

Dr. Dickersin requested that women scientists be included on the BSA, in addition to consumers and minorities.

Dr. Schein requested that the NCAB be kept informed of any fundamental change in any of the programs before they are initiated so that the Board can provide oversight and opinions.

Dr.Rimer offered to provide time at each Board meeting for Dr. Livingston to present an update as well as time for the individual members who are liaisons to the BSA to make presentations.

Dr. Livingston stated that the reviews discussed will be one-time reviews with reports to the Director that will analyze the health of a given program. Once the reviews are completed, the BSA would be the major oversight unit for the extramural activities of the NCI.

Dr. Schein commented that he assumed the reviews will be very authoritative and require a comprehensive effort to reach conclusions and make recommendations. Dr. Livingston responded that it is expected that the reviews will take approximately 6 to 9 months to complete and will be comprehensive. Dr. Livingston agreed to present the scope of the reviews at the next NCAB meeting and will report on the progress of the reviews being conducted. Dr. Salmon stated that two of the initial reviews are in areas where the Board has subcommittees. At the request of Dr. Salmon, Dr. Livingston agreed to provide brief reports to each of the subcommittee meetings.

Dr. Rimer thanked Dr. Livingston for his presentation.

Dr. Rimer introduced Dr. Peter Greenwald, Director of the Division of Cancer Prevention and Control.

XXI. DIVISION OF CANCER PREVENTION AND CONTROL (DCPC) OVERVIEW: CURRENT STATUS AND PLANS FOR THE FUTURE—DR. PETER GREENWALD

Dr. Greenwald stated that structurally the DCPC had not changed significantly since the Board received an overview of the DCPC last year. The DCPC is composed of three program areas (Early Detection and Community Oncology Program, Cancer Prevention Research Program, and Cancer Control Research Program) and one Biometry Branch. The Cancer Control Program includes both surveillance and some of the more behaviorally applied areas such as tobacco control, access to screening, and special populations.

Dr. Greenwald presented some examples of data to highlight surveillance activities. He presented data on the general trends in heart disease and cancer for ages less than 65 and ages 65 and over. The heart disease and cancer mortality rates for under 65 crossed in the early 1980s; the rates are now approaching each other and are projected to meet about the year 2005.

Dr. Greenwald referred to work done by Dr. Arnold Potosky and others to identify trends in early detection and incidence rates of prostate cancer in white and black men. There was a large rise in PSA screening from 1986 to 1991, which has increased the apparent incidence rate for prostate cancer.

Dr. Greenwald stated that the behavioral working group on tobacco will look closely at the data on smoking. The prevalence rate for high school seniors is almost the same for boys and girls, with girls slightly higher. However, for 8th, 10th, and 12th graders, the trend has increased in the past 3 years. Adults are actually quitting smoking; however, one of the biggest concerns in tobacco control is what is happening with youth. A striking difference exists between white and black high school seniors, with the white seniors having a much higher smoking prevalence rate. Dr. Greenwald reported that cigarette advertising and promotional expenses were at $6B in 1993, three times the NCI budget.

Dr. Greenwald briefly discussed a study done by the Glantz group. The *Weekly Reader* and the *Scholastic News* are two magazines distributed to millions of children in the United States. The Glantz group compared the content of both magazines and found that there was a slant in some of the articles in the *Weekly Reader*—described as "Smoker's Rights" articles—and that the owner of the *Weekly Reader* at that time was a major shareholder in R.J. Reynolds. Dr. Greenwald noted that research on policy issues related to tobacco—such as taxation, clean air acts, and availability of tobacco in vending machines—has great potential for impact, and that input from the NCAB as to the NCI's role in such issues is very helpful.

Dr. Greenwald briefly described the Biometry Branch. The statistical group plays a role in observational studies. The group also is involved in animal studies to answer such questions as: How are data handled if you study multiple compounds at the same time? Is it appropriate to do meta-analyses in animal studies? Is there an issue of stages of carcinogenesis in knockout animals? How do you interpret results in animals that have more than one gene knocked out. What is the significance of these results?

Dr. Greenwald presented selected highlights of prevention trials. The Community Intervention Trial (COMMIT) consists of 11 paired communities, with each pair randomly chosen to receive intervention or to serve as the control community. There are great differences in some of the prevention trials compared with traditional therapeutic trials. The Women's Health Initiative (WHI) uses a complex factorial design. The Breast Cancer Prevention Trial (BCPT) has the issue of different endpoints occurring at different intervals from the start of the trial. The Dietary Intervention Study in Children (DISC) was begun by the National Heart, Lung, and Blood Institute (NHLBI) with 600 children, ages 7 to 10 years. Both fat and cholesterol intakes were lowered in DISC, and calories were controlled. The NCI is studying the effect of this diet on sex steroids that may have implications for later breast cancer risk.

Dr. Greenwald reported that the Biometry Branch has been developing scenarios of how data safety and monitoring boards should work. For example, the Data Safety Board of the Women's Health Trial was given different potential outcomes of statistics, such as the heart disease rate or the cancer rate, and challenged to determine what their decisionmaking process would be.

Dr. Greenwald stated that trial methodology is a major research focus. As noted earlier, he mentioned that the screening group is working on a large trial for cancers of the Prostate, Lung, Colon, and Ovary, the PLCO trial. He explained that one of the most interesting and difficult methodologic issues is whether it is possible to do case-control epidemiologic studies on screening. Dr. Greenwald referred to a current issue of *Annals of Internal Medicine* that included an analysis of a heart disease study where meta-analysis was unreliable in predicting clinical trial results. He stated that doing case-control studies of early detection (i.e., retrospectively looking for screening history and trying to draw inferences) has many potential biases. Yet, these case-control studies are fairly easy to conduct. Although clinical trials are expensive and difficult to carry out, they are necessary to test hypotheses definitively.

Dr. Greenwald presented some examples of early detection trials. He noted that Dr. Sudhir Srivastava is leading an effort to look at biomarkers, in conjunction with a network of extramural scientists, to characterize the most promising biomarkers in terms of reproducibility, sensitivity, and specificity. The objective is to validate biomarkers so that they can be used as surrogate endpoints for cancer in clinical trials.

The PLCO cancer screening trial is a very large study of almost 150,000 people. The primary objective of the study is to determine if mortality for these four cancers is reduced by screening. The PLCO trial will evaluate the digital rectal exam (DRE) and prostate specific antigen (PSA) for prostate cancer; chest x-ray for lung cancer; flexible sigmoidoscopy for colorectal cancer; and ovarian palpation, CA-125, and transvaginal sound for ovarian cancer. About 40,000 people have been accrued to date.

Another large trial is addressing the issue of a management strategy for Pap test results for cervical cancer that indicate the presence of low-grade lesions. Types of low-grade cervical lesions include Atypical Squamous Cells of Undetermined Significance (ASCUS) and Low-Grade Squamous Intraepithelial Lesions (LSIL). The questions concerning patient management that are being addressed include: Can Human Papilloma Virus (HPV) testing be used to decide who needs to be treated? Should an immediate colposcopy or other invasive procedures be performed? Should management consist of conservative watching? Dr. Greenwald showed a slide of cervical epithelial cells progressing from normal cells to cancerous cells. Large commercial labs may read many samples of cervical cells as more severe dysplasia that needs medical intervention. About 50 million Pap tests are done each year. Approximately 5 to 15 percent might be LSIL, where the significance of the lesion cannot be determined. For such cases, a substantial number of patients will undergo an invasive procedure, with about 0.5 percent having a side effect, such as stenosis or infection, bleeding, or fertility problems. An average treatment will cost approximately $1,200, resulting in an aggregate national health cost of $3.6B. The hypothesis for this trial is that morbidity and high cost can be avoided if modern virology, such as HPV testing, or other procedures are used. This trial uses a Data and Safety Monitoring Committee and three quality control groups for HPV testing, pathology, and colposcopy.

Dr. Greenwald briefly discussed chemoprevention trials. These trials use a Decision Network that includes outside experts, including at least one or two Board members, who are involved in key decisions. Showing a slide of cancers in Jewish women with cases attributed to *BRCA1* 185delAG mutation, Dr. Greenwald reported that Dr. Jeffrey Struewing and others from the DCEG have found that, within a group of Jewish women under age 50, cancer development will be driven by the gene in about 16 percent of breast cancer cases and in about 39 percent of ovarian cancer cases. A key question is: What kind of intervention research can be done to lower this risk? For example, if there is a correlation of this gene with ductal carcinoma *in situ* (DCIS) or atypical hyperplasia, which occur before clinical cancer, could specific interventions reduce incidence.

Dr. Greenwald referred to a breast cancer chemoprevention trial of biomarker endpoints being done by Dr. Kapil Dhingra of M.D. Anderson Cancer Center. In this study, several weeks before definitive surgery is carried out on women with DCIS or carcinoma less than 10 millimeters in diameter—found by fine needle aspiration or biopsy—the women are randomized to tamoxifen, 4-hydroxyphenylretinamide (4-HPR), both, or neither. It is determined at surgery whether the intervention had an effect. Dr. Greenwald stated that two other Phase II studies, just getting under way, also try to take advantage of the time between diagnostic core biopsy and surgery. One is at the University of Alabama, using difluoromethylornithine (DFMO) as the chemopreventive, and one at Georgetown University using dehydroepiandrosterone (DHEA), a steroid, as the chemopreventive. He stated that fundamental questions that need an aggressive research effort include: How should the breast be sampled to be certain that "before" and "after" the intervention is a valid comparison? How do you relate progression and pathology to genes and other molecular markers? Is it possible to intervene and modulate molecular markers? Can you document that modulation changes incidence?

Dr. Greenwald reported on a contralateral breast cancer trial using 4-HPR that is being conducted in Milan, Italy, by Dr. Veronesi and others. This study involves about 3,000 women being treated for limited breast cancer with 4-HPR, using a 5-year intervention and a 2-year followup. The contralateral breast cancer occurrence results have not yet been published, but they seem to suggest a benefit in the youngest age group and not in older age groups. However, numbers of cases are small and not definitive. Dr. Greenwald reported an interesting result from this study that was published in the *Journal of the National Cancer Institute*. No ovarian cancers occurred in the 1,400 women who received 4-HPR for 5 years; 6 ovarian cancers occurred in the controls. During the followup period, two ovarian cancers were found in the group who had been on 4-HPR; none occurred in the controls. Dr. Greenwald stated that results from the 4-HPR study suggest that chemoprevention with 4-HPR is possible for breast cancer and maybe for ovarian cancer, also.

Dr. Greenwald briefly discussed chemoprevention intervention for prostate cancer. Referring to a previous presentation by Dr. David Bostwick, a pathologist at the Mayo Clinic, Dr. Greenwald stated that Dr. Bostwick pointed out the importance of prostatic intraepithelial neoplasia (PIN). In a study in Detroit, led by Dr. Sakr, the prostates of more than 300 men who had died in homicides or suicides were examined. A striking increase in PIN was found at a much younger age than was expected, in the 20's and 30's. In addition, Dr. Greenwald reported that about 16 percent of the patients seen by urologists the Mayo Clinic have PIN; and about 10 percent of patients seen by a urologic clinic in California have PIN. Such groups may be feasible targets for research. Dr. Greenwald stated that a workshop held last November at the Mayo Clinic, co-sponsored by the American Cancer Society and Dr. Bostwick, addressed PIN and issues such as pathology, diagnosis, and management. Another workshop on how to use PIN for research, being arranged by Dr. Donald Henson, is scheduled for July 1996. One important issue to consider is whether molecular markers associated with PIN can help to determine which PIN lesions are aggressive and which are incidental.

Dr. Greenwald reported that another possible approach to such research involves an entry biopsy, before chemoprevention, and a followup biopsy. The general design involves screening a large number of men. If their PSA is over 4 nanograms per deciliter, which is usually the lower screening level, the urologist may do several sequential PSA measurements. If a biopsy is needed, generally a sextant biopsy is performed. Cases where PSA is elevated and biopsies come back negative—that is, no cancer is evident—may be good candidates for a chemoprevention trial. The usual medical practice would be to have these individuals come back in a year and rebiopsy. In the trial, you would rebiopsy at some point after the intervention to determine if the chemopreventive intervention had an effect.

Dr. Greenwald described three animal models that are being used to help make decisions about which agents to develop for prostate cancer chemoprevention. In the model by Dr. Martin Bosland at New York University, some rats are given high proportions of the maximum tolerated dose of chemopreventive agent, whereas some receive none and serve as controls. This model is driven by the carcinogen methylnitrosourea combined with testosterone, an androgen. Three agents tested by this model—DHEA, oltipraz, and liarozole—have been shown to be active. DHEA, a steroid, inhibits both initiation and promotion in animal models. It decreases glucose 6-phosphate dehydrogenase (G6PDH) and inhibits activation of some procarcinogens. Oltipraz, a dithiolethione, is a sulphur-containing compound that is very similar to compounds in cruciferous vegetables such as cabbage. It was originally developed as a drug for schistosomiasis. Liarozole is an androgen synthesis inhibitor.

The second animal model described by Dr. Greenwald was developed by Dr. Irwin Leav at Tufts University. This model is driven by the androgen 5α-dihydroxytestosterone (5α-DHT), in combination with estradiol, at different dose levels. The agents are similar to the ones used in the Bosland model. The Bosland model uses prostate cancer occurrence in the model. The Leav model uses PIN occurrence as the endpoint.

The final animal model described by Dr. Greenwald was developed by Dr. Jeffrey Green at the NCI. He inserted the T antigen of SV40 into the control element of the rat. The result was 100 percent incidence of dysplasia at 4 months and a 50 percent incidence of invasive cancer at 10 months. The advantage of this model is that it is not driven by androgen. Therefore, it is possible to test some antiandrogen/antiestrogen compounds that cannot be tested in models driven by androgen.

Considering that vitamin E is being tested as a chemopreventive agent for prostate cancer in the Bosland animal model, Dr. Greenwald described an interesting result in the Finland trial (the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study). In this trial, 14,500 men in Finland received vitamin E, and 14,500 received β-carotene and placebo for vitamin E. The planned endpoint was to look at lung cancer. Unexpectedly, the risk of lung cancer appeared to be greater in men receiving β-carotene; prostate cancer risk was not significantly affected by β-carotene. However, only 99 cancers were found in men receiving vitamin E, compared with 151 prostate cancers found in men receiving vitamin E placebo. Therefore, in a double-blind, randomized clinical trial, a one-third reduction in prostate cancer was found in men receiving vitamin E. Because this was not the primary hypothesis, the results should be viewed as hypothesis-generating and not as a definitive result.

Dr. Greenwald mentioned one final large-scale trial. The Prostate Cancer Prevention Trial (PCPT), a primary prevention trial that uses finasteride, is aiming to randomize 18,000 men age 55 or older into the trial. Men will receive either 5 milligrams of finasteride per day or placebo for 7 years. As of October 1995, more than 15,000 men have been randomized.

Dr. Greenwald reported that three major leadership initiatives are in place, including black, Appalachia, and Hispanic initiatives. Dr. Louis Sullivan, a former NCAB member and DHHS Secretary, is heading the Black Leadership Initiative as the Leader of the Minority Health Professionals Foundation.

Moving to the area of diet, Dr. Greenwald briefly described the 5 a Day Program, which is a collaboration with industry to promote consumption of five or more servings of vegetables and fruits a day. The marketing of the 5 a Day Program is an enormous effort, involving about 80 percent of the biggest produce industries and 80 percent of the biggest supermarket chains, and is progressing well.

Dr. Greenwald suggested that more attention should be given to nutrition—or, bionutrition—research. Although scientists at the NCI are very focused on mammalian and microbial genetics, other countries are focused on the genetics of important staple crops, such as rice. Dr. Greenwald noted that the relative contributions of each approach to world health and to the international economy deserves serious thought. He suggested that "nutrition" research might not be the most appropriate term, because it may not convey the fact that research in this area is true science. He pointed out that the following are examples of applied bionutrition research.

About a year ago, the first engineered fruit—the "Flavr Savr tomato"—was approved by the FDA for marketing. Dr. Greenwald explained that tomatoes are picked when green so that they do not become mushy by the time they get to market. Tomatoes contain the enzyme polygalacturonase, which breaks down the pectin that keeps tomatoes firm. The Flavr Savr tomato was engineered using RNA antisense technology. The genes for polygalacturonase were put in backwards; this allowed the tomato to ripen on the vine before being picked and transported to market, without the tomato becoming mushy. Some people are raising concerns about inserting genes into plants.

Another example cited by Dr. Greenwald was a reference to a product developed by the Nutrasweet Company. This company, in the late 1980s, changed the physical form of protein, shaping it into very small spheroidal particles that have the mouthfeel of fat. The product, Simplesse, has been approved for food use and is used in a low-fat ice cream. However, Simplesse is not heat-stable and cannot be used in foods that must be cooked. Another fat substitute currently under consideration by the FDA is Olestra, a Procter and Gamble product. Olestra is heat stable and could be used to replace the fat in potato chips or french fries. The usual fat that is eaten is a triglyceride, a glycerol with the three fatty acids attached. Olestra has a sucrose molecule as its core, which allows eight fatty acids to be attached. When triglycerides are eaten, lipase from the pancreas hydrolyzes the fatty acids, which are absorbed and result in fat in the blood stream. When Olestra is eaten, apparently the lipase cannot physically get to the chemical bond between the sucrose and the fatty acids and, therefore, cannot hydrolyze the fatty acids. As a result, the fatty acids cannot be absorbed. Olestra has the mouthfeel of fat because it is a fat, but it contributes no calories to the diet. The FDA has not yet approved Olestra. The main issue is that Olestra absorbs fat soluble vitamins, including A, D, E and K; supplementing Olestra-containing foods with these vitamins has been suggested. Also, Olestra may result in gastrointestinal problems in some individuals. (NOTE: The FDA approved Olestra on January 24, 1996)

Dr. Greenwald explained that, historically, advances in technology have driven incidence rates in major chronic diseases. The best example, although not fully understood, is stomach cancer. It is believed to be highly likely that changes in preservation techniques for foods, as well as more ubiquitous year-round foods, have driven the significant decrease in stomach cancer. Dr. Greenwald stated that there will be a large variety of new food products available in the future. Subtle differences in fatty acids may have beneficial human health effects. It is possible that, as we start the next century, changes in the food supply may bring down the incidence of colon cancer and possibly breast and prostate cancers.

Dr. Greenwald expressed concern that we are behind the curve, rather than ahead of the curve, with respect to modern nutrition science. The biomedical research community and the leading medical research institutions have not yet recognized the importance of this field. Dr. Greenwald suggested that this issue deserves some deliberation by the Board.

Dr. Greenwald presented a slide that outlined the FY95 budget expenditures of $190M and briefly discussed selected budget items. The largest amount spent ($39M) was for the CCOP, including the minorities CCOP and two large trials on breast and prostate cancer. Chemoprevention research was emphasized ($27M). Smoking prevention and cessation, including ASSIST, was funded at $27M. Dr. Greenwald also presented the expenditures for large-scale prevention trials and noted that, as results from current Phase II trials become available, the NCI will want to do more Phase III trials. He stated that the NCI will welcome advice from the Board with regard to prioritizing these trials.

Questions and Answers

Dr. Becker agreed with Dr. Greenwald that there could be unexpected results from new food substitutes. He suggested that there should be some type of surveillance for these products, especially ones that contain molecules that could alter absorption patterns. Dr. Greenwald agreed and emphasized the importance of understanding the biological implications of changes in foods.

Dr. Rimer commented that most of Dr. Greenwald's examples focused on large prevention trials as opposed to R01 work. She asked what the balance would be over the next few years. Dr. Greenwald responded that he would like to see more investigator-initiated small studies and biomarker studies, but with some quality control. Work has been done with the National Institute of Standards and Technology (NIST) to give people controls, to test blinded samples for levels, and to look at markers. One extremely important area is the validation of biomarkers as to their usefulness in clinical trials. Some of these issues can be addressed by including small "piggyback" studies in the design of large clinical trials. On the issue of large trials, Dr. Greenwald indicated that there was a need for some large trials. However, without a planning process, there is a danger of getting numerous studies of colon cancer and of the agent that is popular that year, but no studies of breast or prostate cancer. Dr. Rimer commented that she had received feedback from prevention researchers who felt that more progress would be made over the next few years by more small studies than by more large studies. Dr. Greenwald responded that both types of studies are needed, as you could have endless small studies and never know whether they really proved the case.

Dr. Salmon asked whether DHEA was a virilizing androgen. Dr. Greenwald responded that it is viralizing, but a fluorinated analog is also being tested that does not have the androgenic properties. Dr. Kelloff commented that DHEA is a natural metabolite in the estrogen/androgen synthetic pathway, and that it peaks at about age 30 to 35, after which it decreases. The fluorinated analog that is under development is about a year away from clinical application. This compound is not part of the estrogen/androgen synthetic pathway. When head-to-head studies are conducted with DHEA and the fluorinated analog, both compounds are quite effective in reducing colon cancer and breast cancer in experimental systems. The DHEA is being held up because of its hormonal activity. There is work in the AIDS field and in lupus using DHEA. Clinical data for patients receiving 300 milligrams a day for 6 months are proving to be safe in terms of hormonal levels. Dr. Kelloff stated that DHEA can be used safely in short clinical trials for presurgical breast and presurgical prostate cancers.

Dr. Sigal asked whether Dr. Greenwald was pleased with the ASSIST program. Dr. Greenwald responded that it was on track and going well. He explained that it was a demonstration program that reaches about 95 million people. Seventeen states are covered and there is some coordinated effort with the Centers for Disease Control and Prevention (CDC) to reach other states. The purpose of the program is to look at whether intensive intervention using mass media and other approaches has an impact. Dr. Greenwald indicated that one thing learned from the COMMIT trial of 11 pairs of communities was that the impact on smoking cessation was good for low and intermediate level smokers. However, it was not good for heavy smokers. As a result, the ASSIST program will be asked to focus more strongly on prevention of onset of smoking in youth.

Dr. Rimer thanked Dr. Greenwald and introduced Dr. Marvin Kalt, Director of the Division of Extramural Activities.

XXII. DIVISION OF EXTRAMURAL ACTIVITIES (DEA) OVERVIEW: CURRENT STATUS AND PLANS FOR THE FUTURE—DR. MARVIN KALT

Dr. Kalt provided an overview of the DEA. He stated that the mission of the DEA is quality assurance. The DEA is organized into four branches: the Research Analysis and Evaluation Branch under Ms. Rosemary Cuddy, the Review Logistics Branch under Dr. Kirt Vener, the Contracts Review Branch under Dr. Wilna Woods, and the Grants Review Branch under Dr. Robert Browning. There are five major functional responsibilities within the Office of the Director and a sixth one is just getting under way. The first and foremost function of the office is the NCAB operations. The second function is the Committee Management Office, which is led by Ms. Carol Frank. This office is responsible for all the NCI-chartered committee activities including meeting communications, charters, nominations, and yearly financial reports.

Another major function of the office is extramural program policy and policy coordination. Dr. Vincent Oliverio is responsible for ensuring compliance with policy in all RFAs and in PAs that appear in the *NIH Guide*. The NCI has approximately 60 to 70 active PAs. In recent years, NCI has been issuing about 30 RFAs a year. It is expected the number of RFAs will decrease to below 20 in 1996. Dr. Oliverio also is responsible for ensuring standardization, especially for grants, and for other NCI-originated documents that appear in the *NIH Guide to Grants and Contracts*. He is also responsible for the coordination of the NCAB annual program review meeting. All program guides are sent to the Director's Office for clearance and publication. Dr. Paulette Gray and Dr. Kalt coordinate and disseminate all extramural policies that come from NIH and serve as the official policy responders to rebuttals and appeals.

The fourth function of the office is research integrity. The NCI currently has ongoing communications with the Office of Research Integrity (ORI) concerning between 15 and 20 open inquiries or investigations, some of which are several years old. Another 23 have been closed over the last 5 years. Approximately 80 percent of these turn out to have no finding of misconduct; those that do are made a matter of public record by the ORI and are published in the *NIH Guide* and are made available over the Internet.

The last function of the office is a programmatic function, the Comprehensive Minority Biomedical Program (CMBP). DEA has a long history of innovation in minority programs starting with the invention of the Minority Supplement Award, which is now an NIH-wide activity.

Dr. Kalt reported that almost $11M was awarded by the CMBP in 1995. There is a co-funding program, the Minority Biomedical Research Support Grants, with the NIGMS. The major activity, which accounts for almost $5M and 132 awards, is providing the supplemental awards for underrepresented minorities. The CMBP also has supplements for disabled individuals, conference grants, minority enhancement awards to deal with outreach, cancer awareness contracts to black colleges, and a small career development program.

Dr. Kalt briefly described the minority supplements. These are administrative supplements that are completed within 8 weeks of the first contact with the awardee. The awardee is an NCI principal investigator who has identified a minority or disabled individual, from the high school level up to the senior investigator level, who is interested in working with the investigator.

Dr. Kalt stated that the last activity in the Office of the Director is a new function and that it is the creation of the Office of Advisory Activities. This is the office within the DEA that will provide the support and management of the BSC and the BSA. Dr. Paulette Gray will serve as the Executive Secretary of the Extramural Board.

Dr. Kalt described the four branches of the DEA. The Review Logistics Branch is the intake point for all applications received by the NCI. There were 2,688 R01s received in 1994. There were 748 small business grant applications, 68 Institutional Research Service Awards, 375 requests for applications, 108 R25 education awards, 300 R29 first awards, 161 U01 cooperative agreements, and 68 career development awards. More than 5,000 applications are received each year. In addition, there are about three dozen contract proposal competitions resulting in about 300 contract proposals received. Dr. Kalt explained that 3,500 applications score above the 65th percentile and are reviewed over the three NCAB meetings.

Dr. Kalt stated that the DEA is responsible for reviewing all of the RFAs, which amounted to about 1,400 applications in 1994.

Dr. Kalt described the Research, Analysis and Evaluation Branch, which is responsible for tracking the nature of the research portfolio and the investigators supported by the NCI. There are two sections within the branch: a technical operations section, which is responsible for the structure and maintenance of the database, and the scientific analysis section, which codes, analyzes, enters, and interprets the data. There are 5,000 to 6,000 active awards that are catalogued. Each of the applications and awards are reviewed and coded based on the cancer research area.

Dr. Kalt stated that the Review Logistics Branch also provides support to DEA's own scientific peer review staff and the two other review branches to deal with the 1,000 applications that are reviewed annually. Once the reviews are completed, the Branch plays a major role in the distribution of summary statements and is responsible for tracking all the different award actions that need to be brought before the NCAB. There is a computing section that is responsible for the design and maintenance of the Information Management System used to track all of the documents.

Dr. Kalt stated that the Contracts Review Branch has responsibility for the review of every research and development contract that is awarded by the NCI. There are several hundred million dollars worth of R&D contracts ranging in size from small support contracts to single intramural laboratory contracts to multimillion dollar contracts to support the Frederick Cancer Research and Development Center.

Dr. Kalt stated that the Grants Review Branch is responsible for reviewing most of the applications and RFAs assigned to DEA. This represents the largest concentration of review staff outside of the DRG.

Questions and Answers

Dr. Calabresi thanked Dr. Kalt and Dr. Oliverio for all of their assistance to the Board.

Dr. Schein asked whether it would be possible for Dr. Kalt to take on the responsibility of reviewing a new set of grants—R01 equivalents in the area of clinical investigation-if a decision were ever made. Dr. Kalt responded that each Institute is doing review under the license and the

sufferance of the DRG. R01 review for investigator-initiated research projects that are unsolicited is routinely assigned to the DRG. However, it is possible to have them reviewed within the DEA. There is a new search under way for a Director of the DRG, who will probably take a look at the whole question of peer review and how best to use funds. The limitation in the DRG is that it has no appropriation and is funded from all of the institutes.

Ms. Brown expressed her appreciation to Dr. Kalt and his staff.

Dr. Rimer announced that the presentation by Dr. Austin on the role of the NCI Staff Extramural Advisory Board would be postponed to the next meeting. Dr. Rimer thanked all of the NCI staff for their presentations. Dr. Rimer adjourned the 96th National Cancer Advisory Board meeting at 3:33 p.m.

Barbara Rimer
sb

Date

Dr. Barbara Rimer, Chairperson