NATIONAL CANCER INSTITUTE ONLINE

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Dr. Greenwald


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

**1st Regular Meeting**
**BOARD OF SCIENTIFIC ADVISORS**
**Minutes of Meeting**

**March 21, 1996**
**Building 31-C, Conference Room 10**
**Bethesda, Maryland**

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## ATTENDEES

The Board of Scientific Advisors (BSA) convened for its first regular meeting at 1:00 p.m. on Thursday, 21 March, 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 1:00 p.m. to 4:00 p.m., for introductory remarks from the Chair, for discussion of procedural matters, and for discussions and presentations regarding two NCI extramural programs. The meeting was closed to the public from 4:00 p.m. to adjournment for the reivew, discussion and evaluation of intramural site visit reports.

**Proposed BSA members present:**

Dr. Frederick R. Applebaum
Dr. David G. Bragg
Dr. Mary Beryl Daly
Dr. Virginia L. Ernster
Dr. Eric R. Fearon
Dr. E. Robert Greenberg
Dr. Amy S. Langer
Dr. Caryn E. Lerman
Dr. Edison Tak-Bun Liu
Dr. David M. Livingston
Dr. W. Gillies McKenna
Dr. Nancy E. Mueller
Dr. Sharon B. Murphy
Dr. Franklyn G. Prendergast
Dr. Allen I. Oliff
Dr. Joseph V. Simone
Dr. Louise C. Strong
Dr. Daniel D. Von Hoff
Dr. Barbara L. Weber
Dr. Robert C. Young

**Proposed BSA members not present:**

Dr. Joan Brugge
Dr. Suzanne W. Fletcher
Dr. David D. Ho
Dr. Waun Ki Hong
Dr. Tyler Jacks
Dr. Enrico Mihich
Dr. John D. Minna
Dr. Stuart L. Schreiber
Dr. Peter K. Vogt
Dr. Alice S. Whittemore
William C. Wood

**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. Livingston called the meeting to order and welcomed the Board members. He informed the Board that the major responsibility of the BSA was to represent the extramural community and to help the NCI think its way through new opportunities to improve the National Cancer Program.

He noted that other responsibilities included: 1) conducting performance evaluations of each Division Director every 4 years and, as requested by the Director, NCI, reviewing the Office of the Director, every 4 years; 2) reviewing new concepts and new initiatives; 3) reporting, at least once a year, to the Director, NCI, on the progress of major segments of cancer research in the United States; 4) identifying opportunities in the extramural research community where the NCI's constructive involvement can make a difference; 5) serving as the "eyes and ears" of the grant holders, the students of the grant holders, the postdoctoral fellows, the colleagues of the grant holders, and in some cases the patients of the grant holders; 6) advising the NCI on new opportunities that might be included in planning for the bypass budget; 7) advocating optimal funding for NCI- supported, investigator-initiated research; and 8) maintaining an intimate relationship with the National Cancer Advisory Board (NCAB), which has the primary oversight responsibility for the whole Institute.

Dr. Livingston gave a brief update on the activities of the current NCI program review groups. He stated that the chair of the Centers Program Review Group, Dr. Joseph Simone, expects the Review Group's report to be completed by summer's end; meetings of the Prevention Program Review Group, chaired by Dr. Edward Bresnick, will begin very shortly and a report is expected within the next six to nine months; and the Clinical Trials Program Review Group, chaired by Dr. James Armitage, is scheduled to have its first meeting on 8 April and the report completed within six to nine months. He informed BSA members that within the next three to four weeks, he and Dr. Klausner would meet with the proposed Chairs of the Developmental Therapeutics Program Review Group to establish a schedule for review.

## BSA PRESENCE AT NATIONAL MEETINGS
## DR. DAVID LIVINGSTON

Dr. Livingston introduced a proposal that would entail BSA subcommittee members, together with NCI staff, attend at least once, and ideally twice a year, a large national meeting such as the American Society of Clinical Oncologists (ASCO) annual meeting and perhaps one other meeting, such as a Cold Spring Harbor Symposium, a Keystone meeting or an American Association for Cancer Research (AACR) meeting. The BSA would hold an open forum at the national meeting in which colleagues would be invited to discuss anything they wished and BSA members could discuss new initiatives with meeting attendees.

A lengthy discussion resulted in the following points:

- Instead of attending two meetings each year, the BSA membership should be broken into five or six groups, with each group going to a different meeting each year, so that a broader range of people could be reached.

- When queried as to the exact role of BSA members at national meetings since members already attend meetings and interact with other colleagues, the Chair stated that this activity is an opportunity for people to really express what is on their minds as opposed to listening to presentations from top NCI staff.

- Towards thinking more broadly about relevant meetings, special areas such as genetics, preventive oncology, and behavioral sciences should be considered. Meetings that facilitate cross fertilization of ideas/interest should also be included.

- Rather than dividing the BSA into four or five subgroups, consideration should be given to rotating BSA attendance among different societies and meetings from year to year.

- Establish a list of national and other meetings of organizations that BSA members presently attend.

- As part of the meeting schedule, include a proposed process to allow for appropriate preparation by meeting sponsors for planned, effective participation by meeting attendees.

A subcommittee was established to produce a proposal on BSA attendance at national meetings. Its charge is to develop a report that suggests how to proceed with this activity, prepare a multiyear schedule for attendance at national and other meetings, and to report back to the Board at its next meeting. Subcommittee members are Drs. Robert Young (Chair), Virginia Ernster, Barbara Weber, and David Livingston.

Dr. Barbara Rimer, the Chair of the NCAB, stated that the NCAB would be very interested in participating with the BSA on this activity.

## BSA PRESENCE AT NATIONAL MEETINGS
## DR. ROBERT WITTES

Dr. Wittes presented a brief overview of the organizational structure of NCI and DCTDC. He informed the Board that DCTDC is a fusion of the extramural parts of the former Division of Cancer Treatment (DCT) and some of the former Division of Cancer Biology, Diagnosis, and Centers (DCBDC). The former parts of DCT are the Cancer Therapy Evaluation Program (CTEP), the Developmental Therapeutics Program (DTP), and the Biology Resources Branch (BRB), which was the extramural part of the old Biological Response Modifier Program (BRMP), which no longer exists as a unit. The DTP is responsible for discovery and preclinical development of new agents. The CTEP is responsible for clinical trials. The Radiation Research Program (RRP) is part of the former DCT and contains both radiotherapy and imaging. The Centers, Training, and Resources Program consists of branches that deal with centers, training, construction, and organ systems. The Cancer Diagnosis Branch was a part of DCBDC and is the only free standing branch in the Division, it is not in a program.

He said that with regards to future scientific directions the Division has been working hard on issues related to major scientific areas in the Division, including developmental therapeutics, molecular diagnostics, and diagnostic imaging, as well as the Clinical Trials Program (CTP). A brief overview of the various programs within the Division was then given.

**Developmental Therapeutics Program** - The Board was told that DTP: 1) initiates the process of drug discovery and development, which continues on in the CTP governed by CTEP; 2) has been the premier cancer drug development organization in the world for decades; has provided probably the single greatest conduit of drugs from the discovery phase into clinical trials; 3) over the years, has served to leverage the high risk that bringing a cancer drug along through development and clinical trials entails for a sponsor; and 4) links its laboratories and branches with the customary functions of a drug discovery and development organization, including acquisition and discovery, screening, development, and the investigator-initiated component, which is an important part of the drug discovery program. Additionally, the research areas of DTP cover both cancer and AIDS.

The resources available at DTP include the compound repository and half are open compounds rather than discreet compounds. He defined discreet compounds as those for which someone else holds the intellectual property rights; thus, distribution is restricted.

Members were informed that DTP has a WEB page available to the public. Two and three dimensional structured databases are being linked to the biological information on the open compounds that have been through the DTP screening program and various biological testing procedures. The WEB page should keep the scientific community current with preclinical drug development in the Program.

Dr. Wittes stated that the cost of operating DTP is about $50 million - $51 million a year. He reminded the Board that the review of DTP will begin within one or two months. Dr. Wittes said existence of a

drug discovery and development program at NIH is unique, and he thinks there should be discussion on whether such a program is still needed.

Dr. Wittes noted that there were several questions that he thought the Program Review Group should address: How should the drug discovery program carry out screening? How should the program generate or sample structural diversity? Should the program keep its interest in natural resources, such as marine sources and plant resources? Should the program add the techniques that have become available for the past few years in combinatorial chemistry and by engineering whole biosynthetic pathways in certain organisms to generate diversity in more directed ways? How can the DTP effectively carry out drug "improvement" after drug "discovery" without the number of chemists that industry has? Are the criteria of the Decision Network for taking substances to clinical trials appropriate or should they be tougher?

**Cancer Therapy Evaluation Program** - Dr. Wittes stated that CTEP coordinates and oversees the Treatment Trials Program in both disease-specific and agent-specific ways; conducts quality assurance and drug distribution; and has an Expert Regulatory Affairs Group, which considers optimal clinical trials methodology. In highlighting the NCI's CTP, he noted that most of the formal evidence in medical and pediatric oncology for the efficacy of various cancer treatments has come from this program. It has generated information that has been crucial to the medical care of cancer patients.

**Clinical Cooperative Groups (CCGs)** - The eleven Clinical Cooperative Groups are largely responsible for developing disease-oriented treatment and are large multicenter organizations that accrue about 20,000 patients a year and follow about 100,000 patients in trial at any particular time. The CCGs are spread around the country in main member institutions and increasingly in the community, in the CCOP program, which is a very important part of the accrual in the CTP.

Dr. Wittes noted that the balance is traditionally in favor of large multicenter studies and questioned whether that balance is correct. He expressed concern about the capability of taking all compounds of interest coming out of the NCI system into clinical trials. He anticipated that there would be a problem in the future dealing with the increasingly large number of compounds being discovered and developed. Dr. Wittes stated that the deliberations of the Clinical Trials Review Group will address this question in explicit terms. p> Another area demanding research attention is AIDS-related malignancies. The Cooperative Groups have not been able to devote adequate efforts to this area. Thus, the NCI organized a consortium of institutions separate from the Group system to try to improve the approach used in early clinical trials, hypothesis-driven early clinical trials, and early Phase II clinical trials. The awards were made a few months ago.

**Clinical Trials Program (CTP)** - Dr. Wittes used a slide to describe briefly the history of cancer drug approval in the United States. He stated that a total of 77 drugs had been approved and that the NCI had had a major role, in most cases, in the development of 50 of those drugs. He further stated that he does not think that cancer drug discovery and development is sufficiently secure to allow the NCI to take a cavalier attitude towards further work in this area. Dr. Wittes emphasized that, even though the CTP has been one of the highlights of the NCI, it is not beyond criticism, and that questions can be asked about it

at all levels. He suggested that the Clinical Trials Review Group begin by asking "What do we need now?"

**Diagnosis Branch (DB)** - Dr. Wittes stated that the Diagnosis Branch has several elements, such as grant-supported, investigator-initiated research. Several important observations that have led to the heightened interest in diagnosis and the understanding of the molecular basis of cancer have come from those investigators. Identification of the adenomatous polyposis coli (APC) gene and the replication error (RER) phenotype, as well as cloning the genes responsible for hereditary nonpolyposis colorectal cancer (HNPCC), are examples of research findings under the Program. The BRCA1 gene for breast cancer is the most recent example announced to the public. Technology development is another element of the Branch.

Dr. Wittes identified accessing tissue resources as a second problem in cancer diagnosis research. Several years ago, the Diagnostics Branch established the Cooperative Human Tissue Network, which comprises five groups, to address the need for tissue procurement of human tissue specimens and human cancer specimens. He clarified that this is not a tissue bank; basically, it is a tissue procurement service that matches tissue requests with appropriate specimens, which are delivered when they become available. There is a WEB site that provides more information on this Tissue Network.

Additionally, there is a breast cancer tissue registry under the auspices of the Diagnosis Branch, which is actually a virtual repository. There are also two Cooperative Networks for the evaluation of markers and biologic properties of tumors; one is for bladder cancer and the other is for glioma. These two networks were developed by an Request for Application (RFA).

Diagnostic Imaging Program (DIP) - Dr. Wittes explained that diagnostic imaging is moving as fast as any area in medicine and observed that imaging is the part of medicine that has changed the most over the years. He informed BSA members that while the Diagnostic Imaging Program has been very active, it needs to be larger and more interactive with both the academic and industrial communities.

The DIP includes investigator-initiated research, a Multicenter Trials Program, efforts in technology development and evaluation centered mainly around breast cancer, and successful efforts to form consortia to promote a diffusion of technologies applicable to imaging. Grant support for diagnostic imaging totals about $50 million.

Showing a series of slides, Dr. Wittes briefly described the areas of the Diagnostic Imaging Program. He noted that the Multicenter Trials Program is centered in the Radiological Diagnostic Oncology Group (RDOG). He stated that the Radiation Therapy Oncology Group (RTOG) is the Cooperative Group that conducts radiation therapy cooperative trials. Dr. Wittes stated that NCI's role in diagnostic imaging must be determined. He posed several questions: What is NCI's role in stimulating discovery and preclinical development of new technologies? Is direct funding of industry proposals appropriate? How would the BSA react if NCI started giving grants to some of the largest companies in the world, such as General Electric?

Dr. Livingston opened the floor for comments. In answer to questions from Board members, the following points were made:

- With regard to overlap in personnel, resources, and expertise between drug development in DCTDC and chemoprevention drug development in other Divisions, Dr. Wittes replied that they are essentially separate enterprises at the NCI.

- With reference to the information presented on drug tests as related to noninvestigator-initiated research, staff was asked to comment on what is happening in investigator-initiated research (the R01 pool) and whether natural products could be scanned for new probes for biological pathways as an intermediate to ultimately looking at therapy. Members were told that a fair number of such projects are ongoing. The National Cooperative Drug Discovery Groups (NCDDGs) are investigator-initiated. Additionally, Program Project Grants are important parts of the drug discovery program.

- A member asked staff to clarify whether the Division is trying to target drugs to molecular targets rather than just screening by serendipity. Staff responded that some categories of agents show an amazing degree of restrictiveness with respect to the cell types they affect. Such agents are in the pipeline for development. Although the reason for such selectivity is still unknown, there is considerable interest in clarifying the mechanism.

- Based on an earlier statement by staff that the "collaboration with industry is a big business here", a member suggested that the BSA have an opportunity to look at how the extramural activities interact with industry. Dr. Wittes stated that he would be very interested in pursuing this with the BSA.

## REPORT: DIVISION OF CANCER PREVENTION AND CONTROL
## DR. PETER GREENWALD

Dr. Greenwald presented a slide which showed the organizational structure of the DCPC. He noted that the Division has only one Branch, the Biometry Branch, that is labeled as intramural. The Biometry Branch is responsible for quality control in the Division; it examines the designs of trials and is also very interactive in consulting with the extramural community.

The Division also includes the: 1) Early Detection and Community Oncology Program (EDCOP), which includes the (a) Community Oncology and Rehabilitation Branch (CORB); Community Clinical Oncology Program (CCOP), which is within the CORB; (b) Preventive Oncology Branch; and (c) Early Detection Branch. The EDCOP was not discussed due to time constraints; and 2) Cancer Prevention Research Program, which includes chemoprevention and nutrition in cancer as the two major areas of interest; and 3) Cancer Control Research Program, which includes the Surveillance, Epidemiology, and End Results Program (SEER), which runs the SEER registry system as well as the behavioral research programs that focus on issues such as special populations and public health applications.

Showing several slides, Dr. Greenwald discussed the SEER registry, breast cancer, prostate cancer screening, trends in colon and rectal cancer between the United States and Japan in both men and women for the 1950's to about 1990.

A brief historical background on cancer control was provided. Dr. Greenwald explained that cancer control is now defined as the reduction of the incidence, morbidity, and mortality of cancer through an orderly sequence, from research on interventions and their impact in defined populations to the broad, systematic application of the research results. He noted that the definition now includes a research component and involves interventions. He described the basic steps in the sequence of cancer control and gave several examples of cancer control research. A brief description of selected DCPC cancer control activities in diet, nutrition, and cancer was given.

In addressing other Divisional activities, Dr. Greenwald informed the Board that NCI has leadership initiatives in place to reach special populations, such as the National Black Leadership Initiative on Cancer, the National Hispanic Leadership Initiative, and the Appalachian Leadership Initiative.

Dr. Greenwald then turned his presentation to the two related areas of diet and cancer and cancer chemoprevention. He estimated that combined total research expenditures are approximately $154 million for these two areas.

Dr. Greenwald informed the BSA that the Chemoprevention Group has been holding about three workshops a year that involve a large number of extramural scientists to evaluate various agents and develop clinical development plans for these agents. He emphasized that a lot of attention is being given to prioritizing agent testing. A Prevention Trial Decision Network has been established to facilitate this

prioritization. He stated that the DCPC looks forward to comments in this area from the Prevention Review Group.

Following a presentation of several ongoing DCPC prevention trials, Dr. Greenwald discussed the budget issues of DCPC. He stated that to make the budget for this year comparable with those in previous years, the budgets for two laboratories, which have been moved to the DBS, were subtracted from the total. The total expenditure for cancer control in DCPC for FY95 was $188 million and $12 million for the SEER cancer registries. About $100 million was spent for contracts. He commented that many projects are conducted in multiple places and they use common approaches so the natural mechanism may be contracts, but that should be discussed. Presenting a slide, he gave a breakdown of the budget for the various programs and trials.

Dr. Livingston opened the floor for comments. In answer to questions from Board members, the following points were made:

- The issue of overlaps in Phase V studies among the American Cancer Society, the Centers for Disease Control and the DCPC will be examined by the Program Review Group for Cancer Control.

- For prevention of breast cancer, more emphasis should be put on the acquisition of high-risk profiles early in life, such as data on exercise and dietary factors. The issue of dietary components and cancer prevention is a concern. Research on -carotene so far has not shown any preventive effect. Yet, the literature shows consistently that a diet rich in vegetables and fruits is associated with low risk. Maybe the direction of prevention trials should be directed to simple, normal dietary changes rather than individual compounds.

- With regards to the inclusion of cost benefit analysis in cancer control, Dr. Greenwald stated that since two of the four economists at NIH are in DCPC, and some economic studies are conducted within the Division, it was felt that cost benefit analysis is incorporated in cancer control. However, it was noted that cost-benefit analysis should be applied to all other areas of cancer research. Prevention research should help set the direction with regard to health service issues by acting in the best interest of the public, while taking the cost-benefit issues into account.

- When queried about the collaborations/interactions among the genetics groups at NIH and NCI in prevention trials, Dr. Greenwald noted that while such collaborations are limited there a is genetic group working with the tamoxifen group. He agreed that this is certainly an important issue that should be addressed aggressively.

- Noting that the results from the large intervention trial, the Community Intervention Trial (COMMIT), were disappointing and that the intervention group had a worse behavior pattern than the nonintervention group, staff was queried whether there should be more trials that are smaller and less expensive to replace large, costly intervention trials. Staff responded that it is

important to have a multidisciplinary process. A suggestion is to have a meeting with an outside group annually to look at large-trial proposals, both those on hand and those that may be coming up. This would be a good idea to help prioritize trial agendas.

- Commenting on whether more careful observational studies of processes and mechanisms to promote better design of intervention trials should be conducted, Dr. Greenwald responded that he has thought about the possibility, but is skeptical about doing more observational studies in the diet area. He is not certain that such studies can be done better. There is no dietary marker for cancer, such as cholesterol for heart disease.

Dr. Livingston introduced Mr. Steven Hazen and explained that Mr. Hazen would discuss the financial issues, particularly issues related to grants, in detail at the next meeting.