NATIONAL CANCER INSTITUTE ONLINE

Attendees

Call to Order and Opening Remarks
Dr. Livingston

Report of the Director, NCI
Dr. Klausner

Unfinished Business: The BSA at Scientific Meetings
Dr. Livingston
Dr. Young

Consideration of Minutes
Dr. Livingston

NCI and the Congress
Ms. Tisevich


**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**Natonal Institutes of Health**
**National Cancer Institute**

**2nd Regular Meeting**
**BOARD OF SCIENTIFIC ADVISORS**
**Minutes of Meeting**

**August 7-8, 1996**
**Building 31-C, Conference Room 6**
**Bethesda, Maryland**

*created: 27sep95 Lorrie Smith revised: 21jul97*

**How the NCI Sets its R01 Payline**
Mr. Amoruso
Mr. Hazen

**Program Review Group Reports**
Dr. Simone
Dr. Bresnick

**NCI Approaches to Managed Care**
Dr. Wittes
Ms. McCabe

**Closed Session**

**Behavioral Research in Cancer Prevention and Control Working Group Report**
Dr. Rimer
Dr. Lerman

**RFA and Contract Concept Policy Changes**
Mr. Amoruso
Dr. Kalt

**RFA and Contract Concepts**
Dr. Kelloff

# Report of the Division of Cancer Epidemiology and Genetics Program Review

Dr. Fraumeni
Dr. Knudson

## ATTENDEES

The Board of Scientific Advisors (BSA) convened for its second regular meeting at 8:30 a.m. on Wednesday, 7-8 August, in Conference Room 10, Building 31, National Institutes of Health (NIH), Bethesda, Maryland. Dr. David Livingston, Professor of Medicine, Dana Farber Cancer Institute, presided as Chair.

The meeting was open to the public from 8:30 a.m. to 4:30 p.m. on 7 August and 8:00 a.m.to adjournment, 8 August, for introductory remarks from the Chair, discussion of procedural matters, and discussions and presentations regarding two NCI extramural programs. The meeting was closed to the public on 7 August from 4:00 p.m. to adjournment for the discussion and disposition of an intramural site visit report.

**BSA members present:**

Dr. Frederick R. Applebaum
Dr. David G. Bragg
Dr. Joan Brugge
Dr. Mary Beryl Daly
Dr. Virginia L. Ernster
Dr. Eric R. Fearon
Dr. Suzanne W. Fletcher
Dr. E. Robert Greenberg
Dr. David D. Ho
Dr. Wuan Ki Hong
Dr. Tyler Jacks
Ms. Amy S. Langer
Dr. Caryn E. Lerman
Dr. David M. Livingston
Dr. Joan Massague
Dr. W. Gillies McKenna
Dr. Enrico Mihich
Dr. John D. Minna
Dr. Nancy E. Mueller
Dr. Sharon B. Murphy
Dr. Allen I. Oliff
Dr. Franklyn Prendergast
Dr. Stuart L. Schneiber
Dr. Joseph V. Simone
Dr. Robert C. Young
Dr. Daniel D. Von Hoff
Dr. Barbara L. Weber
Dr. Alice S. Whittemore
Dr. William C. Wood

**BSA members absert:**

Dr. Allen Oliff
Dr. Louise Strong
Dr. Peter Vogt

**Others present included:** Members of NCI's Executive Committee (EC), NCI Staff, Members of the Extramural Community, and Press Representatives

## CALL TO ORDER AND OPENING REMARKS
## DR. DAVID LIVINGSTON

Dr. David Livingston called to order the 2nd regular meeting of the Board of Scientific Advisors (BSA) and welcomed members of the Board, staff, guest, and members of the public. He reminded members of confirmed BSA meetings dates and asked members to report any conflicts.

Dr. Livingston informed the Board that because the BSA oversees a broad range of issues and makes recommendations to the NCI leadership on a wide range of scientific activities, the BSA would be divided into two subcommittees. For the next twelve months, Dr. Joan Brugge will chair the Subcommittee on Cancer Biology, Epidemiology, and Genetics, and Dr. Waun Ki Hong will chair the Subcommittee on Prevention, Clinical Research, and Therapeutics. Information about the structure, function, and relationships of the Subcommittees, how the BSA will operate, and BSA meeting procedures will be forthcoming. An annual report on BSA activities will be submitted to the NCI Director. The BSA Executive Secretary will draft the report.

**REPORT OF THE DIRECTOR**
**NATIONAL CANCER INSTITUTE**
**DR. RICHARD KLAUSNER**

Dr. Klausner announced several new NCI appointments: Dr. Edison Liu, Director, Division of Clinical Sciences (DCS); Dr. Edward Harlow, Associate Director, Office of Science Policy; Dr. Joseph Harford, Associate Director for Special Projects; Dr. Otis Brawley, Director, Office of Special Populations; and Drs. Carol Dahl and Robert Strasbourg, Assistant Directors, Office of Technology. The functions of the recently established Office of Technology will be presented at the next BSA meeting.

**Budget:** In a brief discussion of the budget, Dr. Klausner indicated that the 1996 NIH budget was $11.939B; the NCI budget was $2.255B, including $10M transferred from the NIH Director's reserve to support initiatives on informatics, translational research, and genetics. For 1997, the proposed President's budget for the NIH is $12.4B, of which $273M is for the construction of the NIH Clinical Center; for the NCI, the proposed budget is $2.28B. The House Committee proposed a budget of $12.747B (a 6.8 percent increase from FY96) for the NIH, which includes $90M for construction of the Clinical Center, with a commitment to fund it over a period of 4 years. The NCI's proposed budget, in the House, increased by $131M to $2.385B.

Members were told that the Research Project Grant (RPG) pool was over $1B for the first time, including an R01 payline at the 23rd percentile. Dr. Klausner expressed his intent to continue the Accelerated Executive Review (AER) and to extend AER to other grants. BSA members were asked to provide feedback in this regard. A brief overview of the AER process was given.

He noted that the budget for Cancer Centers was approximately $167M, which includes approximately $11M for administrative purposes. Examples of administrative usages of high priorities and special opportunities include the Genetics Research Initiative and the Genetic Counseling and Education Initiative in AIDS Malignancies.

**Liaison Activity:** The Board was informed that Dr. Alan Rabson, Deputy Director, NCI, is working on developing a mechanism to improve communication with and involvement of consumer groups. A proposal on how the NCI will proceed with this activity will be presented at a future meeting.

The NCI has begun a new initiative on cancer survivorship, chaired by Dr. Anna Meadows from Children's Hospital in Philadelphia. Dr. Meadows will report to the NCI Director on what the NCI needs to do in terms of coordinating and articulating a research agenda on short-, mid-, and long-term issues, including psychosocial, medical, and scientific issues, raised by cancer survivorship.

**ByPass Budget:** Dr. Klausner stated that the Bypass Budget has served as a useful vehicle and medium for communication with the Congress and the Administration. He encouraged Board members to read the Bypass Budget and provide feedback on: How well does it communicate the goals of the NCI?

What, if anything, is left out? and What could be done to make the next year's Bypass Budget better? He explained how the NCI uses the Bypass Budget for internal planning. He focused on "institutional planning", a planning process that cuts across all Divisions, within the Office of Science Policy. Comments on the Bypass Budget should be addressed to Dr. Klausner or Dr. Livingston.

Dr. Klausner briefly discussed the working groups organized for each initiative in the Bypass Budget. The working groups will look at the general description from an area of opportunity in the Bypass Budget, identify specifics on what the NCI wants to achieve, and develop 1, 3, 5, and 10-year milestones or goals for NCI staff for implementation plans. Current working groups are the Developmental Diagnostics Working Group (DDWG), chaired by Dr. Arnold Levine and the Cancer Genetics Working Groups (CGWG), cochaired by Drs. Albert Knudson and Barbara Weber. Drs. Douglas Hanahan and Robert Horowitz have been asked to serve as cochairs of a Preclinical Models working group. A working group on detection technologies, including imaging, is anticipated.

The DDWG has begun to formulate how to approach making use of technology to analyze the genome and read its expression at the RNA or protein level in terms of discovery and application for cancer. A series of proposals, including an RFA for the proposed Cancer Genetics Network, for the Cancer Genome Anatomy Project (CGAP) will be presented at the next BSA meeting.

National Cancer Policy Board: Dr. Klausner stated that, as a result of NCI's discussions with the NCI, the President's Cancer Panel (PCP), and the National Academy of Sciences (NAS), a National Cancer Policy Board (NCPB) has been proposed, and the concept was approved by the NCAB. The NCPB, a new entity under the NAS, will consist of representatives of all the stakeholders in the National Cancer Program. It will be independent and will be funded by multiple resources, including both federal and nonfederal sectors to provide a neutral forum to discuss pressing issues that are otherwise difficult to address for either structural, political, or institutional reasons. Dr. Klausner indicated that he will report to the BSA on the progress of the Policy Board throughout the year; progress will be presented in the form of concepts for consideration by the BSA.

In answer to questions from Board members, the following key points were made:

- NCI will make decisions for distributing the increase in the House budget based, not only on the needs of new initiatives, but on all of the competing programs. NCI will consider the needs of the intramural program as a whole and also will set budgetary restrictions.

- The NCPB provides a meeting place for consumers, professional organizations, and individuals who participate in federal processes, private academic activities, and various aspects of the private sector. It is important to involve industries that directly affect the National Cancer Program, such as the pharmaceutical industry and health care industry, and also to establish liaison with the media industry.

- The NCPB will be established within the structure of the NAS, but will function as an

independent advisory board similar to the Government University Industry Round Table. The NCPB will have its own agenda, use the structure of the National Research Council (NRC), which is the operating agency of the NAS, and also will use the NAS approved report review process.

## UNFINISHED BUSINESS: THE BSA AT SCIENTIFIC MEETINGS
## DR. DAVID LIVINGSTON AND DR. ROBERT YOUNG

Dr. Livingston reminded the Board that a subcommittee, Drs. Robert Young (chair), Barbara Weber, and Virginia Ernster, was formed during the last BSA meeting to develop a process by which Board members would attend national cancer-related meetings to foster communication with major segments of the cancer research community.

Dr. Young reported that the main idea and the title of the sessions could be "NCI Listens." The purpose of the sessions is to obtain feedback from the research and oncology communities on the problems they face and on what the NCI is doing. He emphasized that it is important to gather comments from the stakeholders, as opposed to comments from the organization, because large organizations are likely to make their interests known to the Director of the NCI, but the constituents within the organizations do not necessarily do so. The BSA has an obligation to report the information back to the organization and to the NCI Director.

The proposed logistical process is that: 1) two BSA members will attend each meeting; one should be a member of the selected organization. There will be one hour sessions, a 15 minute presentation from the BSA representatives and 45 minutes for questions and discussion.

The first round of professional societies are the: American Society of Clinical Oncology (ASCO), American Association for Cancer Research (AACR), American Society of Preventive Oncology (ASPO), and American Society of Hematology.

**A brief discussion resulted in the following points:**

- Attendance between the semiannual Cold Spring Harbor and the American Society of Hematology (ASH) meetings should be rotated.

- The BSA is focusing on organizations that have direct dealings and interactions with the funding and support mechanisms that emerge from the NCI. The lack of nursing and surgical constituencies is recognized. The BSA will include participation of as many different constituencies as possible.

- This activity is a new avenue that allows individual members of organizations to participate. Vehicles are already in place for the leadership of the organizations to get feedback directly to the Director. Organizations will be contacted to determine how to develop the outreach sessions within their society's meetings.

- The meetings will be publicized to a broader audience, Drs. Gray and Young will work on the implementation process.

## CONSIDERATION OF MARCH MEETING MINUTES
## DR. DAVID LIVINGSTON

The minutes of the 21 March 1996 BSA meeting were approved with changes. Minutes will be available to Board members before the meeting.

## NCI AND THE CONGRESS
## MS. DOROTHY TISEVICH

Ms. Dorothy Tisevich, Director of the Office of Legislation and Congressional Activities presented an update on congressional matters. In a series of slides, Ms. Tisevich briefly explained the formation and development of the NCI and reviewed the Institute's legislative history.

In addition to the Legislative Update, which is published 3 times a year, other sources for legislative information exist on the World Wide Web (WWW). The ad hoc group for Medical Research has a homepage that includes the House appropriations report language and the section for NIH. There is also a Web site called THOMAS, that provides information on specific bills and committees. Some congressional members have their own homepages, that include brief biographical sketches or information about their districts. A Web site that includes information on the Legislative Update, committees, testimonies, and hearings will soon be available on the NCI homepage.

In response to questions from Board members, the following points were made:

- Ms. Tisevich confirmed that there is a provision from Sen. John Rockefeller (D-WV) regarding a demonstration project for clinical trials. She explained that the bill would require the Health Care Financing Administration (HCFA) to undertake a demonstration project to provide coverage for clinical trials.

- A member asked about the status of other genetic legislation that is circulating, especially the Genetic Secrecy Act. Ms. Tisevich responded that she thought most of those bills would not be enacted during this congressional session, considering the time remaining.

- When queried about the specific language used in the Kennedy-Kassebaum Bill to prevent discrimination of self-insured individuals, Ms. Tisevich replied that she will look for the language in the Bill.

- A member asked whether the DoD appropriations for breast cancer and prostate cancer research are firm, and whether DoD is going to be the magnet for funding those major initiatives. Ms. Tisevich responded that appropriations can change because the appropriation process occurs every year.

- When asked if her office provides information from the BSA to the Congress so that intrusions into the NCI's flexibility in conducting basic research investigations (including clinical research) can be avoided, and how much the BSA can define the language so that the basic mission to do cancer control research is concentrated instead of diluted, staff responded that there are times when there is not enough communication among Board members, which affects the NCI's ability to respond to emerging opportunities. Ms. Tisevich noted that the current Senate passed the NCI

Revitalization Act, which contains very few changes for the NCI.

- When asked whether the NCI has the responsibility to coordinate the federal and nonfederal research efforts in the National Cancer Program, Dr. Klausner replied that it is a very complicated process, and he does not and should not have control over DoD's money. He stated that the NCI can advance cancer research by speaking as a single voice as much as possible when approaching and influencing the Congress. The NCI should try to set up a mechanism by which voices from different communities can be heard regarding their views on the NCI's priorities.

## HOW THE NCI SETS ITS R01 PAYLINE
## MR. PHILIP AMORUSO AND MR. STEPHEN HAZEN

Mr. Philip Amoruso, Associate Director, Office of Extramural Management (OEM), presented the OEM organizational chart and explained that the reorganization has been in effect for about one year. Mr. Amoruso stated that the Administrative Resource Centers (ARCs) provide all general administrative support as well as personnel support to the extramural Divisions. The ARCs have been established as a one-step approach to streamlining the administrative process. Branches within the OEM includes the: Grants Administration Branch (GAB), which deals primarily with the Extramural Programs; Research Contracts Branch (RCB), which deals with contracts of both intramural and extramural programs; Management Analysis Branch (MAB); newly-created Frederick Cancer Research and Development Center (FCRDC) Management Operations Support Branch, which provides the overall administrative and contractual support at the FCRDC; and the Extramural Financial Data Branch (EFDB).

Mr. Stephen Hazen, Chief, EFDB, stated that the key function of the EFDB is to project the number of applications that will be submitted, identify the effects on the payline, and develop the budget approximately two years in advance. EFDB also has an extensive computer data network, which manages and tracks both grants and contracts.

Mr. Hazen explained that "payline" refers to the percentile ranking or priority score that will be funded within the budget and "setting the payline" refers to the selection process of grant applications that are to be awarded, based on peer-review results. He stated that the NCI sets the paylines for distinct RPG mechanisms, such as R01s, P01s, R29s, First Awards, small grants, and RFAs, as well as paylines for centers, clinical groups, and other grant programs. Using the R01 mechanism, he demonstrated the process of setting the FY96 payline and stated that policy considerations must be taken into account in setting the payline. The paylines for major grant mechanisms in different timeframes was also shown.

In answer to questons from Board members, the following points were made:

- In explaining the rationale for the great R01 variance between years, Mr. Hazen stated that the 1996 appropriation is much larger than it was in 1995 and 1994. Additionally, a change of direction in the NCI moved the use of RFAs away from the RPG pool.

- When queried whether existing obligations for previously funded and previously awarded grants are factors in determining funds for the payline, Mr. Hazen replied that existing commitments are considered first when receiving a new budget; the amount for existing commitments is subtracted from the total amount to determine the remainder available for competing grants.

- When asked how cost management of the grant pool applies to the budget, Mr. Hazen replied that cost management is an overall policy. Although there is variation on an individual basis, in general, there has been a six percent cut for 1996. A member asked whether there is a general

principle used to determine the percentage cut. Mr. Hazen responded that it is more of a mathematical problem. The BSA Chair noted that the cost management guidelines apply to the entire NIH, not only NCI.

- In regards to a price-fixed element in the grant mechanism, staff responded that there are several different mechanisms, each with their own budget limits. The concept of "modular grants" is a reinvention experiment at the NIH. Individuals request funds in $25K increments, and it is not necessary to justify the budget increase in detail. The price-fixed concept has not been formally applied in the NCI.

- With regards to differences among paylines, staff briefly explained that a number of studies are looking at scoring across the NIH, as well as within the NCI. Within the NCI, the different mechanisms are reviewed in different venues. All of the R01s and applications submitted in response to the RFAs are reviewed in the DRG using standard evaluation criteria. There might be differences between raw scores versus percentiles for individual study sections. Within the NCI's review mechanisms, there are different evaluation criteria for different types of applications. Every now and then, a decompression of scoring must be carried out, because the percentiles versus the raw scores become compressed over time. Decompressed scores enable the NCI to make more informed funding decisions.

- When asked whether the new and competing R01s are distinguished from one another when considering paylines, as opposed to funding the highest priority scores regardless of whether they are new or competing, Dr. Kalt replied that this is an issue that has been discussed across NIH, the so-called point-of-funding.

- The two instances where adjustments to the average cost of a grant could be made are to: 1) deal with the amount beyond the inflation-determined mandate, which will occur regardless; and 2) reduce the average cost, such that the number of grants could be increased to increase the payline.

- The NCI reviewed every single contract in the Institute and made a reduction of 10 percent in the total contract program, which was applied to the RPGs. Additionally, the NCI made a policy decision several years ago to phase out the Outstanding Investigator Grant and to recirculate the monies into the RPG pool.

- When queried whether the shift from funding R01s for a full 5 years was the result of a policy decision and/or review, and if the shift is factored into the payline calculation, Mr. Hazen replied that the EFDB is keeping an eye on the duration of support for competing grants, which is one of NIH's cost management principles. Within the payline, the EFDB does not take any reductions in the number of years that are committed compared with those that were recommended by peer-review.

- When asked whether there is information available on the breakdown of R01s and P01s by basic,

clinical, and translational research, Mr. Hazen replied that data are available which approximate the particular varieties of applications, but nothing as precise as the question would really warrant. In future analyses, the EFDB will try to categorize R01 funds.

- A member asked if there is always an across-the-board cut when making a decision to cut budgets to increase the number of grants funded. It was noted that inexperienced investigators who submit realistic budgets might be more adversely affected by the budget cut than experienced investigators. Mr. Hazen responded that the cut is really an average rather than across-the-board, and there is variation on the percentage of cut among programs. Dr. Austin stated that discussions are taking place at the NIH with regard to changing the scoring systems for grants, and also to find other ways to provide more structured information that will facilitate making informed funding decisions.

## PROGRAM REVIEW GROUP REPORTS
## DRS. JOSEPH SIMONE, EDWARD BRESNICK, AND JAMES ARMITAGE

Drs. Joseph Simone, Edward Bresnick, and James Armitage presented updates on the three BSA program review groups.

**Cancer Centers Program Review Group:** Dr. Simone reported that the Cancer Centers Program Review Group (CCPRG) were reviewing five areas: 1) Goals of Centers in the context of the entire NCI Centers program; 2) Structure and function of individual Centers; 3) Guidelines and criteria for the grant application process; 4) Distribution and use of Cancer Centers funds; and 5) How to enhance the influence of the Cancer Centers Program on a regional and national level. Dr. Simone stated that the CCPRG report, with recommendations, is to be completed mid-to-late September and will be presented to Dr. Klausner at that time.

Dr. Klausner noted that he will probably assign Dr. Robert Wittes, Director, Division of Cancer Treatment, Diagnosis, and Centers, and a small group of the NCI's staff to work with him to produce a point-by-point response to the recommendations in the report. A Director's implementation response, similar to the one developed for the Bishop-Calabresi report, will be presented to both the BSA and the NCAB at either the November 1996 or March 1997 meeting.

**Prevention Program Review Group (PPRG):** Dr. Edward Bresnick stated that the PPRG is composed of people from a variety of disciplines, ranging from molecular biology to behavioral sciences to clinical sciences. The PPRG includes BSA, Board of Scientific Counselors (BSC), and NCAB members.

Dr. Bresnick briefly discussed the major activities of the two PPRG meetings. He indicated that plans are to have a draft report completed by the end of the year or early next year.

The Board was informed that the PPRG will establish six subcommittees and operate to a considerable extent by telephone conference calls. The subcommittees will address following issues of: 1) diet, nutrition, and behavioral modification; 2) how to design a network to effect a chemoprevention program at the preclinical level and how it would fit into the network currently in place; 3) how to use new advances such as molecular biology in screening and early detection as it relates to a prevention program; 4) the types of training needed for individuals who choose to enter the prevention field and how this training would fit into the existing training mechanisms; and 5) clinical trials and a network system.

A brief discussion resulted in the following points:

- Quality-of-life will be covered by the cancer control and behavior working group.
- Behavior modification will be discussed to some degree because it is very difficult to talk about

diet and nutrition without talking about modification. The larger part of the discussion on behavioral research will be in the Cancer Control Program Review Group.

**Clinical Trials Program Review Group (CTPRG):** Dr. James Armitage discussed the CTPRG process and showed a slide of CTPRG members. Dr. Armitage stated that the CTPRG is composed of individuals with a variety of orientations to clinical cancer research, physicians from both private and academic settings, biostatisticians, geneticists, nurses, patients, adult and pediatric oncologists, radiation oncologists, and surgical oncologists.

Using a series of slides, Dr. Armitage explained that the CTPRG agenda consisted of the following topics: 1) Ensure there are clinical scientists who are willing to do the work; 2) Determine how to convince Americans of all backgrounds to participate in clinical research and also to understand the importance of it; 3) Identify the implications of managed care and to recognize that not only patients will be affected, but also physicians, institutions, and insurers; 4) How to decide which clinical experiments are of the highest priority and which evaluation standards to use to determine the priority, in terms of the number of patients cured or the biggest chances for improvement; and 5) how to adjust resource allocations based on the relative merits of clinical trials.

## NCI APPROACHES TO MANAGED CARE
## DR. ROBERT WITTES AND MS. MARY MCCABE

Dr. Robert Wittes stated that, for decades, insurance companies have reached a high degree of consensus to either pay for the medical care costs for participants in clinical trials or simply look away and not ask questions. This state of affairs was fairly stable until the mid-to-late 1980s, when Autologous Bone Marrow Transplantation (ABMT), a high-cost procedure, became an area of great investigational interest. He stated that the NCI became interested in the issue of managed care at the time of ABMT development, although the issue was more directed toward general consideration rather than toward ABMT. Some insurance companies and payers started to show increasing discomfort with the costs of Phase I trials, which are shown on the claim forms.

Dr. Wittes noted that two developments in the last few years have made managed care an issue that the community of investigators can no longer afford to ignore: 1) Increasing development of sophisticated informatics systems on the part of the payers, which makes it possible to spot and collate all kinds of information that was difficult for them to access in previous years; and 2) Sweeping changes in the health care delivery system, particularly the increasing end roads of managed care. Now, the insurance industry can effectively enforce research exclusion in managed-care organizations and Health Maintenance Organizations (HMOs) by including clauses in their contractual language that explicitly exclude investigational therapy from reimbursement. He stated that there has been a drop in cooperative group accrual over the last few years, which makes the research community worry that the issue of managed care will become a significant problem.

A brief history of the dialogue NCI has had with insurance companies and managed care organizations was given. As a result of those discussions, the Cancer Therapy Evaluation Program (CTEP) developed a six-part strategy to address the managed-care issue in the clinical trials program, which is to (1) implement a more effectively coordinated clinical trials program; (2) incorporate more public advocacy to support the clinical trials, particularly the payer partners; (3) broaden the assessment of patient outcomes in a manner that includes what one might consider nontraditional, or not exclusively medical, endpoints in the context of cancer clinical trials; (4) heighten the attention to information exchange; (5) heighten demand for access; and (6) establish possible partnerships with federal agencies.

Dr. Wittes stated that more effective coordination of the clinical trials program is needed. In this regards, CTEP is 1) embarking on an ambitious effort, coordinated by Dr. David Parkinson, to determine what informatics improvements need to be implemented so that data collection and analysis in the groups can take full advantage of current technologies and of those that are likely to emerge in the future; 2) publicizing results of noteworthy studies that the NCI has done in the past; 3) establish a Clinical Trials Web site; 4) working to increase attention to broader assessment of patient outcomes in clinical trials; 5) planning to establish an outcomes unit within the DCTDC; 6) talking to the Agency for Health Care Policy and Research (AHCPR) about collaborating with the AHCPR in various ways; 7) establishing an HMO research network; 8) planning to convene a meeting with members of the HMO research network

and to establish areas of common ground; 9) working with the International Cancer Information Center (ICIC) to do a major Physician Data Query (PDQ) expansion that will provide clear identification of all NCI-sponsored trials and a category of sponsorship; and 10) developing strategies to ensure that the purchasers of health care see that providing access to investigational therapy for their employees who either have cancer or have family members with cancer is the correct thing to do, and that there is no reason to think it will result in a significant increase in cost.

Dr. Wittes discussed CTEP's activities with federal initiatives: 1) The DoD signed an agreement that its Civilian Health and Medical Plan of the Uniformed Services (CHAMPUS) TriCare Health Insurance Systems; 2) Ms. McCabe organized a meeting after the recent ASCO meeting with a group of military oncologists; 3) CTEP soon expects to finalize a Memorandum of Understanding (MOU) with the Department of Veteran Affairs (DVA); and 4) CTEP will continue to communicate with the HCFA on the issue of support for clinical research.

In response to questions from Board members, the following points were made:

- With regard to quantifying the contributions of HMOs and other factors, CTEP has not attempted to quantify the contributions of HMOs and other factors that result in the small number of participants in clinical trials. CTEP is trying to do things that will make clinical trials a more inviting prospect for both patients and the physicians.

- To deal with payer organizations, CTEP has had ongoing discussions with the Director's Office at the NIH and also with the National Institute of Allergies and Infectious Diseases (NIAID). For cancer, the focus has been on how to get insurance companies and managed-care organizations to pay for participation in clinical trials and medical care costs. The issue with AIDS is different because of the immense problem of an uninsured population, for which the argument does not apply.

- Approximately fifteen percent of patients are denied access to Phase III studies because of third party carriers refusal to cover the cost.

- There is a paucity of data in the literature about the cost issue. There is no simple answer to the question about whether care in clinical trials costs more than care conventionally for a comparable group of patients. Two major Cancer Centers with medical economics expertise have responded to NCI's request to address this question. The NCI, through the White House Office of Science and Technology (OST), also contracted with the Rand Corp. to analyze the feasibility of using the CHAMPUS database in the DoD agreement.

- One of the fallouts of increasing denial of reimbursement for clinical trials has been constant revision of consent forms to make it more explicit to people considering clinical trials, that they may, in fact, have to pay for much of the costs. This may lead patients to reconsider and decide not to enter the trial. However, it can also offer a window of opportunity to create a demand for

access. If there were mechanisms to refer patients, with some help from support groups with regard to asking insurance companies to reconsider coverage, insurance practices might eventually change.

- Decreased access will change the types of studies. If participation is decreased from 4 percent to 3 percent of patients, clinical trials will not only be slowed, but the nature of the trials will also change. The types of patients who participate in clinical trials will change; this is potentially dangerous because important interaction between certain therapies and genetic backgrounds can be missed due to inherent selection bias.

- The NCI has made it clear to the insurance industry that it is willing to explore cost-sharing arrangements for high-visibility, expensive treatment approaches that may be developed using new technologies.

- In response to a member's comment that pharmaceutical companies need to rethink their paradigms, because their costs are becoming astronomical, Dr. Wittes responded that if the pharmaceutical industry was required to pick up the medical care costs of the clinical trials it sponsored, it would bring dramatically fewer new agents to the Investigational New Drugs (IND) stage, because clinical care costs would reduce the entire IND budget.

- A member suggested that statistical analysis may help identify incentives for insurers to participate in and fund the trials. Questions to be answered include: Are large-scale trials necessary? To what extent does the FDA need to be involved in their adjudicatory processes? Where should the lines be drawn? To what extent does the Cancer Centers Program give recognition to well-designed, well-constructed clinical trials, which yield valuable information even if not funded by the NCI? Dr. Wittes noted that companies might be induced to pay and, in fact, probably now do pay for some of the costs of a clinical trial if it received FDA's approval. However, he does not expect the companies to pay for the medical care cost of trials that do not have FDA's approval.

## CLOSED SESSION

The disposition of the Laboratory of Drug Development Research, and Discovery's site visit report and staff's response to it was discussed.

## BEHAVIORAL RESEARCH IN CANCER PREVENTION AND CONTROL WORKING GROUP REPORT
## DRS. BARBARA RIMER AND CARYN LERMAN

Dr. Barbara Rimer stated that, in July of 1995, the NCI, with active participation from the NCAB, brought together almost 100 people representing behavioral sciences, health service research, medicine, voluntary health organizations, and the government to make recommendations on directions for behavioral research and cancer control. Last spring, a follow-up meeting was convened to set priorities for research in cancer control.

Dr. Rimer presented the bio-psychosocial model that was developed by Dr. Norman Anderson, who is the Associate Director of the Office of Behavioral and Social Sciences Research at the NIH. The model portrays behavior as one of many factors that interplay with environmental, genetic, and physiological factors to produce health outcomes. This model was cited in JAMA.

Dr. Caryn Lerman briefly described the outcomes of the Behavioral Research and Cancer Control Working Group (BRCCWG) meeting held on April 11-12, 1996. Dr. Lerman stated that the Working Group had identified six priority areas: 1) prevent tobacco use in children and teenagers; 2) enhance risk communication and informed decision-making; 3) integrate preventive and early detection services into changing health care delivery systems; 4) improve the outcomes of genetic susceptibility testing; 5) enhance survivorship of cancer patients, specifically, to design interventions that improve functional capacity, increase and improve palliative care, and increase health behaviors that have the potential to reduce second malignancies; and 6) promote a healthy diet and physical activity and design interventions to target these areas, particularly interventions that can be delivered to high-risk populations and underserved minority populations.

Several members of the Working Group felt that a need exists to consider a broader definition of behavioral research to distinguish it from other research areas in cancer and to consider doing more basic research, as well as observational studies. Working group members also noted that it is important for the NCI to collaborate with other partners or Institutes such as the National Heart, Lung, and Blood Institute (NHLBI) to generate trans-NIH initiatives. The Office of Behavioral and Social Sciences Research within the Office of the Director, NIH, is putting together a concept for a trans-NIH RFA that will look at lifestyle behavior changes across a number of diseases.

In response to questions from Board members, the following points were made:

- Concepts developed by program staff will be presented to the BSA for approval. The
- Program Review Group will analyze the cancer control and behavioral research programs at the NCI and provide recommendations.

- There was a general consensus that behavioral and cancer control research needs to move from reliance on RFAs to more R01s, with RFAs used only when there are special needs to be addressed.

- In coordinating the National Cancer Program, the challenge is to determine how to implement the findings with other nonfederal organizations that have traditionally played a strong role or had a high interest in behavioral research and application.

- When queried whether the goals in Healthy People 2000, such as reduction of the death rate from cancer by half, are being reached, Dr. Rimer responded that the actual focus is on several specific aspects of the goals in the Healthy People 2000, such as the area of mammography. The objective of death rate reduction is probably from the 1987 recommendations of the NCI, as opposed to Healthy People 2000.

## RFA AND CONTRACT CONCEPT POLICY AND CHANGES
## MR. PHILIP AMORUSO AND DR. MARVIN KALT

Dr. Livingston called the 8 August meeting of the BSA to order at 8:00 a.m.

**Contract Concept Policy and Changes:** Showing a series of slides, Mr. Amoruso explained the contract concept review process and stated that changes in the process had occurred as a result of the reorganization. He indicated the importance of differentiating between contracts and grant mechanisms, in terms of the Federal Grant and Cooperative Act of 1977. The contract mechanism is well defined and is the best approach for purchasing by the government when specific deliverables are desired. The grant mechanism provides funds to assist the recipient in carrying out research-related work.

Mr. Amoruso also provided an overview of the contract award process and explained concept review, as defined by NIH policy.

In response to questions from Board members, the following points were made:

- A member requested pie charts that show 1) all of the NCI funds and the percentage of those funds that are contract related and 2) a breakdown of the contract related segments into the various kinds of existing contracts.

- When asked to comment on whether the BSA should consider the progress of a contract if it is a continuing contract, Mr. Amoruso stated that one criterion of progress in the concept review is to monitor the contract in terms of the deliverable and what the contract is doing specifically for the program. This is usually done by the Division on a year-to-year basis. It can also be part of the 4-year program review.

- A member asked about the distinction between contracts that are issued only to Master Agreement (MA) holders and contracts that are issued to the scientific community. The contract policy seems to differ with regard to who has primary responsibility for the data. An explanation of the mechanisms and decisions regarding MA holders and non-MA holders and clarification as to whom decides the number of qualified applicants for an MA, and whether a decision is made on a renewal by a resurvey of the field or whether a simple continuation is used was requested. Mr. Amoruso responded that the recompetition is carried out as part of the competitive process that begins when people bid to become a part of an MA. The MA enables the OEM to streamline the competitive process and make awards within the MA pool more quickly than with the usual 13-month award process.

- In clarifying the nature of the peer-review process, Mr. Amoruso replied that, after BSA approval, the project goes to the Division of Extramural Activities (DEA). At least 75 percent of contract reviewers, who evaluates and ranks the proposals, are from the outside research

community.

- With regards to why the BSA was considering the current group of concepts since they were not new and did not appear to have changes in work scope, Mr. Amoruso replied that the Division reviewed the projects that are going to expire and identified the ones that should go to the EC. Dr. Greenwald added that the major contract concepts that would be presented to the Board are a continuation of the Chemoprevention Program. According to contract regulations, an extension is not allowable so they must be recompeted. The EC recommended that the BSA review the concepts because they are large contracts.

- A member asked if the framework of the MA had been successful and inquired about the fairness of the recompetition process. Staff stated that each year the Research Contracts Branch (RCB) issues a solicitation which provides the opportunity for others to enter the MA pool. Over a period of 5 years, the number of MA holders may increase from 10-15 to 20-25. With regard to initial awards, anyone who receives a technically acceptable rating is given a contract. In other mechanisms, the RCB usually makes only one or two awards depending upon the total score. In the MA process, if a technically acceptable rating is received, an MA is awarded, regardless of the score, and the recipient is entered into the MA pool.

- Data on projects and contracts that have received funding for the second time which indicates scientific progress from the initial round of funding was requested.

**RFA Concept Policy and Changes:** Dr. Marvin Kalt, Director, Division of Extramural Activities, stated that Request for Applications (RFAs) are used to solicit grants or cooperative agreements. RFAs are forms of assistance given when available funding warrants that the NCI can award a certain amount of money to applications that are of high scientific merit for a particular scientific undertaking.

Showing a series of slides, Dr. Kalt explained the process of and the criteria used in developing and awarding RFAs. He stated that a RFA can be used when the particular nature of the research being undertaken requires NCI staff involvement; lack of an influx of high-quality applications in an area; lack of research in an area; to establish a specific research program; and a Congressional mandate. RFAs synchronize the review and award processes in a particular field. All applications are received at one time, and the applications generally go to one review committee.

Dr. Kalt noted that after an analysis of the current research portfolio to determine need and feasibility, potential cost for the RFA is also considered. This analysis is formulated into the draft of the concept that is brought before the EC. If a decision to approve is made by the EC, the concept will be brought to the BSA. The presentation at the BSA is the first public airing of the possibility that the NCI will issue an RFA in a particular area and gives the scientific community an opportunity to begin making plans for application.

Dr. Kalt explained the internal clearance of the RFA concept if approved by the BSA. He also explained

the process from concept approval, by the EC and BSA, peer review, NCAB concurrence, to publication of the awards.

In response to questions from the Board, the following points were made:

- In defining the determining factors that favor RFAs versus contracts and Program Announcements (PAs), Dr. Kalt replied that PAs are general statements of interests or priorities of the NCI. PAs can be done with first round set asides of awards in combination with an RFA. However, the scientific community has the perception that the NCI has not singled out for exception for funding applications submitted in response to PAs. Therefore, typically, the PAs attract new investigators (Type I applications).

- In explaining the differences between percentiles for RFAs and R01s, Dr. Kalt stated that, for both types of awards, percentiles depend on how many applications are submitted and the total amount of funds.

- When queried about the requirements for R01s to be converted to cooperative agreements, Dr. Kalt replied that cooperative agreements relate to population research, either clinical, prevention, or intervention and control in which NCI staff must be involved as the study is developed and implemented. This is an NIH-wide policy that the NCI applies to its own research portfolio.

- DEA has not tried to quantify the relative benefits of an RFA versus a PA. Dr. Kalt stated that it will require an extensive amount of work, and he is not sure what the control mechanism would be. He pointed out that the majority of RFAs are not R01/RFAs; therefore, it is difficult to have a comparable pool. A member requested a listing of program announcements.

## RFA AND CONTRACT CONCEPTS
## DR. GRAY KELLOFF

Dr. Gary Kelloff, Chief of the Chemoprevention Branch, DCPC, introduced seven concepts that constitute the NCI Chemoprevention Drug Development Program. The endpoint of the Contract Research Development Program is to conduct clinical Phase II studies of drugs that have sufficient efficacy and safety, in support of hypotheses to be tested in large-scale clinical trials. Of the concepts, one was a small clinical efficacy study; two related to both preclinical and clinical safety, and were mandated by the FDA; one related to intermediate biomarkers; and three related to identification and screening of candidate chemicals for preclinical efficacy.

Dr. Kelloff stated that the seven contract concepts would entail $22M in 1996. The concepts started in 1992 at about $5M and scaled up over the last 5 years. The seven concepts represent a drug development program for chemoprevention. Candidate drugs are being evaluated in preclinical systems. If promising in terms of efficacy and safety screening, the candidate drugs move to Phase I clinical studies. Program staff has looked at endpoints and identified clinical opportunities for each major target organ. Surrogate markers have been identified that can act as cancer surrogates to evaluate drug effectiveness and models have been and are being developed to facilitate methods development and to validate biomarker modulation in terms of correlation with cancer incidence reduction.

Questions from Board members resulted in the following points being made:

- Large trials and intermediate-size trials in chemoprevention have been going on for about 12 or 14 years, primarily through grant-based research. More than 20 of these compounds are regimens that have been developed because they are either safe for people or were generally regarded as safe, such as vitamins. Approximately 16 chemopreventive agents either have or are being tested in smaller Phase II studies.

- A member commented that agents that interfere in tumor progression are not included in the chemoprevention program and questioned whether this is a result of the confusion in the field on whether early tumor progression or inhibition of early tumor progression could be considered chemoprevention. Dr. Kelloff clarified that when there is an invasion of the basement membrane, the chemicals that are of primary interest will not be suitable for chemoprevention. He stated that the Chemoprevention Program is not looking at anti-angiogenic compounds, because they seem to be more suitable for progression. The DCPC has not yet been carrying out research on anti-invasion chemical agents.

- The drug discovery program was historically carried out by the former Division of Cancer Treatment (DCT), now DCTDC, where they are interested in discovery of chemotherapeutic compounds and the creation of a network of academic-based institutions to work on drug development. There is no similar analog in chemoprevention, although a few program projects

that are related to chemoprevention drug discovery have come through the grant pools in other divisions.

- The major contribution of the MA is that it allows the Division to conduct clinical trials so that decisions are made early in terms of triaging.

- Approximately 15 chemical agents at the bottom of the pyramid are now in Phase II studies. Initially, 2,000 chemicals were identified in the published literature. Some chemicals already have sufficient data developed, such as the preclinical toxicology data, so they do not have to start as Phase I studies. Phase II studies are unique because they are concerned with the surrogate endpoints that correlate with cancer incidence reduction.

- All contract concepts are for 5-year competitive renewals, and the NCI is committed to 5-year funding for the programs that are approved by the BSA. Grants are real commitments that have longevity, but contracts can be stopped. The NCI does not usually put money in MA contracts until they are competed.

- The selection and validation process for animal models used for preclinical efficacy is still ongoing. Dr. Kelloff predicted that some validations will be available in the next 2 or 3 years.

- With regards to the mechanistic information on the action of DFMO, staff responded that DFMO is a very poor agent for affecting polyamine pools. On the other hand, some very powerful agents have been developed that are posttranscriptionally inhibiting all the synthetic decarboxylases. It is important to have mechanistic data when selecting a compound. Dr. Kelloff agreed that DFMO is an early compound in a class that now has more effective compounds coming behind it. He commented that the data on the spermine-spermidine ratios of DFMO are available in humans and in animals.

- The NCI is communicating with scientists who are interested in chemoprevention, both nationally and internationally, to explain further the process of identifying the chemicals that are to be entered into animal models and the evaluation process for selecting candidates for preclinical toxicity testing. The NCI has demonstrated its efforts to raise research interest in chemoprevention through the 10 chemoprevention conferences held in the last 4 years. Dr. Kelloff stated that a certain amount of data is required before an agent can be entered into the Chemoprevention Program. Currently, about 400 compounds are being screened for their chemopreventive potential. After sufficient data are collected, a chemical can then be moved into clinical studies.

- In response to members indicating a concern with a need to either define the contract concept report or identify a responsible party to define the report, a subcommittee was established to develop BSA guidelines on contract concept review. Drs. Frederick Appelbaum (chair), Eric Fearon, and Enrico Mihich were appointed to the subcommittee.

**Motion:** The motion made to fund the seven chemoprevention concepts for five years, with a progress report, following BSA guidelines as to what should be included in such a report, as soon as it is feasible, but within 2 years was unanimously approved.

## REPORT OF THE DIVISION OF CANCER EPIDEMIOLOGY AND GENETICS PROGRAM REVIEW
## DRS. JOSEPH FRAUMENI AND ALBERT KNUDSON

Dr. Joseph Fraumeni informed the Board that the DCEG was created from the Epidemiology and Biostatistics Program, which had been previously located in the former Division of Cancer Etiology (DCE). The DCEG was established to strengthen and expand NCI's program in cancer epidemiology, genetics, and statistics, and to ensure that the momentum of recent and ongoing discoveries in molecular genetics and cancer biology was accelerated and broadened through population-based etiologic studies. The goal of the DCEG is to identify every human gene that predisposes people to cancer, and to use this information to transform medical practice, and to identify and solve the psychosocial, ethical, legal, and other dilemmas associated with cancer genetics. To examine the coordination of research initiatives, the DCEG has responsibility for both intramural and extramural activities and reports to both the BSC and BSA.

In a series of slides, Dr. Fraumeni summarized the new initiatives and opportunities in the extramural area. The DCEG 1) places a major emphasis on the interdisciplinary approach toward epidemiologic research into cancer; 2) looks at the interface where clinical and basic sciences overlap with population-based studies in the hope of deriving insights that cannot be achieved by any single discipline; 3) is forging closer interactions and collaborations with other intramural and extramural divisions at the NCI and the NIH, as well as with other agencies and the extramural community; and 4) has a special mandate to enlarge its research activities into the genetic determinants of cancer.

The intramural and extramural groups in the DCEG have moved in various ways to enhance the programs in cancer genetics. Specifically, DCEG is looking at the risks of brain cancer and childhood leukemia associated with exposure to electromagnetic fields, as well as a wide range of other possible risk factors for these tumors; conducting a large-scale, case-control study of breast cancer on Long Island that was prompted by public and congressional concerns over the high incidence rates in that geographic area; identifying unusual exposures or variations in cancer occurrence, particularly in geographic areas that may require epidemiologic assistance from the NCI; updating the cancer incidence rates through 1992; and completing a case-control study of esophageal adenocarcinoma in several areas to search for causal factors.

A new program is being developed to train NCI investigators in the interdisciplinary aspects of cancer genetics. The DCEG is also collaborating with the NCI training branch to develop similar extramural programs. It has a vigorous intramural program in radiation epidemiology, and works closely with the Radiation Effects Branch, Division of Cancer Biology (DCB).

Using a series of slides, Dr. Fraumeni indicated that there are three DCEG programs: Intramural Human Genetics Program (HGP); Intramural Epidemiology and Biostatistics Program (EBP); Extramural Epidemiology and Genetics Program (EEGP). The EEGP consists of four groups: Genetics Group;

Epidemiology Group; Nutrition Group; and Biometry Group. Additionally, there are six EBP intramural branches: Biostatistics Branch; Environmental Epidemiology Branch; Occupational Epidemiology Branch; Nutritional Epidemiology Branch; Viral Epidemiology; Radiation Epidemiology Branch. The three branches under HGP are: Genetic Epidemiology Branch, Clinical Genetics Branch, and Laboratory of Human Genetics.

Dr. Fraumeni explained that, in the extramural area, a major initiative has been the formation of the Cancer Genetics Working Group (CGWG), cochaired by Drs. Weber and Knudson, with Dr. Giusti serving as the Executive Secretary. The first charge of the CGWG is to advise the NCI on the development of strategies, resources, and programs to address the scientific opportunities and the pressing needs associated with the anticipated demand for genetic testing in cancer.

The DCEG has also developed several internal advisory committees that help ensure strategic planning, coordination, and quality control: The Senior Advisory Group, Protocol Review Committee, Contract Utilization Committee, and Promotion and Tenure Review Panel.

Showing a list of cloned hereditary cancer genes, Dr. Knudson noted that the intramural and extramural programs in the NCI have been very active in cloning cancer genes such as CDKN2, HNPCC, ATM, BRCA1 and BRCA2.

Dr. Knudson mentioned that the current extramural program in cancer genetics focuses on the topics of diet, chemicals, hormones, viruses, radiation, statistical methods, and formation of registries. In describing some of the new initiatives of the DCEG, he indicated that there is a great interest in high-risk populations and preneoplastic lesions and that registries and consortia are being organized. There is also an initiative on studying BRCA1 mutations in the Ashkenazi Jews and an initiative on ATM, the ataxiatelangiectasia gene, and breast cancer. Training in family counseling and establishment of a genetics network are also included.

In response to questions from Board members, the following points were made:

- To avoid duplication on the research of interaction between genetic and environmental factors, there has been a great deal of scientific interaction, particularly in studies on nutritional factors that are collaborative projects between DCEG and the Division of Cancer Prevention and Control.

- The issue of how the Cancer Genetics Network (CGN) will interface with some of the site-specific registries to avoid overlapping is under discussion.

- When asked whether there is a reason for the DCEG not being separated into extramural and intramural activities as are other Divisions in the NCI, Dr. Knudson responded that separating the Division into intramural and extramural programs for genetic research is not a very practical approach. Dr. Fraumeni explained that sometimes it is more cost efficient and scientifically

sound not to separate intramural and extramural programs. In addition, considering the large United States population, there is concern that there could be conflict if both the intramural and extramural programs tried to obtain access to these populations.

- As for training grants for genetic epidemiology other then cancer, Dr. Fraumeni responded that the Human Genome Project can probably address the issue of training on genetics across the board, but the focus within the NCI is on cancer. Dr. Fraumeni noted that they wrote an RFA 3 years ago on this subject, and this RFA will be reissued by the Cancer Training Branch.

- In regard to disseminating the model curriculum that DCEG is developing in-house to the extramural community, Dr. Fraumeni replied that the actual curriculum has not been developed, but will make it available when it is ready.

- A member asked Dr. Knudson to comment on the major focus and function of the new research programs in cancer genetics, in addition to setting up the high-quality cancer genetics laboratories. Dr. Knudson stated that setting up a laboratory is the single most important effort because one of the difficulties they anticipated was that they might not be able to find a suitable contractor. As a result, there is enthusiasm about establishing an intramural laboratory that has some capability of mapping genes. Dr. Knudson commented that a laboratory that can directly address problems of crucial interest to the DCEG, such as the mapping of genes, will be beneficial.

- When asked to elaborate on his plan for the new Clinical Genetics Branch, Dr. Knudson replied that the present group in genetic epidemiology includes a couple of clinicians, but does not have enough depth when discussing the issue of counseling and treatment and the problem remains unsolved. In response to the suggestion to coordinate with the Medical Genetics Branch under the National Center for Human Genome Research (NCHGR), which has a strong cancer emphasis, Dr. Knudson responded that the NCHGR is not in a position financially to coordinate with the Clinical Genetics Branch.