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

Summary of Meeting
September 21 & 22, 1992

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

Department of Health and Human Services
Public Health Service
National Institutes of Health
National Cancer Institute
National Cancer Advisory Board
Summary of Meeting[1]
September 21 & 22, 1992

The National Cancer Advisory Board (NCAB) convened for its 83rd regular meeting at 8:00 a.m. September 21, 1992, in Building 31, C Wing, 6th Floor, Conference Room 10, National Institutes of Health (NIH).

NCAB Members

Dr. Paul Calabresi (Chairman)
Dr. Frederick F. Becker
Dr. Erwin P. Bettinghaus
Dr. David G. Bragg (absent)
Mrs. Zora Brown
Dr. Kenneth Chan
Dr. John Durant
Dr. Bernard Fisher
Dr. Phillip Frost
Mrs. Brenda Johnson
Dr. Walter Lawrence, Jr.
Mrs. Marlene A. Malek
Ms. Deborah Mayer
Mrs. Irene S. Pollin (absent)
Dr. Sydney Salmon
Dr. Howard M. Temin (absent)
Dr. Samuel A. Wells, Jr.
Dr. Charles B. Wilson

President's Cancer Panel

Dr. Harold P. Freeman (Chairman)
Mrs. Nancy G. Brinker
Dr. Henry C. Pitot

Alternate Ex-Officio NCAB Members

Captain Bimal C. Ghosh, DOD
Dr. John Johnson FDA
Dr. Hugh McKinnon, EPA
Dr. Lakshmi Mishra, CPSC
Dr. Kenneth Olden, NIEHS
Dr. Raymond Sphar, DVA
Dr. Ralph Yodaiken, DOL

Members, Executive Committee, National Cancer Institute, NIH

Dr. Samuel Broder, Director, National Cancer Institute
Dr. Daniel Ihde, Deputy Director, National Cancer Institute
Dr. Richard H. Adamson, Director, Division of Cancer Etiology
Mr. Philip D. Amoruso, Associate Director for Administrative Management
Mrs. Barbara S. Bynum, Director, Division of Extramural Activities
Dr. Bruce A. Chabner, Director, Division of Cancer Treatment
Dr. Peter Greenwald, Director, Division of Cancer Prevention and Control
Dr. Werner Kirsten, Associate Director, Frederick Cancer Research and Development Center
Dr. Alan S. Rabson, Director, Division of Cancer Biology, Diagnosis, and Centers
Mrs. Iris Schneider, Executive Secretary, Assistant Director for Program Operations and Planning

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

Liaison Representatives

Dr. Eve Barak, Associate Director for Cell Biology, Division of Cellular Biosciences of the National Science Foundation, representing the National Science Foundation, Washington, D.C.

Dr. Robert Beart, representing the American College of Surgeons

Dr. R. Davilene Carter, representing the American Association for Cancer Education

Mr. Alan Davis, Vice President for Public Affairs for the American Cancer Society, representing the American Cancer Society

Dr. Robert W. Frelick, Past President, Delaware State Tumor Registry, representing the Association of Community Cancer Centers.

Dr. Edward P. Gelmann, Chief, Division of Medical Oncology of the Vincent Lombardi Caner Research Center, representing the American Society of Clinical Oncology

Dr. Kathy Bryant, Associate Director, Government Relations, the American College of Obstetricians and Gynecologists, representing the American College of Obstetricians and Gynecologists

Dr. Edwin A. Mirand, Associate Director and Dean, representing the Association of American Cancer Institutes.

In addition to NCI staff members, meeting participants, and guests, a total of 40 registered members of the public attended the meeting.

I. CALL TO ORDER AND OPENING REMARKS—DR. PAUL CALABRESI

After calling the meeting to order, Dr. Calabresi introduced Dr. Charles B. Wilson, a new member of the National Cancer Advisory Board (NCAB); Dr. Henry Pitot, a new appointee to the President's Cancer Panel; and several guests representing medical, research, and professional organizations. He welcomed the members of the public and informed them that they could express their views on issues discussed during the meeting by writing to the NCAB Executive Secretary, Mrs. Barbara Bynum, within 10 days of the meeting. He then called for approval of the previous meeting's minutes, which were unanimously approved without change.

Dr. Calabresi next announced meeting times and locations of subcommittee meetings, noting that the AIDS Subcommittee meeting had been canceled due to illness of its Chair, Dr. Howard Temin. The Board made a resolution to send its best wishes to Dr. Temin. Dr. Calabresi reminded the Board of the closed session at 3:00 p.m. and encouraged attendance. Future meeting dates were confirmed as stated on the agenda.

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

Dr. Freeman, Chairman of the President's Cancer Panel, began by announcing that the Panel's Special Commission on Breast Cancer, chaired by Ms. Nancy Brinker, will convene for approximately 12 meetings to examine the entire spectrum of breast cancer. He then described two future meetings of the President's Cancer Panel. The first will discuss the relationships between volunteer organizations and the National Cancer Institute (NCI). The purpose of the meeting is to provide a forum in which the Nation's cancer-oriented volunteer organizations can express their ideas for bringing together government and volunteer efforts in the fight against cancer. Representatives of key volunteer organizations will attend, including the American Cancer Society, the Leukemia Society of America, the Damon Runyon-Walter Winchell Fund, STOP Cancer, the National Coalition for Cancer Survivorship, Candlelighters, Cancer Care, and CAN ACT. The second meeting, focusing on prostate cancer, will be held November 13, 1992.

Dr. Freeman closed by saying that, because of the critical importance of full participation of the private and volunteer sectors in the National Cancer Program, the President's Cancer Panel would like to work closely with the NCAB Subcommittee on Interactions with Voluntary Organizations on this issue.

III. REPORT OF THE DIRECTOR, NCI—DR. SAMUEL BRODER

Announcements

Dr. Broder welcomed the new members of the NCAB and the President's Cancer Panel, distributed a handout listing a number of honors recently awarded to NCI staff, and announced several significant staff changes. He informed the Board that the Institute had requested an *ex-officio* seat on the National Advisory Board on Medical Rehabilitation Research, adding that Dr. Leslie Ford, Chief of the Community Oncology and Rehabilitation Branch of the Division of Cancer Prevention and Control (DCPC), had been selected to represent the Institute.

Noting that NCI breast cancer programs range from molecular and genetic studies to public education, Dr. Broder announced meetings of the Special Commission on Breast Cancer scheduled for September 23rd to discuss nutrition, etiology, and prevention and on October 23rd to hear comments from patient advocates and voluntary organizations concerned with breast cancer.

Dr. Broder also announced a workshop scheduled for September 23rd on the current state of taxol knowledge and specifically on taxotere, a semisynthetic taxol analog. He thanked the NCI staff, and particularly the Division of Cancer Treatment, for having solved the national taxol supply problem. He stated that, as a practical matter, every woman in the country with refractory ovarian cancer who has a medical indication for taxol may now receive the drug. Because this class of drugs is expected to have a major impact on breast cancer as well on ovarian cancer, NCI has set up a treatment referral program within the network of cancer centers to help with the availability of taxol for breast cancer.

Dr. Broder next mentioned a President's Cancer Panel meeting on prostate cancer, another high-priority area, on November 13th. The Institute has made a strong commitment, he said, to a number of multidisciplinary approaches to understanding the etiology, prevention, diagnosis, and treatment of urologic cancers, including epidemiologic and genetic studies to investigate the reasons for the increase in urologic tumors, particularly the elevated incidence of prostate cancer in African Americans. He called attention to two new clinical trials on urologic tumors in the Institute's drug development program and described a screening study in which 37,000 men will be tested for prostate, lung, and colorectal cancer (and in which a similar number of women will be screened for lung, colon, and ovarian cancer). The assay for prostate-specific antigen (PSA) will be among the diagnostic tools evaluated in this trial as a screening modality to reduce mortality through early detection.

Dr. Broder reported on the Specialized Program of Research Excellence (SPORE) initiative, the purpose of which is to speed research in areas of high priority, particularly breast, prostate, and lung cancer. Of the approximately 20 proposals for prostate studies received in the first wave of grant applications, at least two will be funded at a total of $4.4 million. Feasibility grants, also considered SPOREs, will allow five additional groups to maintain their staffs, engage in planning activities, remain active in the SPORE program, and plan to compete for appropriate upgrading when resources become available. Three of the 19 applications that were received for breast cancer research will be funded at a total of $7.7 million, with an additional five feasibility grants funded at lower amounts.

Reminding the audience that NCI is truly a national program, Dr. Broder described the effects of Hurricane Andrew on the University of Miami Cancer Center; the storm left many of its employees homeless and temporarily closed its cancer information service. In response to the damage and disruption at the Perrine Primate Breeding Center in South Florida, NIH is sending several specialized workers to help with emergency reconstruction. The hurricane also destroyed 60 to 70 percent of the rare plants at the Fairchild Tropical Garden in Miami, a valuable research facility; an emergency team from NCI and the New York Botanical Gardens was assembled to collect the damaged plants, and over 200 specimens were shipped to the Frederick Cancer Research and Development Center to be evaluated for anticancer and anti-AIDS properties.

Dr. Broder announced a special showing of a videotape on the National Center for Medical Rehabilitation Research. The center was established by the National Institute of

Child Health and Human Development to sponsor research to enhance the quality of life for individuals with disabilities.

Budget Presentation

Dr. Broder compared the fiscal 1992 budget estimate of $8.9 billion for NIH and $1.95 billion for NCI with plans for fiscal year 1993. The President's FY93 budget and the Senate's proposed allocations include approximately $2.010 billion for NCI; this represents an increase of just under $63 million, or approximately 3.2 percent. The House of Representatives has recommended an appropriation that includes an increase for NCI of roughly $51 million, approximately 2.6 percent, to $1.999 billion. Dr. Broder emphasized that these figures will be modified during conferences between the House and Senate. The revised House allowance includes a $20 million transfer; thus, the total NCI budget as proposed by the House would be approximately $1.979 billion, representing an increase of $31 million, or 1.6 percent. The Senate version does not yet contain a written revised allowance.

The research project grant line, Dr. Broder asserted, is usually the most protected portion of the budget in all Institutes throughout NIH, including NCI. The budget for research project grants, he said, was approximately $876 million for 1992. For 1993, the House has proposed approximately $923 million, an increase of about 5.4 percent.

Dr. Broder explained that the apparent 1.7 percent decrease in the budget for the Cancer Centers Program, as shown in his slides, is deceptive because NCI allotted more money to the program than the President's budget called for in 1992; the line item for Cancer Centers is, in fact, flat between 1992 and 1993. The SPORE program, which appeared for the first time in 1992 with a budget of about $17.5 million, will see approximately a $2 million dollar increase. Based on the House allowance, several other programs remain essentially flat between 1992 and 1993, including the Research Career Program, the Cooperative Groups, and Minority Biomedical Research Support. The Cancer Education Program shows a slight decrease. Dr. Broder concluded that the total grant-in-aid program in the House budget would be funded at $42 million above the $1.14 billion estimated for 1992, for an increase of roughly 3.7 percent.

Comparing other FY93 House budget estimates with 1992 figures, Dr. Broder said that the National Research Service Awards (NRSAs) are essentially flat; research contracts show a slight decrease; intramural research shows a very slight increase; and Research Management and Support shows a substantial decrease, nearly 8 percent. He added that Research Management and Support provides general administrative backup and includes certain activities of the Office of the Director of NCI that are important for the functioning of the Institute but that don't qualify as research in the usual sense of the term.

Concerning the Cancer Prevention and Control line item, Dr. Broder stated that the budget for 1992 is approximately $107 million. The House action would reduce this sum to just over $100 million in FY93, for a 6 percent decrease. Construction funding is also decreased in the House allocation.

Turning to the subject of grants, Dr. Broder said that the number of noncompeting research project grants in 1992 will total about 2,280. The number of new and competing grants for 1992 is listed at 1,066, but Dr. Broder predicted that the actual number will be

higher. He expressed the opinion that this year will see the largest number of new and competing research project grants in NCI's history.

The number of new and competing grants for FY1993, he continued, will fall at the level of the President's FY1993 budget; while the number of total grants will go up to about 2,477, the number of competing grants will be reduced to 921. The House allowance also shows the total number increasing, but the competing grants decreasing to 881. Thus, Dr. Broder explained, the total for all research project grants funded in the three budgets (the President's budget, the Senate, and the House) is almost flat, but the amounts allocated for competing grants varies.

Dr. Broder projected that the success rate for all investigator-initiated grant mechanisms in 1992 will be about 35 percent. He estimated that, based on the President's budget, the 1993 success rate would be approximately 29 percent; based on the House allowance, it would be about 28 percent. The 1992 figures reflect a reduction made at the discretion of the NIH Director, who had been given the authority to remove $30 million from NCI's budget to support cancer-related research within other Institutes.

Dr. Broder explained that in the budgets proposed by the House and Senate there are targeted areas, which he referred to as earmarks, for which NCI must meet specific goals, even though there is not a concordant increase in the total budget. He reviewed specific amounts committed to breast, cervical, ovarian, and prostate cancer programs in the various budgets being discussed, as shown below:

	Budget Estimates (Millions)			
	FY 1992	FY 1993 Proposals		
Programs		President	House	Senate
Breast Cancer	133	137	176	220
Cervical Cancer	32	32	42	42
Ovarian Cancer	20	20	26	26
Prostate Cancer	28	28	37	37

House and Senate Appropriations Reports

Dr. Broder noted that the Board should pay particular attention to language used in reports from House and Senate Appropriations Committees, emphasizing the fact that the Institute interprets such language, if it survives House/Senate conference negotiations, as having the force of law, even if it is not found in the actual legislation.

He explained that the General Accounting Office is to evaluate the extent to which Centers for Disease Control activities duplicate public health intervention campaigns conducted at NIH and biomedical or behavioral research supported by NIH and the Alcohol, Drug Abuse and Mental Health Administration (ADAMHA).

Dr. Broder noted that, as a result of the reorganization of ADAMHA, three research institutes—the National Institute on Drug Abuse, the National Institute on Alcohol and Alcohol Abuse, and the National Institute of Mental Health—are returning to NIH; the NIH budget will appear to increase due to the addition of the budgets of those agencies. He added that the NIH Strategic Plan should review ongoing expenditures as offsets to fund new initiatives. NIH, he said, should review the size and cost of the entire intramural program and report to Congress. There will be a 1 percent transfer to the

Public Health Service capital improvement fund. In 1993, travel funds will be held to 96 percent of the 1992 budget, and the Research and Management Support level in 1993 must be kept below the 1992 level.

Dr. Broder explained that both houses of Congress are asking NCI to reach "beyond the current cancer establishment" as part of its effort to conduct a fundamental review of the research programs sponsored by the Institute. Dr. Broder is to report to the House Appropriations Committee on how NCI will conduct this overview and how it will reach out to individuals not classified as part of the cancer establishment.

The House report contains increased funding for breast, ovarian, cervical, and prostate cancer and the Cooperative Groups are instructed to increase participation in programs targeting these diseases; there is to be an increase in funding for DES research and education; proton beam research is to be funded at slightly under $10 million, and funding for initial construction costs at one or more of the relevant sites must continue. There is language in the report to the effect that geographical diversity and population considerations must be taken into account if determining awards for proton beam facility construction. NIH and NCI are expected to reflect the importance of cancer prevention and control in the budget for 1994, which, Dr. Broder suggested, is a reasonable request. NCI is also expected to increase its emphasis on cancer prevention and control in the areas of environmental and occupational research.

Turning to the Senate, Dr. Broder noted that their report asks NCI to establish an independent panel to evaluate achievements of the National Cancer Program relevant to the overall investment to date. The Senate report mandates $1.5 million more for DES research and education than the President's budget. NCI is asked to work with DES organizations to implement DES education and research amendments and to implement recommendations from a DES conference held last April. The Institute is also expected to conduct a study on factors causing high breast cancer mortality rates in Connecticut, Delaware, Maryland, Massachusetts, New Hampshire, New Jersey, New York, Rhode Island, Vermont, and the District of Columbia. The Senate report also commits funds to vaccine development and gene therapy research.

Other important requests in the report, Dr. Broder continued, include organization of training events on research skills, methodology, and proposal development for Native American investigators; creation of high-priority community oncology programs; emphasis on breast, ovarian, and cervical cancer through the clinical cooperative groups; better geographic distribution for the Cancer Center Program, especially in the upper Midwest; investigation of the impact of psychosocial counseling on survival; and cooperation with the National Institute of Arthritis and Musculoskeletal and Skin Diseases on studies of cancer and bone disorders.

Program Projects

Dr. Broder turned the focus of his presentation to program project grants, or P01s. He cautioned the Board that there would be contradictions in the slides being presented that could lend themselves to varying interpretations; some might conclude that the program is doing well while others might assume that it is in trouble. He emphasized that NCI is committed to the importance of program projects and uses them more extensively than most other Institutes; he described the program as an important mechanism for moving "from the lab to the bedside" and asserted that it requires special attention.

Dr. Broder explained that the broad term "research project grants" includes traditional investigator-initiated research project grants, or R01s, as well as P01s and other mechanisms (Outstanding Investigator, MERIT, FIRST, and other grants). He explained that NIH, the Congress, and many others count the number of research project grants as an index of progress—every Institute is given a target for the number of grants it is expected to meet. This year NCI went above the target. One difficulty for NCI, Dr. Broder observed, is that both R01s and P01s count as single units in this count, even though a program project may be five times as expensive and have multiple subprojects.

While the number of P01s grew between 1988 and 1992 from 159 to 177 and the number of competing P01s has increased from 45 to 48, during the same period the number of traditional R01s has fallen slightly—R01s declined from 2,300 to 2,073 and competing R01s declined from 698 to approximately 594.

Dr. Broder pointed out that the total number of research project grants in all categories has increased in recent years, from 3,060 in 1988 to an estimated 3,346 in 1992. In 1988, the total amount of funding for research grants was $665 million. The 1992 estimate for research project grants is approximately $876 million, an increase of about 32 percent.

In the same time period, P01 funding has gone from approximately $170 million to slightly more than $202 million, an increase of 14 percent. Dr. Broder described this as bad news because it means that appropriate growth has not been permitted in the P01 program compared with the research project grant pool as a whole.

Dr. Broder examined the average costs of research project grants. The average cost of a grant increased from $218,000 to $262,000 between 1988 to 1992, an increase of 20 percent. The average cost of an R01 increased from approximately $158,000 in 1988 to about $205,000 in 1992, an increase of almost 30 percent. The average cost of a P01 grew from approximately $1 million in 1988 to just over $1.1 million in 1992, an increase of only 7 percent. Dr. Broder suggested that for every percentage point of growth desired in the P01 program, given the current budget breakdown, the Institute would have to choose not to fund 10 R01s.

Turning to what he described as positive news for P01s, Dr. Broder noted that the success rate (the number of funded applications versus those reviewed) for P01s is consistently higher than that of R01s. In 1992, he said, NCI is expecting to achieve a success rate of approximately 57 percent for P01s; for R01s, the success rate is about half that figure. As an aside, Dr. Broder suggested that two conclusions can be drawn concerning the success rate of P01s: either NCI has been giving special attention to P01s by permitting a high success rate, or they truly deserve their success rates because of their synergistic, collaborative translational value and because of the inherent excellence of the investigators involved.

Dr. Broder brought to the Board's attention the phenomenon of score compression among P01s—the operating payline for P01s went from 150 in 1988 to 130 in 1991. He said that this compression could be due to at least two factors: 1) peer reviewers, in addition to making a priority score decision, also wish to make a funding decision, and therefore are more concerned with assigning the appropriate priority score for funding purposes; and 2) P01s have become more important and have improved scientifically.

If this trend continues unchecked, Dr. Broder continued, priority scores could begin to fall within a tight range close to the best score of 100, making the ranking of proposals more difficult. In 1988, P01s scoring 150 or better received funding with almost no exceptions, and even those scoring worse than 150 had a good chance of success. In 1991, P01s with a priority score of 130 or better were funded with no exceptions.

Turning to the question of what percentage of recommended dollars are actually being awarded, Dr. Broder said that for R01s in 1991, those proposals in the upper quartile (the vast majority of successful R01s) received 90 percent of peer-recommended funding levels; the small group of those funded in the second quartile receive 83 percent of peer-recommended levels. The upper quartile of P01s are held to the same standards as R01s, receiving funding at roughly 90 percent. In the second quartile there are still many more P01 grants being funded, but only at 68 percent. Some grants are funded even in the third quartile, albeit at about 41 percent of the peer review recommended amount.

Dr. Broder concluded by stating that the Institute has many funding decisions on which it needs the advice of the Board. In fiscal year 1992, he said, 48 P01s will be funded. However, if the P01s are funded in rank order at full recommended rates without attempting to reach those in lower quartiles, that number would have to be cut to 32, resulting in one-third fewer program project awards.

He ended his presentation by repeating that the data he presented could be interpreted in two ways: 1) P01s are in trouble and have felt a significant impact from various fiscal realities; or 2) NCI has made a special effort to keep the P01 program going, specifically by funding P01s that are in a lower quartile than normally would be funded in the R01 program. Dr. Broder stressed the fact that NCI recognizes the importance of P01s and will make every effort to keep the P01 program functioning.

Questions and Answers

Dr. Calabresi thanked Dr. Broder for his report, and noted that the Planning and Budget Committee had been working on this problem for the past 6 months. Dr. Sydney Salmon asked whether there were any trends in the nature of grants that have been funded. Dr. Broder replied that NCI gives a high priority to the translational type of grant. He remarked that, for the first time, the Institute has issued a Request for Applications (RFA) for P01s—in this case, to address the issue of gene therapy research. This RFA requires applicants to have a performance plan to translate findings from the laboratory to the clinic. He expressed the opinion that this translational activity is most often the defining function of the P01 mechanism, but added that purely basic research proposals can still compete well in the P01 program.

In reference to Dr. Broder's slide on P01s and R01s in the second quartile, Dr. Frederick Becker observed that the two programs were almost identical in number but enormously different in terms of percentage. Dr. Broder agreed, adding that an R01 placed in the third quartile by a standing study section has an extreme probability of not being funded, whereas P01s in the third quartile have a fighting chance, though not a great chance, for partial funding.

Dr. Becker pointed out that it looked as if 33 percent of the P01s in the second quartile would receive reasonable funding. Dr. Broder replied that this illustrated the

point he had been trying to emphasize—that any individual could look at the figures and come to opposite conclusions. Some people in the R01 community may feel that too much stress is put on P01s, while others, including some in the P01 community, feel that NCI has abdicated its commitment to P01s. Dr. Broder, arguing that there is both good and bad news regarding P01s, stated that he personally rejects the hypothesis that NCI has damaged the P01 program and has not paid enough attention to it.

Dr. Erwin Bettinghaus remarked that one way of explaining the difference between 1988 and 1991 is the fact that the announcement of P01 scores ahead of time occurred in 1991, but not in 1988. He said that Principal Investigators not only discuss this, but also find ways of introducing the numbers into their presentations.

Dr. Broder said that he hoped the Planning and Budget Subcommittee would discuss this issue during its afternoon meeting. He expressed the opinion that what is needed is not a priority score but a rank ordering; this, he added, is why he introduced the idea of quartiles.

Dr. John Durant remarked that in 1988 the Board approved a procedure wherein the study sections would set general priorities for P01s but at the same time provide a more expert scientific evaluation of P01 applications. Now, he said, a good fraction of the P01s are being funded as exceptions, which means that someone else is prioritizing the funding of P01s. He asked which is the lesser of two evils, the less-expert review or the funding of so many exceptions?

Dr. Broder expressed concern with this issue. Almost every administrative decision in science, he noted, involves setting priorities. The ad hoc process of review for P01s, he suggested, is analogous to selecting a university dean by asking separate search committees to review each candidate and give them priority scores with no communication between groups. Dr. Broder asked the NCAB for advice on developing a mechanism through which there would be some prioritization of P01s by peers.

Dr. Pitot asked for an estimate of the proportion of basic science P01s versus translational and clinical P01s. Dr. Broder stated that there are more translational projects selected for exception funding, and said he would get the rest of the information for Dr. Pitot later that afternoon. Amended P01 applications, he noted, have received superior scores because the Principal Investigator takes the peer review comments seriously. He added, that as a growing member of P01 applications are amended, this might be one reason for the score compression.

Dr. Kenneth Chan asked about the numbers of projects in the P01s and the average dollar amounts for the component projects. Dr. Broder replied that there are five projects and three cores in the typical P01, with basic science P01s having fewer cores. Dr. Chan asked whether one could judge the cost saving from P01s versus R01s because of synergism. Dr. Broder replied that it would be worth looking at, but would require making a difficult value judgment because approximately 40 percent of the P01 dollar pool comes from the Division of Cancer Treatment, bringing up issues of treatment-oriented research versus other types of research.

IV. LEGISLATIVE UPDATE—MS. DOROTHY TISEVICH

Ms. Tisevich began her presentation by noting the deaths of two elected officials with responsibilities related to NCI—Representative Ted Weiss, (D-NY), and Senator

Quentin Burdick (D-ND). Representative Weiss chaired the Subcommittee on Human Resources and Intergovernmental Relations and was well known in the NIH community. Senator Burdick was a member of the Senate Appropriations Subcommittee on Labor, Health and Human Services, and Education, which handles the NCI budget.

Ms. Tisevich reported that, since the last NCAB meeting, there was only one hearing at which NCI staff testified. On June 24th, Dr. Michael Grever, Associate Director of the Division of Cancer Treatment's Developmental Therapeutics Program, testified before Senator Bennett Johnston (D-LA) on the taxol program. Senator Johnston introduced the Senate companion to the Pacific Yew Act, which calls for management and conservation of the Pacific yew. The bill was signed into law on August 7, 1992. NCI's responsibility under this act is to promptly notify the Secretaries of Agriculture and Interior, and, subsequently, the designated House and Senate Committees, once sufficient quantities of taxol are available from resources other than the Pacific yew.

Ms. Tisevich announced that another hearing is scheduled at which Drs. Bernadine Healy and Lance Liotta, accompanied by Drs. Steven Rosenberg and Charles Meyers, will testify. This hearing, highlighting several successes of NIH's intramural research program, is a follow-up to Representative Oberstar's (D-MN) visit to NIH in June. Dr. Rosenberg will discuss his gene therapy research and Dr. Meyers will describe his research on prostate cancer. Ms. Tisevich also announced an upcoming hearing to be held by a new House Republican Task Force on Breast Cancer; NCI, she noted, might be asked to testify.

Several other pieces of legislation are scheduled for further action during this session, including the appropriations bill Dr. Broder referred to earlier. Ms. Tisevich explained that this bill faces a possible Presidential veto for two reasons: 1) a veto is likely if the bill exceeds the President's funding request (currently, the House bill is within the President's budget and the Senate's bill exceeds it); and 2) the Senate bill includes language overturning the Administration's gag rule regarding abortion counseling and broadens circumstances under which federal funds could be used to pay for abortions. Ms. Tisevich said if these provisions are included in the final bill when it comes out of conference, and if the bill gets through both chambers again, a Presidential veto could be expected.

Referring to the DES earmarks Dr. Broder mentioned earlier, Ms. Tisevich said that the language was probably inserted into the Senate bill because of pending legislation introduced by Senator Harkin (D-IA) and Representative Slaughter (D-NY). These bills authorize an intensified education and information program on DES and encourage additional research by NIH. The House version of this bill has already been passed, and the Senate Committee on Labor and Human Resources will take it up shortly.

Another bill pending in Congress is the NIH reauthorization bill, a previous version of which was vetoed by the President because of language concerning fetal tissue transplantation research and because funding levels for several programs exceeded the President's budget request for 1993. Senator Kennedy (D-MA) and Representative Waxman (D-CA) have introduced revised bills addressing these concerns. The fetal tissue provisions have been addressed by the inclusion of a requirement for establishing fetal tissue banks that would be the primary source of all tissue for federally funded fetal tissue transplantation research. In order to address the President's concerns regarding excessive funding, all dollar authorizations have been deleted from the bill, with certain notable exceptions including breast cancer and prostate cancer research.

Ms. Tisevich reported that one of the items included in the Senate Appropriations report was a provision for NCI to conduct a study of factors causing high breast cancer mortality rates in the northeast and mid-Atlantic states. She said a similar provision is included in the reauthorization bill; however, the responsibility for conducting the study was given to the Centers for Disease Control (CDC).

Ms. Tisevich reviewed the Mammography Quality Standards Act of 1992, formerly known as the Breast Cancer Screening Safety Act, which would establish inspection and certification requirements for mammography equipment facilities and personnel. Staff from several components of the Department of Health and Human Services, including NCI, the Health Care Financing Administration, CDC, and the Food and Drug Administration, recently briefed Representative John Dingell's (D-MI) staff on this bill.

Ms. Tisevich cited language in the House Appropriations report mandating NCI to review and report on cancer research programs, including those outside the current cancer establishment, as part of a fundamental review of the research programs sponsored by the Institute. She highlighted similar language in the Senate report, which also calls for a plan for future research across the broad spectrum, including basic biology; cancer control; aftercare and rehabilitation; and barriers to state-of-the-art cancer treatment that are a detriment to addressing cancer in some populations, particularly minorities and older Americans. The Senate committee, she continued, also recommends that the President's Cancer Panel convene an ad hoc group to assist in deliberations reflecting various constituencies and scientific disciplines.

Ms. Tisevich concluded by observing that both the House and Senate have a very strong interest in the progress being made against cancer as well as in exploring new opportunities, including areas that traditionally may not have been as prominent in the National Cancer Program's research agenda. She added that the review activities they recommend will provide an important opportunity to assess the strengths and weaknesses of the National Cancer Program and explore the need for new approaches, strategies, and relationships to address them.

V. UPDATE ON TAMOXIFEN STUDY—DR. BERNARD FISHER

Before introducing Dr. Fisher, Dr. Peter Greenwald, Director of the Division of Cancer Prevention and Control, gave a brief overview of the Breast Cancer Prevention Trial using tamoxifen, the first large-scale chemoprevention trial using a pharmaceutical agent. He said the trial, which is expected to benefit women at high risk for breast cancer, is being conducted by the National Surgical Adjuvant Breast and Bowel Program (NSABP) led by Dr. Bernard Fisher.

Dr. Fisher began his presentation by providing a perspective on the need for a prevention trial. Recounting the statistics of breast cancer—175,000 women per year get breast cancer, approximately 30 percent die of the disease, and there is an increase in incidence with age—he commented that these statistics do not begin to portray the magnitude of the problem. Those 175,000 women per year, Dr. Fisher added, are "the tip of the iceberg," representing only a small part of the female population whose breasts contain a heterogeneous array of aberrations.

Dr. Fisher observed that when he first entered the field, breast cancer could only be found by clinical examination. Later, with the advent of mammography, it became

possible to find phenotypically expressed lesions at an earlier point in time. Researchers realized that there must be phenotypically expressed breast lesions that exist even below this level of detection. Dr. Fisher explained that, even before phenotypically expressed lesions occur, there are changes in women's breasts, including biological and biochemical changes and phenotypic gene alteration. Dr. Fisher referred to these as biological breast cancers. He stated that women who have no putative risk factors for breast cancer may still develop the disease, as they experience environmental changes, diet changes, and hormonal activity.

Dr. Fisher emphasized the fact that breast cancer does not occur on the day it is detected; women who are likely to get clinically detectable breast cancer next year already have the disease this year. He explained that, based on the current knowledge of kinetics, by the time a tumor reaches 1 centimeter, it is presumed to have gone through 30 doublings and has taken as long as 8 years to reach that level. It is conceivable, he said, that there may be as many as 1 million women today who have breast changes that are not breast cancer in the classic sense, but have the potential of developing into breast cancer. Many other women do have phenotypically expressed breast cancer that will eventually become clinically perceptible.

Dr. Fisher described two clinical investigative strategies currently directed toward breast cancer. One is to devise better methods for the systemic treatment of clinically and mammographically detectable disease, including new drugs, methods to overcome drug resistance, and the use of biological approaches to treatment. The second research approach relates to increased detection of lesions when they are small but still phenotypically expressed. The likelihood of improvement in picking up smaller lesions with mammography, he stated, is questionable. Therefore, the aim is to pick up as many lesions as possible.

Not much progress has been made in this regard, Dr. Fisher noted; in 1990, only 50 percent of women with breast cancer were in Stage I breast cancer, 25 percent were in Stage II, and 25 percent were in Stage III. Nevertheless, he said, concerted efforts must continue on detection of lesions below the level at which they are currently found. Dr. Fisher expressed the opinion that the types of breast cancers that are determined mammographically are more important than how many are detected.

The prevention trial using tamoxifen, Dr. Fisher emphasized, is the first study directed at preventing breast cancer expression. The ideal agent, he said, for use among women who are at increased risk or those with preneoplastic lesions should be an antipromoter, an anti-initiator, or both, and should have minimal toxicity during prolonged therapy. Tamoxifen is the agent the Institute chose to appraise for this purpose. Dr. Fisher described tamoxifen as the most widely prescribed antineoplastic agent for the treatment of breast cancer in the U.S. The understanding of how tamoxifen works is rapidly increasing, he said. It is known that tamoxifen modulates the production of certain growth factors, increases sex hormone binding globulin, increases natural killer (nk) cells, decreases insulin-like growth factor, and has an effect upon angiogenesis factor.

Dr. Fisher summarized information indicating that tamoxifen inhibits tumor initiation and tumor promotion. It has been shown to inhibit the growth of estrogen-dependent breast cancer cells in culture by competing for receptor sites or by increasing concentration of tamoxifen and related receptor affinity. This drug has also shown an effect on transplantable mammary tumors. There are also benefits to its use in Stage I and II diseases, and a reduction has been shown to occur in the incidence of a second

breast cancer in the contralateral breast of patients who have had one breast cancer. Dr. Fisher's group has shown that the incidence of second breast cancer can be decreased by 50 percent more.

Concerning the toxicity of tamoxifen, Dr. Fisher described a Stage I breast cancer study in which half the women received a placebo; there were just as many adverse reactions to the placebo as there were to tamoxifen. Sixty-three percent of the women on tamoxifen experienced hot flashes, which would appear to be a high percentage; however, 43 percent of the placebo women also experienced hot flashes, as well as other symptoms that the tamoxifen-treated women experienced. For example, patients receiving the placebo experienced nausea as often as tamoxifen patients. Observing that the quality-of-life issues women reported were equivalent in the placebo and the tamoxifen group, Dr. Fisher said a large component of his study will assess the quality of life in all patients.

Dr. Fisher addressed association of tamoxifen and thromboembolic disease; in his own study, he said, there is some increase in thromboembolism in older women related to the fact that some of these women had a history of phlebitis, thromboembolism, or varicose veins. This problem has been much less frequent but still present among premenopausal patients. Dr. Fisher is not incorporating women with a history of thromboembolic disease, varicose veins, or similar problems into the prevention trial.

Speaking specifically of liver cancers, Dr. Fisher said that there has been a demonstrated increase in liver tumors among rats who receive 20 to 200 times the dose of tamoxifen used in humans. Estrogen increases the incidence of hepatic neoplasms in humans and experimental animals, and birth control pills are associated with an increase in liver cancer. Therefore, he concluded, the effect of tamoxifen in rats may be related to the estrogenic effect of the drug. No tumors have been noted in several thousand NSABP patients, as well as no liver tumors in those patients receiving tamoxifen. Liver cancer became a concern in a 1989 study in which some patients receiving daily doses of 40 milligrams of tamoxifen developed liver tumors. Patients in Dr. Fisher's study will receive 20 milligrams daily.

Addressing endometrial cancers, in which tamoxifen has been shown to stimulate endothelial growth in mice, Dr. Fisher stated that the women who develop endometrial cancers are all postmenopausal, and many have had prior estrogen therapy. He added that he does not know how this confounded their conditions; however, he said it is unlikely that the risk of endometrial cancer is greater than that which occurs following estrogen replacement therapy in normal women.

Dr. Fisher said there may be some ocular changes resulting from tamoxifen. He cited a Greek study in which 4 of 63 women on long-term low-dose tamoxifen demonstrated retinopathy that was reversible upon discontinuation of the drug. The prevalence of vision problems will be examined in the NCI prevention trial.

Dr. Fisher presented a brief history of the development of the clinical trial. In 1984, the NSABP submitted a proposal to NCI to evaluate the use of tamoxifen as a chemopreventive agent in Stage I breast cancer patients; the application was not accepted. In 1990, Dr. Brett and associates from California submitted a proposal to the FDA to study the use of tamoxifen as a preventive agent. This study was intended to focus on victims of the Chernobyl disaster. The FDA was interested in the idea, but did not approve this particular study.

Concurrently, NCI released an RFA on tamoxifen; the NSABP responded and was eventually selected for funding. Following several months of discussions, there was a meeting with the FDA, whose response was favorable pending some adjustments. Shortly thereafter, the NSABP solicited applications from institutions interested in participating; by October 1991, 182 applications had been received. These were carefully studied by three independent reviewers and rank ordered by total score. The first public announcement of the trial was made in April 1992, and the first risk assessment was completed on the day after the announcement. As of September 18th, 2,325 participants had been randomized; this represents approximately 15 percent of the total needed.

Concerning tamoxifen's relationship to coronary artery disease, Dr. Fisher stated that the effect of lipids and lipoprotein, as related to estrogen, reduces mortality from coronary heart disease in postmenopausal women. Tamoxifen, he said, has many of these same lipid-lowering properties. Tamoxifen, he added, may have the same effect as estrogen on osteoporosis—decreasing rapid bone loss and bone resorption.

Dr. Fisher listed several major goals of the prevention trial, including evaluation of the effect of tamoxifen in: 1) reducing invasive breast cancer; 2) reducing the overall incidence of breast cancer; reducing incidence of breast cancer mortality; 3) reducing cardiovascular mortality; and reducing, or at least stabilizing, bone fractures and osteogenic changes in bone. Dr. Fisher expressed his confidence that the basic requirement for initiating a study such as this—the presence of a significant biological justification—has been met.

As mentioned earlier, the study is also investigating other issues, such as ocular events, evaluation of endometrial changes, and bone densitometry. Even more important, Dr. Fisher observed, are the liaisons being established with the country's leading geneticists, who view the study as a valuable resource for improving our knowledge in breast cancer genetics.

Dr. Fisher explained that study participants will include women ages 60 and older and women ages 35 to 59 with additional risk factors. Age, he noted, is the strongest risk factor. Women in their early 60s have a projected lifetime risk of about 10 percent for developing breast cancer. But those same women, he said, also have substantial and increasing risk of coronary artery disease. While a sizable proportion of the morbidity and mortality attributed to breast cancer occurs among women ages 35 to 60, there is concern about the potential tamoxifen-related reproductive effects and toxicity that must be taken into account. These risks associated with the use of tamoxifen require that only younger women with a substantially increased risk be included in the study.

Because years lapse between tumor inception and detection, Dr. Fisher stated that a preventive intervention may be more effective when used early. There is strong evidence that women with a family history of premenopausal breast cancer tend to develop the disease earlier than their first-degree relatives. He and his group feel strongly that younger women should not be denied the opportunity for participation, since many have been subjected to alternative therapies whose effects are often worse than tamoxifen. In addition, excluding premenopausal women from the trial might limit the generalizability of the findings.

Dr. Fisher said that younger women are accepted into the study when their risks are at least as great as the 60-year-old woman's risk. The Gayle model (developed by Mitch Gayle of NCI), which provides information on women with characteristics likely to be similar to those of women in this trial, is being used. Dr. Fisher listed the variables

used to obtain the risk assessment profile—the number of first-degree relatives with breast cancer, age at first live birth, number of benign breast biopsies, atypical hyperplasia, age at menarche, and lobular carcinoma *in situ*. This information is entered into a computer that produces a risk profile that, in conjunction with the age-specific rates, will be used to determine relative risk.

The net event rate, he continued, is ascertained by subtracting the beneficial events from the detrimental events. A beneficial event is one that prevents breast cancer and myocardial infarction. Detrimental events include the occurrence of endometrial or liver cancer or death from thromboembolism. Dr. Fisher noted that this information was examined for women in three age brackets: under age 40; ages 40 to 59; and ages 59 and above. In every situation in which this method of calculation was used for all the populations, the benefit was positive. The potential impact of this study could reach a reduction of 70,000 in the annual incidence of breast cancer and myocardial infarction.

Two-hundred-seventy-eight institutions are participating in the study, including 118 primary participants and their satellites distributed across the United States and Canada. The age distribution of the 19,000 eligible women who have had risk assessments shows a greater number of younger women than in the 50-to-59 or 60-plus age brackets. Dr. Fisher noted that a period of up to 2 months occurs between risk assessment and randomization, during which gynecological examinations, mammograms, EKGs, and other tests are administered. Thus, the fact that many potential participants who have been through risk assessment have not yet been randomized does not mean that the NCI is having difficulty getting participants into the study. Dr. Fisher presented an overview of one data set of 6,000 risk assessments, of whom 4,000 were eligible and 1,302 randomized; this rate of 32 percent randomization of eligible subjects is higher than the 10 percent rate anticipated in the study design.

Dr. Fisher addressed the low levels of racial and ethnic minorities receiving risk assessments. Only 4 percent of those receiving risk assessments were minorities; 3 percent were eligible and 2 percent have been randomized. He observed that the difficulty of recruiting economically disadvantaged persons has been noted before; the NCI is making every effort to improve this recruitment and is open to any suggestions or assistance.

A second problem relates to insurance; Dr. Fisher noted that very few insurance plans cover prevention services; in addition, there are 36 million Americans without any health insurance, which further reduces access to the prevention study. Dr. Fisher praised the innovative efforts of the investigators in solving monetary problems.

Dr. Fisher closed his presentation by asserting that this study is a carefully conducted application of the scientific method for clinical problem solving and will serve as a prototype for studies in the future. Dr. Calabresi opened the floor for discussion.

Questions and Answers

Dr. Salmon asked whether there are plans to implement a cap on any particular age group to create balance. Dr. Fisher, acknowledging that this has been taken into consideration, referred the question to Dr. Lawrence Kessler, who replied that the only real concern is relative to cardiovascular disease and osteoporosis. He added that it would be difficult to make those judgments only 3 months into the trial. Dr. Salmon

stated that he would be concerned only if there was an underaccrual of participants for the study.

Dr. Wilson asked 1) if there was any association between breast cancer and cardiovascular disease, and 2) what role Health Maintenance Organizations (HMOs) have played in the study. In response to the first question, Dr. Greenwald replied that there is not a one-to-one association of the two diseases; fortunately, he added, measures that appear to be beneficial against cancer, such as avoiding fats, consuming dietary fiber, and not smoking, are also beneficial against heart disease. In answer to the second part of Dr. Wilson's question, Dr. Kessler replied that two Kaiser Permanente HMO facilities on the west coast have successfully competed for the trial and have been successful in randomizing and assessment.

Dr. Becker asked about the question of smoking among Dr. Fisher's patients. Dr. Leslie Ford replied that demographic and etiological conditions regarding smoking history are being collected, as well as diet, alcohol, and exercise history. Dr. Greenwald added that the criteria for exclusion have to do with history of thromboembolism and not smoking.

Mrs. Bynum said that Dr. Fisher seemed to imply that all of the Black women included in the study are socioeconomically disadvantaged; she also asked whether any attempts were being made to broaden participation of Blacks in the study. Dr. Fisher replied that he does not know the economic status of Black versus White participants. He said that the problem of minority participation is of great concern and is the one aspect of the study with which investigators are unhappy. Dr. Greenwald added that there would be a meeting the following week to address this issue. Dr. Freeman commented that there is often an association made between being Black and being poor; he argued that the study would be much more important in its conclusions if the meaning of poverty in the study could be separated from the meaning of race.

Dr. Bettinghaus expressed interest in the fact that the tamoxifen study will probably be the first time in a study that so many women are guaranteed to have their Pap smears and mammograms at the appropriate time under appropriate control conditions. He suggested that as much will be learned about "normal" populations receiving appropriate preventive measures as about tamoxifen. Dr. Fisher added that he views clinical trials as a very important health care delivery system.

Dr. Chabner asked whether anyone has done an analysis to predict what the excess risk of endometrial cancer would be over the lifetime of the average patient, adding his own conclusion from the data that it would be very hard to project a 2 percent risk. Dr. Fisher interjected that the risk is higher. Dr. Ford said risk benefit analysis shows a 2 percent increase in endometrial cancer, which is consistent with clinical trial data from women with breast cancer and is also consistent with data for estrogen replacement therapy, which would raise the odds from 1 in 40 to 1 in 20. Dr. Broder asked whether this was with estrogens alone, opposed estrogen, or unopposed estrogen. Dr. Ford replied that the data she referred to were from the literature on unopposed estrogen, not from human trials.

VI. UPDATE ON BLACK, HISPANIC, AND APPALACHIAN LEADERSHIP INITIATIVES—DR. CLAUDIA BAQUET

Dr. Greenwald stated that over the past decade there has been considerable growth in NCI's commitment to minority and underserved populations and that this commitment has been even more profound under the leadership of Dr. Broder. Dr. Greenwald pointed out that in 1984, Dr. Claudia Baquet joined the National Black Leadership on Cancer (NBLIC) as an expert in the Special Population Studies Branch, later becoming chief of that branch. Dr. Baquet is now Associate Director of the Cancer Health Science Program and will soon be promoted to Deputy Secretary for Minority Health in the Department of Health and Human Services.

Dr. Greenwald noted that Dr. Baquet has made enormous contributions to cancer control among minority and underserved populations. In the mid 1980s, Dr. Baquet and Dr. Louis Sullivan began building a network of Black leadership for cancer control that was expanded upon Dr. Sullivan's appointment to the NCAB. Dr. Baquet has worked to ensure that Hispanic, Appalachian, and other underserved populations are included in all of NCI's programs.

Dr. Baquet presented a brief update on the NBLIC, asserting that Black Americans are experiencing a disproportionate burden in terms of their cancer profile. A comparison of Black Americans with their White counterparts shows that this population experiences a 10 percent greater risk of developing cancer. Dr. Baquet said that Blacks have a lower 5-year survival rate and a 30 percent higher mortality rate, substantially higher site-specific age- adjusted incidence and mortality rates; and lower survival rates for cancers of the oral cavity, pharynx, esophagus, stomach, liver, pancreas, cervix, uteri, and prostate than their White counterparts. She pointed out that while Black Americans have lower incidence rates for some cancers, the mortality rates for these cancers are equal to or substantially exceed those of Whites.

Dr. Baquet described a number of factors that contribute to the lower survival and higher mortality rates among Black Americans and other underserved populations. As a whole, Black Americans have disproportionately lower socioeconomic status (SES); more than 26 percent of Blacks live below poverty level, compared with 7 percent of Whites. Twenty percent of Black Americans have completed less than 8 years of education, compared with 8.4 percent of Whites; 51.2 percent of Blacks have graduated from high school, compared with 68.8 percent of Whites. The median family income for Blacks is $12,598, compared with $20,835 for their White counterparts.

Dr. Baquet added that a number of other contributing factors play a part in survival and mortality rates, all of which are linked to socioeconomic status. The major risk factors and exposures include a higher prevalence of tobacco use in the Black population; the combined effects of tobacco and heavy alcohol use, contributing to a significant number of head and neck cancers and cancers of the esophagus; diet and nutritional factors; and high occupational exposure.

Knowledge, attitudes, and practices, coupled with pessimistic attitudes prevalent among Blacks, Hispanics, and other culturally diverse populations, have had a significant impact on disease stage at diagnosis and treatment, early detection, and care-seeking patterns. Dr. Baquet stated that delay in seeking diagnosis and treatment for cancer among Blacks ranges from 6 to 12 months after a cancer warning sign or after diagnosis; sometimes there is also a delay of up to 12 months for therapy. She stressed the fact that medical resource distribution is closely tied to socioeconomic condition. State-of-the-art

early detection and diagnosis and treatment services are not utilized at the same rates in culturally diverse groups, including Blacks, compared with the general population. This has an impact on quality of care and compliance.

Referring to Dr. Freeman's remarks about the malignant neglect of the poor, Dr. Baquet acknowledged that poor families often seek care at the last minute because the need for food, clothing, and shelter, as well as the avoidance of crime, are first priorities, rather than the prevention of a disease that may take 10 to 15 years to develop.

Dr. Baquet related that in 1986 Dr. Sullivan, as a member of the National Cancer Advisory Board, spoke about the need to educate Black leadership at various levels about the realities of cancer in the Black community and the opportunities for reducing that burden. Issues specifically addressed were the elevated rates of tobacco-related cancers in the Black population and the heavy subsidization of Black organizations and print media by the tobacco industry. Dr. Sullivan chaired a national working group to mobilize leaders of the Black community to address the cancer burden in a systematic, structured way. The National Executive Committee sponsored a series of six regional meetings between 1987 and 1988 in Los Angeles, Chicago, Atlanta, New York, Houston, and Washington, DC.

These meetings resulted in increased national and regional attention to the seriousness of cancer in the Black community and the development of strategies to address these issues. In 1989, as a result of this effort, NCI funded a 3-year follow-up phase to the NBLIC. During this follow-up phase and in the future, the NBLIC will facilitate the establishment of a network of active Black leaders throughout the Nation to organize, implement, and support cancer prevention, early detection, and treatment programs at local and national levels. Dr. Baquet also pointed out that the NBLIC has enhanced a number of NCI-supported programs and improved geographic representation of Blacks in some prevention and early detection trials.

To date, the NBLIC has established six regional offices with volunteer chairs and full-time paid directors, recruited lay and health professional volunteers, and established 55 community cancer coalitions across the Nation. These coalitions have engaged in a variety of high-impact outreach activities, including the campaign against R. J. Reynolds Tobacco Company's Uptown Cigarette. Over a single weekend, Philadelphia's Stop Uptown Cancer Coalition ended the marketing of the Uptown cigarette brand to the Black community. In Denver, in Milwaukee, and most recently in Harlem, the NBLIC has engaged in a number of fund-raising activities to provide free or low-cost mammograms and guaranteed appropriate follow-up to high-risk individuals. In addition, the NBLIC has conducted national free rectal and Pap smear examinations with guaranteed referral.

Dr. Baquet mentioned that each NBLIC region participates annually in Minority Cancer Awareness Week, which reaches a large number of Blacks through public service announcements (PSAs) and has attracted a number of Black celebrities, including Greg Morris, Dionne Warwick, Diane Carroll, Marla Gibbs, Phyllicia Rashaad, Patti Labelle, and the late Sammy Davis, Jr., whose wife permitted the use of his PSA after his death. The Los Angeles Coalition coordinated Cancer Warning Sign Sunday, which enlisted approximately 270 churches to incorporate educational outreach activities in their services.

Dr. Baquet also noted that a number of the NBLIC regions are participating in the NCI National Basketball Association initiative. This initiative has drawn regional attention to the importance of mammography, smoking cessation, and other prevention

strategies, and has generated fund-raising resources to support free services for their local communities. Through the NBLIC follow-up phase, a number of effective organizational networking relationships have been established, including those with voluntary agencies at the national, State, and local levels with grassroots organizations, special interest groups, news and entertainment media, professional organizations, and the clergy. Churches were actively involved in mobilizing the Anti-Uptown Initiatives in Philadelphia, Dr. Baquet added.

The NBLIC has worked through churches, print media, radio and television, health fairs, workshops, community group meetings, cancer education meetings and conventions, and the *NBLIC Newsletter* to make a significant impact on public awareness. As a result of the NBLIC's success in these areas, NCI has issued a request for cooperative agreement applications to fund the extension of the NBLIC initiative. This open competition has resulted in the submission of a number of applications.

Dr. Baquet said that the NBLIC hopes to continue to support a national structure for efforts to reduce the burden of cancer among Black Americans. This will translate into enhanced survival rates and a reduction in cancer incidence and mortality. The committee hopes that its initiatives will address barriers that keep Blacks from gaining access to quality cancer control and will stimulate greater participation of Black Americans in community cancer outreach activities. Other objectives of the committee are to increase the number of community coalitions; to collect, summarize, and disseminate effective intervention outreach strategies in the Black community; and to evaluate the effectiveness of these national initiatives. Dr. Baquet noted that the NBLIC's active volunteer force across the Nation now exceeds 1,000 people who are taking the word out into the communities.

Dr. Baquet added that NBLIC also served as a model for two recently developed initiatives, the National Hispanic Leadership Initiative on Cancer (NHLIC) and the Appalachian Leadership Initiative on Cancer (ALIC). Existing data strongly suggest that Latino and Hispanic populations experience overall lower cancer rates than the general population; however, rates for certain cancers are increasing among Hispanics when compared with Anglos. Some data also suggest that smoking will dramatically increase among Latino or Hispanic populations because of increased tobacco advertising in their communities; rates of smoking among Hispanic sixth graders are already higher than those among Anglos of the same age group. Recently, there have been increases in the incidence of breast, lung, colon, rectal, and prostate cancers among Hispanics. Dr. Baquet stated that language, culture, and economic barriers to cancer prevention and treatment also exist in this community. There are also barriers to screening in the Hispanic community because the population is often hard to reach and underserved. She added that Hispanic attitudes concerning cancer and cancer prevention, fear of the disease, lack of optimism regarding opportunities for cure or survival, and lack of awareness of the causes and warning signals of cancer also act as barriers to prevention and treatment. Project activities have been organized to mobilize leaders of lay and health professional communities and to increase the number and utilization of cancer prevention and control programs by Hispanics.

The other new initiative described by Dr. Baquet is the Appalachian Leadership Initiative on Cancer, which focuses on an area that has experienced much higher mortality rates for some cancers than the national average. Risk factors in this region include heavy usage of a variety of tobacco products, poor access to quality preventive health care, and underutilization of health services. Drawing on the experience of the

NBLIC, NCI expects the Appalachian Leadership Initiative on Cancer to have a positive impact on the lives of more than 20 million Americans who live in Appalachia.

The Institute, Dr. Baquet concluded, believes that to win the war on cancer, especially in populations that are disproportionately affected with heavy cancer burdens such as Blacks, Hispanics, and Appalachians, an established support structure must be implemented to get the word out at the regional and local levels.

Dr. Baquet thanked Veronica Chollette of the NBLIC, Frank Jackson of the Hispanic Leadership Initiative on Cancer, and Nancy Simpson of the Appalachian Leadership Initiative on Cancer for their efforts in this area.

Questions and Answers

Ms. Brown thanked Dr. Baquet for her presentation and stated that, having had the opportunity to work with the NBLIC the past year, she knows that the continuation of its work is important.

Dr. Bettinghaus commented on the figures that were presented for age of smoking among Hispanics. Suggesting that the sixth grade figures may be a little misleading, he noted that in many cases the sixth grade Hispanic child is, unfortunately, a year older than the sixth grade Anglo child because language problems have caused them to be held back. Therefore, he said, a different approach may have to be developed for Hispanic children in the classroom than for Anglo children in the same grades.

Dr. Kenneth Olden inquired about current accrual rate of Blacks in clinical trials compared with accrual rates before the National Black Leadership Initiative was instituted. He noted that in Dr. Fisher's presentation, the accrual rate was very depressing, and said that his guess is that they are comparable to a few years ago. Therefore, he wanted to know whether NBLIC had any impact on accrual rates in clinical or prevention trials. Dr. Greenwald responded by stating that steps have been taken to address accrual rates within the Community Clinical Oncology Program (CCOP), which is a major means of recruiting for both therapy trials and prevention trials; groups were established that had to demonstrate the capability of accruing more than 50 percent minority patients in order to be funded. He also pointed out that in the Women's Health Initiative, three minority feasibility studies have been funded; one focused on Black populations, one on Hispanics, and one on underserved populations.

Dr. Olden observed that to win the war against cancer among the socioeconomically deprived, which includes many Black Americans, we are going to have to address the issue of environmental equity—not just smoking and other behaviors that can be controlled, but also the problems caused by living in polluted environments, which is something poor people cannot control. Dr. Greenwald agreed and expressed enthusiasm for working with the Board on this issue.

VII. CLOSED SESSION

A portion of the first day of the meeting was closed to the public because it was devoted to a meeting of the Special Actions Subcommittee. A total of 1,464 applications were received, requesting support in the amount of $278,583,822. Of those, 1,033 were recommended as being eligible for funding at a total cost of $245,107,803.

VIII. SURVEILLANCE, EPIDEMIOLOGY, AND END RESULTS (SEER) PROGRAM DATA—DR. EDWARD SONDIK

Dr. Greenwald briefly explained that the surveillance, Epidemiology, and End Results (SEER) Program, headed by Dr. Brenda Edwards, collects and analyzes cancer statistics, which are published in an annual volume that is of fundamental importance. These data provide a bottom line for assessing progress and also enable scientists to focus on cancers causing the greatest morbidity and mortality.

Dr. Edward Sondik, Deputy Director of NCI's Division of Cancer Prevention and Control, began by defining incidence and mortality, for the purposes of his presentation, as numbers of cases and deaths per 100,000 people. Dr. Sondik's figures are age-adjusted to account for changes in the population profile—over the past several years, he noted, the average age of the country's population has increased.

Two measures of survival were discussed in this presentation: 1) 5-year observed survival, which is the typical clinical measure of the percentage of patients alive 5 years after diagnosis; and 2) a measure adjusted for other causes of death, which estimates the percentage of patients who would be alive 5 years after diagnosis if cancer was the only cause of death.

Dr. Sondik listed several sources of data for his presentation: population figures from the Bureau of the Census; mortality figures from the National Center for Health Statistics; and incidence figures from the SEER Program, gathered from nine areas around the country and representing about 10 percent of the U.S. population.

Turning to the magnitude of the cancer problem, Dr. Sondik observed that cancer ranked second in 1989 among causes of death in the U.S., accounting for 23 percent of the total number of deaths, with lung cancer alone accounting for 6 percent. There are seven cancers that account for two-thirds of all cancer cases and deaths and, thus, can be used to judge progress in mortality and incidence.

One extremely useful and important way of analyzing the data on cancer, Dr. Sondik said, is looking at the cancer experience of different groups based on factors such as race or geographic area. He cited the mortality rate among Black males, which is 47 percent higher than that among White males, as an example; for Black females, he added, the figure is 18 percent higher. The cancer survival rate among Black males is 33 percent, compared with 48 percent among White males; the respective survival rates for Black and White females are 44 and 58 percent. The SEER data can also be used to compare experiences in the United States with those in other countries. These kinds of data are important because they provide a perspective on differences in the cancer experience that are important to cancer research, prevention, and control efforts.

Dr. Sondik stated that, even though progress is being made in many areas, the cancer problem appears to be growing. The fact that cancer rates increase with age accounts for a large part of this growth; between 1970 and 1990, the total population increased 22 percent while the population age 65 and older increased more than 50 percent and the population age 85 and above increased 100 percent. During a similar period, there has been an increase of about 50 percent in cancer deaths, from 300,000 to 500,000 per year. While the crude death rate has gone up 23.5 percent, the age-adjusted rate has increased only 6.3 percent.

Regarding the relationship between changes in cancer and heart disease, Dr. Sondik observed that the mortality rate from heart disease has fallen tremendously, from a rate of over 2,500 to about 1,800 per 100,000 for persons 65 and older, while the cancer rate has increased. These figures suggest that cancer will overtake heart disease as the number one cause of death in this country, if the trends continue as they are, before the year 2020.

Looking at cancer mortality by age group, Dr. Sondik said that there has been a slight overall increase in mortality, about 6.1 percent, over a 16-year interval. There has been an almost 4 percent decline in mortality for persons under 65, but there has been a 13.8 percent increase among persons 65 and above. Discounting lung cancer, there has been an overall decline of almost 3 percent in mortality from all other cancers and an 11 percent decline among those under 65.

Dr. Sondik then discussed individual cancers and their trends. Lung cancer mortality in women of all ages has gone up 118 percent; colorectal cancer has declined approximately 13 percent in that same period of time. Lung cancer incidence in males appears to be decreasing, and Dr. Sondik said that he expects to see a decline in mortality in the future. The incidence of lung cancer has been holding steady and, in fact, begun a slight decline, among Whites; the downward trend among Blacks is more pronounced. Black and White female lung cancer incidence rates show essentially the same increases.

Dr. Sondik cited a continuing decline in the colorectal cancer mortality rate among White males and females, which he attributed principally to changes in diet. However, there has been an increase in mortality from this cancer among Blacks in all but the youngest age group.

There was an increase in diagnosed breast cancers among women over age 50 in the early 1970s, which Dr. Sondik suggested was a result of the well-publicized breast cancer experiences of Ms. Ford and Ms. Rockefeller. This did not represent, he added, an increase in the true incidence of the disease. Dr. Sondik also attributed more recent increases in breast cancer incidence to increases in screening, observing that reported (annual) mammogram screening increased from 17 to 33 percent between 1987 and 1990. The same patterns apply to women under age 50. Dr. Sondik suggested that the peaks in breast cancer incidence caused by transient increases in early detection are less of a problem than the overall trend—over the last 50 years, he said, breast cancer incidence has increased by about one-half percent to 1 percent per year. Mortality declined between 1973 and 1983, and has shown slight increases since then; mortality has declined for women under age 50 but increased among Black women in all age groups.

Dr. Sondik displayed a slide illustrating a new set of figures on the probability of developing breast cancer. By age 50, he noted, a woman has a 1 in 50 chance of developing breast cancer; by age 60 the chance is 1 in 24. To provide a more specific example, Dr. Sondik explained that the chance of a 40-year-old White woman developing breast cancer within the next 10 years is 1 in 62, while her chance of developing breast cancer in the next 20 years is 1 in 25.

The trend in non-Hodgkin's lymphoma continues to show a very steep increase. Dr. Sondik suggested that are were two distinct reasons for this. One has to do with increases in incidence and subsequent mortality for younger people. For males ages 40 to 44, there has been an incidence rate of about 10 per 100,000; between 1974 and 1988, this rate increased to approximately 18. It is believed, Dr. Sondik added, that AIDS has been the driving force behind this increase. On the other hand, there has been a large increase

in non-Hodgkin's lymphoma in persons age 70 and above, from 55 cases per 100,000 to almost 80. This increase is currently under active study. Although a relationship has been established between pesticides and non-Hodgkin's lymphoma, only a 10 percent increase was found among pesticide-exposed farmers in Kansas.

Dr. Sondik said that the incidence of prostate cancer continues to increase. There is a large difference between cases among Black and White males—Blacks have a higher incidence not only in the United States but globally. The overall increase is considered to be due, in large part, to the fact that latent disease is being detected as populations age. On the other hand, he said, there is also an increase in mortality, which is probably also related to increased detection that facilitates determining the cause of death. Other reasons for the increase are not clear, Dr. Sondik noted, but diet could be a factor. He also observed that the incidence of bladder cancer continues to increase while the mortality continues to decline.

Dr. Sondik next addressed trends in cancer among children. The mortality for cancers in children under age 15 continues to decline, although there has been an increase in incidence. Part of this increase, he stated, is due to brain cancer cases and is probably attributable to improved detection techniques.

Declines in the incidence and mortality from stomach cancer, Dr. Sondik explained, are thought to be largely due to improved refrigeration and diet. There have been declines in many other developed countries, but rates remain high in other parts of the world. Several Board members suggested possible factors other than refrigeration, including risks related to salt-cured foods, the benefits of the year-round availability of fresh fruits and vegetables, and the possible effects of preservatives as anticarcinogens.

Turning to the subject of cervical cancer, Dr. Sondik asserted that, because of the availability of early detection, this is one of the most preventable of cancers. The incidence rate continues to decline, but at a lower rate than in the past. Mortality also continues to decline, but there are pockets in the country that have much higher mortality rates of cervical cancer than the national average.

Dr. Sondik stated that melanoma has seen an enormous increase over the last few years; this has been attributed to increased exposure to solar radiation. The rate of increase in mortality from melanoma is second only to the increase in lung cancer mortality. Dr. Salmon commented that education measures are mostly effective on adults, even though there is evidence that early exposure is a factor in the development of melanoma. Dr. Sondik agreed that changes in incidence have been seen primarily among older people and that further public awareness and prevention efforts are needed for all age groups.

The mortality trend for pancreatic cancer has decreased slightly; this is primarily due to a slight decrease in incidence, which, Dr. Sondik said, has not been explained. Survival from this cancer remains very low.

In terms of cancer survival in general, Dr. Sondik provided figures showing an increase from 49 to 52 percent since 1974. For Whites, the increase has been from 50 to 54 percent; for Blacks, there has been essentially no change. For some cancers, Dr. Sondik continued, the differences in survival rates among groups are noteworthy. For example, the survival rate of corpus uterine cancer for White women is 84 percent, compared with a rate of 54 percent among Black women. Dr. Sondik also presented

overall data comparing cancer incidence among Blacks and Whites, revealing that the incidence rates among Blacks are much higher for a large number of cancers.

Dr. Sondik concluded by observing that data from the SEER Program provide a mixed picture of cancer, including both good and bad news. The growing magnitude of the problem, caused primarily by ongoing demographic changes, presents the Institute with a very complex research agenda.

Questions and Answers

Ms. Brenda Johnson asked whether data are available on smokers versus nonsmokers with lung cancer. Dr. Sondik replied that, although such information is very difficult to obtain, lung cancer incidence is increasing among nonsmokers.

Dr. Salmon suggested that the NCAB discuss passing a resolution recommending that the Federal Government discontinue support of tobacco products. Dr. Bettinghaus said he would support that idea, and proposed that the appropriate subcommittee write a proposal for the January NCAB meeting. Dr. Richard Adamson noted that about 10 to 15 percent of the incidence of lung cancer is due not to smoking but to other factors, such as exposure to industrial chemicals, pesticides, smog, second-hand smoke, and radon gas. Ms. Johnson volunteered her subcommittee, the Subcommittee on Women's Health and Cancer, to discuss this issue and draft a resolution. Dr. Calabresi added that it might be appropriate for more than one subcommittee to discuss the issue.

Dr. Becker made three comments. He described an early detection program in Texas, based on interactive video, that hopes to reduce the high incidence of cervical cancer in women ages 20 to 25; he suggested that lower mortality associated with certain tumors in the Black population is an area ripe for examination; and he asked why early detection of breast cancer showed no improvement in the mortality rate. Dr. Greenwald replied that most of the increase in mammography has occurred since 1982; the rise in mammography use is expected to begin having an impact on the mortality rate by 1996.

Dr. Wilson commented that, since most people believe that we eat, drink, and breathe large amounts of carcinogens, one would expect the incidence of multiple cancers at different sites to increase. Dr. Sondik replied that he did not have any data addressing that issue. Dr. Adamson said that there are multiple cancers associated with some genetic syndromes but that few diagnosed multiple cancers are attributed to environmental factors. Dr. Greenwald added that approximately one fourth of those with mouth and throat cancers develop second primary cancers. Dr. Adamson responded that this was probably due to the combined use of tobacco and alcohol.

Dr. Calabresi asked whether Dr. Salmon's program was involved in any efforts to teach teenagers about the association of sun exposure with melanoma risk. Dr. Salmon replied that the prevention program has a number of initiatives, including the Arizona Sun Awareness Program and curricula used in elementary schools. They also have interventional chemoprevention trials in the early developmental stages. He added that major public education programs are underway throughout the Cancer Centers and the American Cancer Society.

Dr. Broder congratulated Dr. Edwards and her staff for the work they had done on the SEER data; he stressed the fact that the SEER Program is an integral part of the Division of Cancer Prevention and Control and plays a role in policy planning. Many

oncologists, he suggested, are not fully aware of these statistics; Dr. Broder asked for the help of the Board in disseminating the SEER Program's findings. While it is important not to appear overly pessimistic or to underplay the progress that has been made, Dr. Broder said that it is extremely important that problems are accurately portrayed, and that those in the National Cancer Program identify where progress is slower so that critics are not the first to point this out.

Dr. Samuel Wells agreed with Dr. Broder, and observed that the way in which this information is reported by the press, often noting only the bottom line, can be dangerous; the subtleties of the information, he said, are sometimes lost in the reporting.

Dr. Broder reminded the Board that the SPORE program exists to identify substantial, common cancers that present an extreme hardship to American public health. The program's first targets include breast, prostate, and lung cancers. The Institute, he suggested, needs to think about where other SPORE programs may be valuable, such as brain tumors and melanoma. Dr. Broder said that with lung cancer, it is critical that smoking prevention not be NCI's only response; ongoing programs are needed in molecular biology, innovative diagnosis, and novel approaches to therapy.

IX. PRECLINICAL CHEMOPREVENTION RESEARCH—DR. LEE WATTENBERG

Dr. Greenwald introduced Dr. Lee Wattenberg, referring to him as one of the founders of the chemoprevention field. Dr. Wattenberg conducts fundamental research on the prevention of cancer. Currently, he chairs a committee of the American Association for Cancer Research (AACR) that is reviewing the field of chemoprevention to determine how it can be advanced most effectively in order to prevent cancer in human subjects. He is also President of the American Association for Cancer Research.

Dr. Wattenberg defined chemoprevention as the use of one or more compounds to prevent the occurrence of cancer. He estimated that there are at least 30 separate groups of chemopreventive compounds. These groups are composed of anywhere from 1 to 50 individual chemicals. The goal, he said, is to learn how to exploit these chemopreventive agents.

Dr. Wattenberg identified two major categories of chemopreventive chemicals—blocking agents and suppressing agents. Blocking agents act as a barrier to the causative agents of cancer; whereas suppressing agents prevent the development or evoluation of the neoplastic process. Many carcinogens require activation in order to target specific cellular sites. Blocking agents interfere with this targeting either by preventing activation of precarcinogens to carcinogens, by increasing detoxification of carcinogens, or by intercepting carcinogens before they reach target sites. These are three major mechanisms by which blocking agents work.

Dr. Wattenberg presented examples of experimental models of blocking agents. He described an experiment using d-Limonene before exposure to NNK, a tobacco carcinogen. This agent greatly reduces the development of benign lung tumors in mice. He stated that similar results are obtained using citrus fruit oils that contain 95 percent d-Limonene. This study demonstrates that, in some circumstances, administering the chemopreventive agent shortly before the carcinogen challenge can provide protection. This is important, Dr. Wattenberg added, because most carcinogens consumed in the diet

require metabolic activation. Preventing activation can result in marked effects in preventing carcinogenesis.

Dr. Wattenberg said that detoxification systems can be thought of as a counterpart to the immunological system. The activity of immunological systems rises and falls in response to foreign proteins or organisms. In a parallel manner, detoxification system activity can be enhanced by exposure to foreign chemicals. The objective of a prevention strategy with detoxification is to enhance the activity of these enzymes and, thus, decrease responses to carcinogens. Dr. Wattenberg presented as an example the glutathione-S transferase system, which detoxifies a large number of chemical carcinogens by binding the reactive constituent to the sulfhydryl group of the glutathione. The conjugate formed is then excreted. Compounds occuring in cruciferous vegetables, such as cabbage, broccoli, and brussels sprouts, are very good inducers of increased glutathione-S transferase activity. Dr. Wattenberg displayed a slide showing that mice that had received administrations of benzylisothiocyanate had two and one-half times the normal level of glutathione-S transferase. When these animals were challenged with the carcinogen benzo(a)pyrene, there was a very sharp reduction in the number of tumors in the forestomach.

Compounds inducing an increase in activities of detoxifying enzymes can be placed into two categories: (1) those that increase Phase I enzymes, which are oxidative enzymes; and (2) those that increase Phase II enzymes, which are conjugating enzymes. Phase I enzymes are very complex and can sometimes enhance carcinogenesis. It is not advisable, Dr. Wattenberg said, to use Phase I enzyme inducers in intervention studies. On the other hand, Phase II enzymes are almost totally protective. Dr. Wattenberg gave as an example the compound Oltipraz, a pure Phase II enzyme inducer. Oltipraz has been used in treating parasitic diseases in humans. It has very little toxicity. Serious consideration is being given to using this compound to enhance the detoxification of aflatoxin in geographic areas where high exposures to aflatoxin exist.

Dr. Wattenberg briefly discussed other blocking agents that trap reactive carcinogenic species, observing that thioles and antioxidants perform this function. There is evidence showing that oxidative damage may result in at least one of the phases of carcinogenesis, and antioxidants can prevent the targeting of active oxygen species to DNA. He referred to investigations currently being conducted to determine how antioxidants may be used as a preventive strategy. In summary, he noted the existence of at least 20 groups of blocking agents, both naturally occurring and synthetic.

Dr. Wattenberg then moved on to a discussion of suppressing agents. Since knowledge of the basic mechanistic events in the neoplastic process is incomplete, researchers are in effect dealing with a "black box" in the study of many suppressing agents. He stated that his discussion would focus on four known mechanisms, the first of which is prevention of endogenous formation of attacking molecules or inactivation of those that are formed. There are several groups of suppressors that will do this, including protease inhibitors and arachidonic acid cascade inhibitors. Dr. Wattenberg described an interesting new suppressing agent, epigallocatechin gallate, which is found in green tea. A second group of suppressing agents counteracts the consequences of genotoxic events. One of the strategies with this type of chemoprevention involves the use of terpenes, which inhibit the isoprenylation of the *ras* protein. Mutation of this oncogene is very commin in neoplasia in both humans and animals. The *ras* protein must be modified before it can migrate and anchor to membranes. This involves three events, one of which is farneslyation of the protein. Terpenes and citrus fruit oils can inhibit farneslyation. Exploitation of this inhibition could provide protective agents.

The third mechanism by which suppressing agents work is by producing differentiation. Retinoids are effective in this regard. Dr. Wattenberg said that the retinoids currently are the most widely used chemopreventive agents. Other ligands for nuclear receptors also can produce differentiation. The last mechanism by which suppressing agents work is by the selective inhibition of cellular proliferation. Dr. Wattenberg described two basic areas in which inhibition of proliferation is useful for chemoprevention. One of these entails the use of difluoromethylornithine. Ornithine decarboxylase activity is increased in a number of early neoplastic processes, particularly tumor promotion. Compounds that inhibit ornithine decarboxylase can suppress carcinogenesis under some circumstances. Dr. Wattenberg reported that studies of inhibition of carcinogenesis of the large bowel are being planned using difluoromethylornithine as a chemopreventive agent. The second situation in which selective inhibition of cell proliferation is being used entails hormone antagonists or inhibitors of hormone activation reactions. Tamoxifen falls into this category.

Naturally occurring suppressing agents exist in foods of plant origin. To highlight the importance of this source of suppressing agents, Dr. Wattenberg cited the effects of cruciferous vegetables on carcinogenesis. He described a study in which rats were injected with carcinogens and subsequently fed relatively small amounts of cabbage or broccoli. A striking inhibition of carcinogenesis was seen. Why this occurs has not been determined, but it signifies the interrelationship of dietary manipulation, chemoprevention, and cancer.

Dr. Wattenberg pointed out that a number of chemopreventive agents are effective relatively late in the carcinogenic process. Both retinoids and tea tannins can cause regression of skin papillomas. The arachidonic acid cascade inhibitors, piroxicam and indomethacin, also can act relatively late in the carcinogenic process. In a study in which arachidonic cascade inhibitors were administered 3 months after carcinogens, cancer was prevented, although not as effectively as when the agents were administered earlier. In humans, arachidonic cascade inhibitors can cause regression of adenomatous polyps of the large bowel. Monoterpenes, which are citrus fruit constituents, cause regression of some breast tumors in animals. Suppressing agents, Dr. Wattenberg observed, are now a major focus of chemoprevention. They can be used to target high-risk groups as well as older individuals.

Dr. Wattenberg went on to discuss two risk categories for the application of chemopreventive agents. One is the general population. For these individuals, the first priority would be blocking agents and, later, suppressing agents. An exceedingly important consideration in general population chemoprevention is toxicity, which is a major issue in all chemoprevention. The fact that very significant chemopreventive effects are achieved by dietary manipulation suggests that there may be nontoxic agents that are quite effective for use in the general population. With higher-risk groups, the major focus is on suppressing agents. Nevertheless, further damage to genetic materials should be avoided when working with high-risk patients, thus blocking agents merit consideration. Identification of the high-risk group is an important consideration. Dr. Wattenberg suggested that soon, perhaps within a decade, general medical examinations will include biomarker studies that will provide information about increased risk from cancer in one or more organs. With this information, intersecting routes of chemoprevention will be used to avoid the occurrence of cancer.

Moving on to a pragmatic area, Dr. Wattenberg said that starting with a compound that has never before been used for chemoprevention and ultimately bringing it to human use can be costly in time and money, possibly 10 years and $100 million. Developing a

food constituent or a pharmaceutical compound already in use for some other purpose might reduce the expense and time considerably.

Dr. Wattenberg concluded by stating that there is a major focus in chemoprevention on preventing common solid cancers such as those occurring in breast, prostate, large bowel, and lung. For the breast and prostate, hormone antagonists and retinoids are now in use and the potential use of compounds altering hormonal metabolism is being considered. Arachidonic acid cascade inhibitors may be of major importance for chemoprevention of cancer of the large bowel. The fact that aspirin users may be at lower risk has enhanced the focus on these compounds as inhibitors of large bowel carcinogenesis. Difluoromethylornithine is also being studied for this purpose. The major focus on chemopreventive agents effective against carcinogenesis of the lung is on retinoids and beta-carotene.

Questions and Answers

Dr. Salmon commented that his prevention group has observed that topical Vitamin E in skin papillomas appears to prevent photocarcinogenesis. He added that the cosmetic industry will likely include Vitamin E, an antioxident, in its products. Dr. Becker said that retinoids, especially in combination with interferon alpha, have shown an enormous protective effect.

Dr. Calabresi asked whether Dr. Becker could add any information from M.D. Anderson's work on retinoids and interferon in carcinoma of the cervix, particularly in the Mexican population. Dr. Becker said that the study has not yet been finalized, but that certain squamous cell carcinomas of the face and neck have shown a significant regression of tumors and, in some cases, total elimination of tumors that were resistant to all other therapies.

Dr. Walter Lawrence asked whether a suppressive agent in cabbage and broccoli has been identified. He remembered reading about Paul Talalay's identification of a protective compound. Dr. Wattenberg replied that a blocking agent, a Phase II enzyme inducer, has been identified. He added that the study is extremely important because the Phase II enzymes have the capacity to detoxify a very wide range of carcinogens; with Paul Talalay's technique, the entire food supply could be screened for a particular Phase II enzyme inducer in 3 years at a cost of less than $1 million. This could set the stage for screening for other enzyme inducers as well. Dr. Lawrence asked which enzyme was studied by Dr. Talalay, and Dr. Wattenberg replied that it was NADPH diaphorase, an enzyme closely related to glutathione transferase.

Dr. Salmon asked whether any foods should be eliminated from the diet, noting that Dr. Wattenberg had referred to carcinogens in mushrooms. Dr. Wattenberg said that he attended a conference where risk assessment for mushroom consumption was discussed, but that no consensus was reached.

Dr. Chan asked whether monoterpenes other than d-Limonene could be used as chemopreventive agents. Dr. Wattenberg replied that there is a whole family of related compounds. He stated that d-Limonene was singled out because the general population already consumes a reasonable amount of citrus fruits in which d-Limonene is found. Dr. Chan then commented that data suggest that some monoterpenes are harmful.

Dr. Phillip Frost said he understands that citrus fruit oils are found primarily in the fruit's skin, and asked if there is any real consumption of the oils. Dr. Wattenberg replied that when these fruits are consumed naturally, there is not much consumption of the oil. Most consumption, he said, is through flavorings in such products as orange drinks.

Dr. Calabresi commented on the connection between aspirin consumption and the reduction of colon cancer. He asked at what point one should begin to take aspirin, keeping in mind gastrointestinal bleeding as a complication of long-term aspirin use. Dr. Greenwald replied that aspirin is protective, but that more information is needed before making a recommendation. Dr. Calabresi noted that many people are taking aspirin as prescribed by their cardiologists, and that there should be additional information so those taking the aspirin do not become ill. Dr. Lawrence asked whether any studies on aspirin have produced negative findings. Dr. Greenwald said that there is a study at the University of Southern California with evidence showing aspirin to be beneficial against heart disease and possibly cancer, but also associating aspirin with strokes.

Dr. Wattenberg commented that in animal models, data exist showing that aspirin is effective as a preventive agent against carcinogenesis in this organic site.

X. HIGH PRIORITY CLINICAL TRIALS—DR. CHARLES COLTMAN

Dr. Charles Coltman presented an overview of the National Cancer Institute's Clinical Trials Cooperative Group Program, with special reference to the program's High Priority Initiative. Dr. Bruce Chabner, in his introduction, noted that the High Priority Initiative was developed in 1988 to stress certain clinical trials that, if completed in a timely fashion, could have a major impact on public health.

Dr. Coltman began by listing the four primary causes of newly diagnosed cancers in the United States in 1991, presented in order of the frequency by which they result in death: lung cancer, colorectal cancer, breast cancer, and prostate cancer. Of the 1 million new cancer cases diagnosed each year in this country, only 2.1 percent have been entered into the Cooperative Group Clinical Trials. NCI's High Priority Initiative was funded to promote accrual of additional patients to selected clinical trials, to disseminate information on these high-priority trials through the Physicians Data Query (PDQ), and to create a greater awareness and enthusiasm for clinical trials through the NCI Office of Cancer Communication.

The initiative began with the distribution of a Request for Application (RFA) to the Cooperative Group Chairs. The Cooperative Group Chairs responded with detailed proposals and budgets for capitation, operations, offices, and statistical center activities. For example, the Southwest Oncology Group (SWOG) mailed 4,000 RFAs to oncologists. One hundred and seventy eight applications were reviewed and 49 were selected. Selection criteria included prior experience in clinical trials, data management capability, and the potential to accrue 10 patients per year. Four different series of high priority initiatives were selected by Cooperative Group Chairs.

Series I, initiated in June 1988, included five clinical trials; four are closed or will close by 1992 and one, a clinical trial of neoadjuvant chemotherapy for bladder cancer, is accruing very slowly. Series II, which began in June 1989, included six clinical trials; three are closed or will close by 1992, one is accruing above the projected rate, and one on occult Stage 1 breast cancer is accruing very slowly. In June 1990, Series III began with three clinical trials; one closed in record time, one is expected to close in 1992, and

one is accruing at the projected rate. Series IV began in June 1991 with seven clinical trials; one accrued above projected rate, two are accruing at twice the projected rate, three are open, and one trial that compares hormonal manipulation with surgery for Stage D1 prostate cancer is accruing very slowly.

Dr. Coltman reviewed the structure of the NCI Clinical Trials Cooperative Group Program, which involves 1,300 institutions, 4,600 clinical investigators, 483 therapeutic clinical trials, and some 23,181 patients. Of these patients, 18,124 were entered in phase III clinical trials. Between June 1988 and September 1991, 17,784 patients have entered the high priority clinical trials program. During the past 12 months, approximately 5,552 patients have been accrued. During 1991, 13 of the 183 phase III clinical trials—7 percent of the total—were selected as high priority clinical trials. The accrual to high priority clinical trials represents 31 percent of the total phase III accrual. In other words, 7 percent of the trials accrued 31 percent of the patients during 1991.

To illustrate how the high-priority designation may have affected accrual to clinical trials, Dr. Coltman described several studies occurring either before or during the high priority clinical trial program. One trial of treatment with levamisole and 5-fluorouracil (5FU), intergroup 0035, in colon cancer was completed prior to the development of the High Priority Initiative. This trial has historical significance because its relapse-free survival difference was so profound that the early stopping rule was invoked. Detailed results were reported in the *New England Journal of Medicine*, February 8, 1990. The trial, which was initiated on January 15, 1985, had a total of 1,296 patients when accrual ceased on October 15, 1987. A subsequent trial of 5FU and levamisole, intergroup 0089, in colon cancer was designated as a high priority clinical trial in June 1989. This trial was a comparison of 5FU with low-dose leucovorin, 5FU with high-dose leucovorin, 5FU with levamisole, and 5FU plus low-dose leucovorin and levamisole. Accrual was initiated on September 15, 1988 and was revised and expanded on September 29, 1989. When accrual was completed July 30, 1992, 3,651 patients had been entered. Thus, the accrual rate of the intergroup 0089 high priority clinical trial is twice the accrual rate of the historical intergroup 0035 clinical trial. Dr. Coltman also described a Series I study of chemotherapy in lymphoma in which accrual rates increased after designation as a high priority clinical trial.

Dr. Coltman next addressed the problem of slow accrual in 3 of the 21 high priority clinical trials. Dr. Ron Natale, of the University of Michigan, has created a videotape to help patients understand the process of randomization in the intergroup 0088, Series I, neoadjuvant chemotherapy for bladder cancer clinical trial. This videotape was distributed to participating investigators in the trial to improve accrual, and there is some indication that the video has helped to increase accrual rates. Dr. Coltman noted that a Division of Cancer Prevention and Control (DCPC) Cancer Control Research Trial will examine the impact of this video on patient attitudes about entering this and other randomized clinical trials.

The second clinical trial with slow accrual rates is an NSABP study of adjuvant therapy for women with node negative breast cancers that are 1 centimeter or smaller is under examination. This study, Dr. Coltman said, is difficult to explain to patients; in the past 37 months, only 417 of the required 1,350 patients have entered the study. The third trial with slow accrual is EST 3886, a comparison of hormonal manipulation versus surgery for D1 prostate cancer with medical versus surgical castration as the randomization. Dr. Coltman said that in the past 53 months, only 91 of some 240 proposed patients have entered the clinical trial.

Dr. Coltman expressed hope that some of these trials will have increased accrual as a result of public awareness through such mechanisms as the videotape, but expressed doubt that accrual rates for the prostate trial will improve.

Dr. Coltman reported that the total budget of the cooperative group program is $76.95 million from the Cancer Therapy Evaluation Program (CTEP), with approximately $8 million being added through the DCPC, for a total cooperative group budget of $84.95 million. Based on the total patient accrual of 23,181 mentioned earlier, this amounts to a cost per patient of $3,665. In contrast, the High Priority Initiative has a budget of $1.78 million, with an input of $110,000 from the Office of Cancer Communication, for a total budget of $1.89 million. This amounts to a total cost per patient of $1,658, including the costs of administration, statistical center support, and capitation.

At the end of 1991, the Southwest Oncology Group included 125 investigators in 25 different institutions who accrued 583 patients in the first 3 years of the High Priority Initiative. Of these patients, 35 percent were minorities, and 67 percent were women. These patients were accrued through unfunded institutions and were reimbursed by capitation to the individual high priority institutions. The total accrual for the Southwest Oncology Group to the high priority clinical trials during this 3-year period was 3,452, including the 583 reimbursed patients, with the remainder coming from funded institutions.

Dr. Coltman suggested that an important byproduct of the intergroup program that has been enhanced by the High Priority Initiative is intergroup disease committee collaboration. Disease committee chairs and their associates from the major multidisciplinary groups meet regularly; through scientific and intellectual exchange, plans are formulated for multiple future studies and sharing and coordination of the statistical support for future intergroup clinical trials. He stated that this collaboration has led to an effective format for rapid accumulation of patients into important clinical trials.

Dr. Coltman concluded by reiterating that the high priority designation substantially enhances accrual to selected clinical trials and that this mechanism is also a cost-effective approach to increasing accrual rates.

Questions and Answers

Dr. Bettinghaus asked whether any data have been collected or if any evidence exists to indicate that the Cancer Information Service (CIS) has had an impact on the process of accruing patients to clinical trials. Dr. Coltman replied that, although there is no concrete evidence, accrual rates have increased and it is suspected that the CIS has contributed to this increase.

Dr. Calabresi asked for Dr. Coltman's interpretation of the lower accrual rate for the prostate cancer trial. Dr. Coltman suggested that the reason for the lower accrual is the randomization between surgical or medical castration. The decision, he said, is a difficult one for patients to make and for physicians to propose. Dr. Calabresi raised the subject of radiation, to which Dr. Coltman replied that he had introduced a radiation therapy clinical trial, recommended by the Consensus Conference, that has not been designated as a high priority trial. He observed that this trial died for lack of accrual, and added that it may ultimately be resurrected as a registration-only trial to allow patient outcomes to be followed in the absence of a randomized prospective approach.

Dr. Salmon agreed with Dr. Coltman's conclusion that the High Priority Initiative is cost-effective and valuable; however, he added that the cost per patient would be substantially higher without the infrastructure on which this program was built. He continued by asking to what extent Dr. Coltman thought physicians' biases affected the studies. Dr. Coltman said that the physicians often blame themselves because of their difficulty in being unbiased in the description of randomization. He expressed hope that the videotape will have an impact on this difficult question.

Dr. Wilson asked about the breakdown between prostate patients who receive medical castration versus surgical castration. Dr. Coltman replied that there are no data, but noted that the Southwest Oncology Group, in an intergroup setting, provided leadership for an intergroup trial looking at prostate cancer in which patients with Stage D disease were treated with an LHRH agonist with or without fludamide, which is an antiantigen. The trial, with no surgical treatment alternative, accrued very quickly. He added that clinical trials comparing LHRH agonist with castration are now ongoing to scientifically address the question.

Dr. Lawrence asked whether any evidence shows that the Cancer Centers have actually increased their participation in cooperative group trials. Dr. Coltman answered that there are a large number of NCI Cancer Centers in the cooperative group that are increasing accrual to clinical trials. He stated that one problem is the limited amount of financial resources available to accommodate more patients in clinical trials. Dr. Michael Friedman agreed that financial resources are limited, and added that the Cancer Centers also generate new ideas for pilot studies, conduct innovative small studies that then lead to major definitive group trials, improve and strengthen coordination and collaboration, and provide a smooth transition from small trials in individual institutions to major group trials.

Dr. Broder suggested that the peer review process could help ensure that institutions meet a number of criteria, especially interaction in the high priority clinical trials program, in order to be designated as Comprehensive Cancer Centers. He also recommended that the problem of prostate cancer clinical trials be addressed through several alternatives; for example, a massive education or outreach program could be implemented so that all medical and surgical disciplines speak the same language. He added that it might be necessary, though not desirable, to do a prostate cancer study in another country where health care practices would permit more reasonable accrual. Dr. Broder also asserted that any study requiring 7 to 8 years to finish should be reevaluated and possibly removed from the high priority clinical trials program. He said that it is no way to realistically explain why it would take 7 years to complete a high priority clinical trial study. One of the strengths of the high priority system, Dr. Broder continued, is that it has a reputation for getting things done quickly. He stressed the fact that interested lay parties must know that this mechanism moves quickly.

Dr. Coltman reemphasized that the ultimate decision to enter clinical trials rests with the patients. He added that their decisions are influenced by fiscal situations as well as their physicians' concerns.

XI. INTERNATIONAL ACTIVITIES: BILATERAL AGREEMENT UPDATE—DR. FEDERICO WELSCH

To introduce Dr. Welsch, Associate Director of NCI for International Affairs, Dr. Broder explained that NCI has a statutory responsibility not only to improve American

public health relating to cancer, but also to make a global impact on cancer-related health. International research and information exchange are clearly addressed in the language of NCI's authorizing legislation. NCI, as a result, plays an important role in international relations and supports the principle that science and the scientific method are appropriate avenues for solving problems.

Dr. Welsch began by explaining that NCI's international programs fall into three categories—grants and contracts, the visiting program, and other programs. The total cost of all international programs is approximately $20 million. Most of that amount is divided equally between grants and contracts and the visiting program; approximately $2 million are spent for other programs. These other programs, Dr. Welsch added, are the ones with which his office is involved.

Dr. Welsch described the types of activities that his office oversees, which include scientific exchanges, a workshop program, an information dissemination program, and an international relations program. Scientist exchanges range from less than 1 year to 4 years; Dr. Welsch noted that, during his tenure, the average number of short-term exchanges per year had increased from 58 in 8 countries to 250 in 46 countries; this 400 percent increase in the size of the program was accompanied by only a 100 percent increase in the budget. This was accomplished by asking colleagues in the extramural community to share costs.

In 1990, Dr. Welsch said, the Senate Appropriations Committee asked NCI to pursue international collaboration in cancer prevention more aggressively, with special emphasis on training and information dissemination. As a result, the three CD-ROM demonstration sites instituted in 1990 grew to 50 by 1992. Six other sites are being funded by NCI at minority institutions in the United States. In addition to their obligation to disseminate cancer information, these sites are also required to be involved in cancer prevention; a particular emphasis has been placed on prevention in the eastern European countries. Cancer information dissemination activities are being expanded to Latin America through electronic mail. Dr. Welsch predicted that in 3 to 4 years, electronic mail will replace CD ROM in many places.

Dr. Welsch described the international workshops program as an additional means of disseminating information to scientists at the forefront of their research fields. The number of workshops has increased from 18 in 1988 to 33 this year. Six to 10 Americans and 6 to 10 foreign counterparts are brought together to discuss confidential, unpublished research results. The most notable recent workshops have been meetings with Japanese scientists.

Questions and Answers

Dr. Salmon asked about specific areas in which electronic mail will replace CD-ROM technology. Dr. Welsch said that educational programs sponsored by the Pan American Health organization send information to locations such as the University of Santiago, Chile, via communication satellites. They transmit compressed data so that the use of satellite time is limited. In eastern Europe and the former Soviet Union, he added, telephone lines are so poor that CD-ROM will be required for a long time.

Dr. Broder added that CD-ROM technology has made a profound difference in many countries. He related the story of a Mongolian health minister who insisted that the

CD-ROM equipment be delivered by diplomatic courier to ensure its safe arrival, illustrating the emphasis placed on this service.

Dr. Broder suggested that another area worth investing in might be assistance to scientists in the Soviet Union, where it only costs $3,000 to $5,000 to fund a top-level scientist working on a cancer-related problem. This would not only have scientific value in itself, he added, but would also have a stabilizing effect on the scientific establishments of emerging countries.

Dr. Welsch noted that CD-ROM subscriptions cost $1,560 per year. Dr. Salmon asked which databases are included in the subscription; Dr. Welsch replied that the two major files included are PDQ and CANCER LIT.

XII. SUBCOMMITTEE REPORTS

Activities and Agenda Subcommittee (Working Group)

Dr. Calabresi announced that the Working Group of the Subcommittee on Activities and Agenda met at Chicago's O'Hare Airport on July 23rd. The three major topics of discussion included: the annual NCAB program review meeting; the regular NCAB meeting; and the scheduling of subcommittees. The annual NCAB program review meeting will convene in December, instead of November.

Dr. Calabresi referred members to the minutes prepared by Dr. Paulette Gray. He suggested that the upcoming program review meeting should provide Board members with an overview of the programmatic balance of the total NCI Program, both intramural and extramural, noting that this emphasis is important because the focus has traditionally been on the intramural program. He asked members to utilize handouts, mailed out in advance of meetings. Dr. Calabresi also asked that charts and structures be used to disseminate administrative information or explain organizational structures, stating that this would save time during meetings for division directors or their appropriate staff to summarize the key advances and programmatic thrusts.

The Board restructured regular NCAB meetings last year, Dr. Calabresi noted, to incorporate a 2-day format on Mondays and Tuesdays, so that persons covering long distances could travel on Sundays. A third day would be used, if necessary, for additional business. Because of a conflict with the American Society of Clinical Investigation meetings that are held on a Monday each May, the May NCAB meetings will begin on Tuesdays.

Following a discussion of the regular NCI Director's report to the Board, the committee reached a consensus that detailed budget reports are not necessary and voted to recommend that only significant budgetary changes should be discussed at the NCAB meetings. The committee also suggested that legislative presentations include only key issues, such as items of interest to the majority of members or issues for which action on the part of the Board is needed. The committee suggested that scientific presenters should include a mixture of extramural and intramural investigators, to give a more balanced picture of the national cancer program, and also suggested the inclusion of at least one foreign presentation.

The committee reaffirmed their feeling that Dr. Broder, Director of NCI, and Dr. Calabresi, Chair of the NCAB, should determine agenda items, with input from Board members. Dr. Calabresi observed that the number of subcommittees has increased during his tenure and suggested that some could be combined or phased out. He added that, in the future, subcommittee meetings will be scheduled to make it easier for members to move from one to another.

The committee requested a meeting with Dr. Broder during the fall to discuss optimizing the use of Board members' time and talents. Dr. Calabresi agreed to organize a meeting with Dr. Broder to address these issues.

Dr. Lawrence commented that, while he did not have a clear understanding of the Board members' role, he interpreted the role as two-fold—to serve as advocates and evaluators. He expressed his opinion that the Board should evaluate the National Cancer Program, rather than review operational details of the National Cancer Institute, and suggested that subcommittees should have the responsibility of identifying issue areas where additional research and education are needed.

Dr. Calabresi asked Dr. Broder to respond to Board members' desires to meet with him to discuss their concerns, including the issue of how their talents can best be utilized. Dr. Broder agreed that it is critical for the Board to identify and assess important, global topics for the National Cancer Program. He suggested that the Board should also advise the Institute concerning overall philosophy and principles. He added that, in his opinion, the best way to apprise the group about overall philosophy and principles is through the various subcommittees, which should utilize an analytical process, request additional data if necessary, and make recommendations to the full Board.

One area in which NCI could use some advice, Dr. Broder noted, is in developing a user-friendly way for clinical researchers to apply for R01s, the funding mechanism that is most likely to grow. He listed several other issues on which the Institute could use the Board's input, perhaps through subcommittees: how to involve surgical disciplines more frequently in clinical trials; expediting clinical trials in urology; training of scientists and clinicians and the numbers of specialists needed in each area; research that overlaps with other Institutes' concerns and requires interdisciplinary cooperation, such as brain tumors; and advice on how much emphasis to place on environmental carcinogenesis and chemoprevention.

Dr. Broder asked members to keep in mind that all meetings fall under the jurisdiction of the Federal Advisory Committee Act, which governs the administrative procedures of such meetings. He volunteered to assist in planning regional subcommittee meetings if the Board is interested in such arrangements.

Dr. Broder observed that the Cancer Centers Subcommittee is a good example of a subcommittee whose input has been very helpful to the Institute. Many of the subcommittee's ideas, he said, have been incorporated into operating policies, particularly those related to comprehensive criteria, geographical distribution, and planning grants.

Dr. Salmon observed that issues that have appeared before the Board often resulted in the presentation of resolutions to Congress and the development of policies that affect the way NCI does business. He suggested that it is the Board's responsibility to decide on areas in which to become involved.

Aging and Cancer Subcommittee

Ms. Deborah Mayer began by thanking Dr. Marvin Kalt, the Executive Secretary, for his support. The Aging and Cancer Subcommittee met to review the mission of the subcommittee, current aging specific research, and several current initiatives in ovarian, breast, and prostate cancer. They agreed on four specific areas of activity: scheduling a series of presentations by NCI divisional staff on cancers affecting the elderly and cross-divisional activities; inviting a liaison from the National Institute of Aging to explain their programs and identify common areas of interests; considering a conference to highlight potential areas for research; and encouraging subcommittee members to keep aging-related issues in mind when reviewing grants to help identify strengths and gaps.

Cancer Centers Subcommittee

Dr. Salmon said that the report of the Cancer Centers Subcommittee is a draft and that a final report will be submitted later for approval. The first issue discussed by the subcommittee, which had been raised at the Cancer Center's Workshop, concerned the review of the clinical research cores on grants for both clinical and comprehensive cancer centers. Problems arose because few applications were getting through the new R01 approach to clinical research. As the R01 mechanism becomes more effective, Dr. Salmon said, there will be easier-to-follow application guidelines.

The subcommittee discussed clinical protocols of a pilot/phase I nature. The Cancer Centers staff plans to look at these in an effort to maximize opportunities to provide the necessary justifications for a clinical research core; this could help spawn new pilot studies that will lead to larger studies in cancer prevention, treatment, and other areas.

Another item discussed was the use of Cancer Center Support Guidelines (CCSG) funds for institutions expanding outside the primary area served by either a clinical or comprehensive Cancer Center. No consensus could be developed on this topic and NCI staff were asked to pursue it further with the Subcommittee and the full NCAB in the future. It was concluded that the draft committee report would not be voted on until members of the subcommittee had time to review the report. Dr. Broder noted that collegiality among centers carrying the NCI designation is an issue on which NCI would like feedback from the Board.

Dr. Salmon noted that some centers considered it a hardship to report data requested for a database. The Cancer Centers staff, he said, could work closely with the centers to avoid any undue hardship in data collection. Also addressed at the subcommittee meeting were quality of life issues—pain management, rehabilitation, and psychosocial services—raised at the last NCAB meeting. The general opinion was that, while these areas are important and appropriate and should be addressed by all clinical and comprehensive cancer centers, the NCI should continue emphasizing their importance and constantly encouraging progress, rather than developing specific requirements that might be impossible to meet and interpretated as micromanagement of institutions.

Environmental Carcinogenesis Subcommittee

Dr. Becker said that the Environmental Carcinogenesis Subcommittee meeting focused on studies of chemical carcinogens in the environment. A few years ago, he related, Dr. Takashi Sugimura in Japan reported on a spectrum of potent mutagens and carcinogens found in cooked foods, especially meat, that were later identified as heterocyclic aromatic amines (HAAs). Questions have since arisen regarding their human exposure and significance in human carcinogenesis.

Dr. Elizabeth Snyderwine of NCI's Division of Cancer Etiology explained to the subcommittee that the products usually appeared as a result of the heating of muscle tissue; and studies have shown that they result from the heated interaction of creatinine and common amino acids. Approximately 17 heterocyclic aromatic amines have been discovered in cooked meats, fish, and chicken; they have been associated with a wide spectrum of cancers in animals. Dr. James Felton, Senior Scientist of the Lawrence Livermore Laboratory, told the subcommittee that he has isolated and identified several HAAs and although they occur to the greatest extent in cooked fish, fowl, and meat, especially when cooked at high temperatures, they do occur in other foods but to a lesser extent. Both presenters pointed out that there are simple procedures for reducing the amount of mutagens in cooked meat, fish and fowl; for example, brief pre-exposure of meat to microwaves not only reduces the fat content, but also results in a lower amount of the most potent mutagens.

Dr. Scheuplein from the Food and Drug (FDA) reported to the subcommittee that the FDA has no regulatory authority over products described as "natural foods." Dr. Scheuplein also revealed that many food enhancers, such as artificial colors, contain compounds that could lead to the production of heterocyclic aromatic amines. While he was unwilling to recommend or state his opinion of the risk for human exposure, he did say that some of the heterocyclic aromatic amines in foods were more potent as mutagens and possibly carcinogens than the synthetic compounds that are not allowed as food additives.

Dr. Salmon asked whether heterocyclic aromatic amines were found in processed foods. Dr. Becker replied that the compounds were found in foods after they were cooked. Dr. Adamson added that the compounds can be found in any meat that has been fried or broiled at high, but normal, cooking temperatures. Meat extracts sometimes used to flavor various foods may also contain these HAAs. Dr. Becker noted that anticarcinogens may counter some of the compounds found in foods, as noted in the earlier presentation by Dr. Wattenberg.

Information and Cancer Control for the Year 2000 Subcommittee

Ms. Marlene Malek reported that the Subcommittee on Information and Cancer Control met and conducted a concept review for seven contracts for the NCI Office of the Director. The projects, which are in the process of being recompeted, received unanimous approval; they are listed in the subcommittee's minutes.

The subcommittee discussed a suggestion to sponsor a second round of public hearings similar to those held in 1987 and 1988. Ms. Malek explained that the first event consisted of five hearings designed to showcase local activities that supported NCI cancer control objectives in prevention and screening. Eight recommendations for private sector expansion were provided in the NCAB final report on the hearings. The proposed second

round of public hearings would enable the NCAB to assess the implementation of those eight recommendations. The subcommittee proposes to the Board that four or five hearings be held in late 1994 and early 1995.

The second project discussed by the subcommittee is a second round of regional breast cancer summits. The Komen Foundation cosponsored the 1992 regional summits and is interested in cosponsoring another round. The subcommittee voted to initiate planning for another set of regional summits focused on increasing breast cancer screening. Competition would be open to all NCI-designated cancer centers and sponsorship would be broadened to include community-based organizations and voluntary groups. Ms. Malek concluded by reporting that the subcommittee would like to refer the proposals for the hearings and the summits to the NCAB Subcommittee on Interaction with Voluntary Organizations for its concurrence and assistance.

Interactions with Voluntary Organizations

Dr. Lawrence began his presentation by paraphrasing the charge given to the Subcommittee on Interaction With Voluntary Organizations—to explore, improve, and advance interactions and collaborations with voluntary organizations that share the anticancer goals of NCI. After discussions with Drs. Broder, Calabresi, and Freeman, the committee identified voluntary organizations that share NCI's goals. The group decided that it would be very beneficial to work with health organizations that include both lay and medical membership.

Dr. Lawrence reported the committee's interest in working with voluntary health organizations on the Breast Cancer Summit mentioned by Ms. Malek. Drs. Broder and Freeman have also suggested inviting outside voluntary organizations to participate in the panel scheduled for October 5th. Dr. Lawrence listed several organizations that have been asked to speak, including the American Cancer Society, the Leukemia Society, and the Damon Runyan Cancer Research Fund.

At its next meeting, the subcommittee will review the outcomes of the cancer panel chaired by Dr. Freeman. Outside organizations will be invited to subcommittee meetings and to assist with the planning of the cancer summits. The subcommittee members felt that the preliminary planning meetings would be an effective mechanism for increasing the level of interaction between voluntary organizations and the committee.

Minority Health Research and Training Subcommittee

Ms. Malek summarized the Minority Health Research and Training Subcommittee meeting; NCI staff presented an overview of training programs and activities. Other programs discussed included the minority recruitment plans, minority health professional training initiatives, and the recent NCI workshop on Native American training opportunities. The committee discussed the need for outreach activities to specific minority populations designed to ensure equity for minority research and training activities.

Ms. Malek cited four recommendations made by the subcommittee: interaction and coordination with other NCAB subcommittees; early release of information on NCI initiatives, objectives, and budgets; dissemination of information on research training to

minority schools and leaders; and ongoing outreach initiatives to minority students and leaders.

Planning and Budget Subcommittee

Dr. Bettinghaus highlighted key agenda items discussed during the Planning and Budget Subcommittee: an update on the NIH strategic plan, "Advantage America"; a draft document about the R21 grant mechanism; and the P01 grant mechanism, a topic that required a great deal of discussion by the subcommittee. Dr. Kalt presented an interim report on the grant's fiscal information and how the grant is being used.

Dr. Bettinghaus reported that the NCI working group has been asked to present its review and recommendations on the overall operation of the program grant mechanism at a future subcommittee meeting. He added that the subcommittee would like a recommendation from the working group establishing a separate study section to review the P01 mechanisms.

Dr. Salmon asked Dr. Broder whether the interactive R01s and P01s that are oriented toward clinical activities might have NCI-chartered study sections. Dr. Broder responded that, ideally, groups of interactive R01s would always be reviewed together in the same DRG study section. He and Dr. Kalt have discussed the matter and plan to give a report to the NCAB and the Boards of Scientific Counselors once a determination is made. The goal is to develop a system with the right balance. The first batch of interactive R01s will be reviewed for the January 1993 NCAB meeting.

Women's Health and Cancer Subcommittee

Ms. Johnson stated that the Women's Health and Cancer Subcommittee welcomed Dr. Kathy Albain, Medical Oncologist at the Loyola University Medical Center, who attended the subcommittee meeting. Dr. Albain also chairs the Committee on Women's Health (CWH), of the Southwest Oncology Group (SWOG). During the meeting, Dr. Albain explained that the focus of the CWH is to explore gender-specific cancers and gender differences in cancers not unique to one sex. The CWH also pays close attention to the number of women accrued to clinical trials and encourages technology transfer of research findings to all women. The CWH includes SWOG members from other committees and has both an internal and external advisory board.

Dr. Albain discussed CWH's monitoring of accrual to trials through the development of standard face sheets containing information on socioeconomic status, insurance, and gynecological history. The subcommittee also discussed SWOG's interaction with breast cancer patients. There is a strong interest in and need for research on the health effects of reconstructive implants in breast cancer patients.

During the meeting, Dr. Becker advised the CWH to focus on innovative public health topics not being addressed by other researchers, especially those that relate to the effects of socioeconomic and minority status. Asked how NCI could facilitate the networking needed, Dr. Becker stated that private foundations and development offices at participating institutions would be likely sources of support for program development.

Ms. Johnson noted the presence of Dr. Vivian Pinn, Director of NIH's Office of Research on Women's Health, at the meeting. The office has released its report on the

1991 Conference on Research Opportunities in Women's Health. The subcommittee will discuss significant parts of the report, in particular the information on malignancy, at its next meeting.

XIII. NEW BUSINESS — DR. PAUL CALABRESI

Dr. Salmon asked about the NCI's view on the evolution of the issues of conflict of interest. Dr. Broder stated that the Office of Government Ethics is reviewing the issue. The Ethics Reform Act of 1989 proscribed honoraria on a government-wide basis; Government employees cannot receive honoraria for talks, but can still conduct consultations where no conflicts of interest exist.

XIV. ADJOURNMENT—DR. PAUL CALABRESI

There being no additional business, Dr. Calabresi thanked the group for their participation and adjourned the 83rd National Cancer Advisory Board proceedings at 2:09 p.m., September 22, 1992.

_____ _____

Date Dr. Paul Calabresi, Chairman

MINUTES

NCAB Subcommittee on Interactions with Voluntary Organizations
6 p.m., September 21, 1992

NCAB Members Present: Dr. Walter Lawrence, Jr., chairman; Dr. Paul Calabresi; Dr. John R. Durant; Mrs. Brenda L. Johnson; Mrs. Marlene A. Malek; Ms. Deborah Mayer; Dr. Harold Freeman (Ad Hoc). Executive Secretary: Mr. Paul Van Nevel

1) Dr. Lawrence said that the subcommittee's charge is to explore, improve, and advance collaborations with voluntary organizations that have missions similar to that of the National Cancer Institute. There are a number of areas where collaboration takes place, or could be improved. These include the ASSIST program, Regional Breast Cancer Summits, the Tamoxifen trial, research funding, general information and education programs, and relationships between cancer centers and local chapters of voluntary organizations.

2) Dr. Harold Freeman reported that the President's Cancer Panel will meet October 5 to explore inter-relationships on the role of voluntary organizations. Large national voluntary organizations will testify. He said there needs to be better coordination between the government and private sector, and that better collaboration could help move the results of research into the neighborhoods. Members of the committee agreed, and said that better collaboration could avoid duplication and lead to complementary activities, allowing dollars available to all groups to go further.

3) The group discussed future activities. It decided that it would concentrate first on collaborations with voluntary organizations, as opposed to scientific societies.

Discussion concentrated on the agenda for the subcommittee's December meeting. That meeting will open with a report from Dr. Freeman on the President's Cancer Panel meeting of October 5. This will provide a needed overview of the inter-relationships of voluntary organizations. The agenda will then concentrate on planning, in collaboration with the Subcommittee on Information and Cancer Control, for a second set of Regional Breast Cancer Summits. The goal will be to broaden sponsorship and participation by a number of other organizations. In the past, the Summits have been sponsored by the NCI and the Komen Foundation. The committee will invite the American Cancer Society and the National Coalition for Cancer Survivorship, along with the Komen Foundation, to attend the December meeting to discuss collaboration on future Summits. The group believes that the involvement of additional sponsors will enhance the effectiveness of the Summits by focussing the efforts of several organizations on a common purpose.

If it is decided to hold Public Participation Hearings in 1994-1995, as suggested by the Subcommittee on Information and Cancer Control, the Subcommittee on Interactions with Voluntary Organizations would work to foster participation of other organizations.

Another potential agenda item for the Subcommittee is a followup session on ASSIST, bringing together both ACS and NCI staff to review the collaborative effort. Other areas that cut across activities of many organizations, including pain control, rehabilitation, and prostate cancer, may also be explored.

MINUTES

NCAB Subcommittee on Information and Cancer Control
7 a.m., September 21, 1992

NCAB Members Present: Mrs. Marlene A. Malek, chair; Ms. Zora K. Brown; Dr. Erwin P. Bettinghaus; Dr. Walter Lawrence, Jr. Executive Secretary: Paul Van Nevel.

1) The Subcommittee conducted a concept review for seven contracts from NCI's Office of the Director[1]. All are for projects being recompeted; none is for new work. All received unanimous approval. They are:

- ADP Support Services for Cancer Information Dissemination.
- Cancer Information Dissemination and Analysis Center--Cancer Diagnosis and Therapy.
- Support for NCI Local Area Networks
- ADP Support Service for the Division of Extramural Activities
- ADP Support Service for the Grants Administration Branch
- International Scientist-to-Scientist Information Exchange Program
- Latin American Cancer Research Information Project

2) The Committee also considered possible projects it might undertake.

First, an idea proposed by Dr. Bettinghaus and others was to hold a second round of NCAB Public Participation Hearings to followup on NCAB Hearings held in 1987 and 1988. The first set of 5 hearings was designed to showcase excellent local activities in support of NCI's cancer control objectives, particularly in prevention and screening. The hearings also were designed to identify gaps, where more needed to be done. The NCAB final report on the hearings made eight recommendations for expanding private sector cancer control activities. A second round of hearings would enable the NCAB to see whether or not the Board's recommendations were implemented, and to once again showcase excellent community activities and to identify gaps.

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[1] In July, 1992, a mail ballot of the subcommittee was conducted for the purpose of obtaining concept review approval to extend, in time and amount, an ongoing contract procurement entitled "Cancer Prevention Awareness: The Black College as a Resource." A majority of the subcommittee approved the request for a 2-year extension of this initiative. The documents detailing the request for concept approval are attached as an addendum to these Minutes.

The first set of hearings cost about $300,000, took a year to plan, and required the participation of all the NCAB members. The hearings were held in 5 cities, each hosted by a Board member. The host, with NCI assistance, arranged the local hearing agenda.

A motion was made and approved that the subcomittee propose to the full Board that another set of four or five hearings be held in late 1994 and early 1995 (fiscal year 1995). The timetable would allow enough time for planning and budgeting. The project would require involvement of the whole board in both the planning and conduct of the hearings.

Second, the Subcommittee considered the advisability of holding a second round of Regional Breast Cancer Summits. Evaluation data on the eight Summits held in 1992 are not yet available, but Mrs. Malek--who has attended most--said that preliminary reports are very promising, and it appears the Summits were very successful. It is known that the Komen Foundation, cosponsor with NCI of two national Summits and the 1992 regional Summits, is interested in cosponsoring another round of regional meetings.

After discussion, including whether to broaden the Summit topic beyond breast cancer, the Subcommittee voted to initiate planning for another round of regional Summits, concentrating again on increasing breast cancer screening. The Subcommittee favors opening competition to all NCI-designated cancer centers and not limit the grants to Comprehensive Centers, as was the case in 1992. The Subcommittee also suggests that consideration be given to broadening sponsorhip by including community-based organizations such as the American Cancer Society and other voluntary groups.

The committee suggested that the proposals for both the Hearings and the Regional Summits be referred to the NCAB Subcommittee on Interaction with Voluntary Organizations for concurrence and help.

Finally, the Subcommittee respectfully requests that it not have to meet at 7 a.m. anymore.

Attachment

NATIONAL CANCER ADVISORY BOARD

Subcommittee on Information and Cancer Control for the Year 2000

REQUEST FOR CONCEPT APPROVAL

BACKGROUND:

In late 1986, the Comprehensive Minority Biomedical Program (CMBP) of the Division of Extramural Activities (DEA), jointly with the NCI Office of Cancer Communications (OCC), issued a solicitation for proposals to utilize the Historically Black Colleges and Universities (HBCUs) as a resource for heightening the awareness of those in their respective communities or regions through the effective dissemination of information about cancer. The concept for that procurement was approved by the National Cancer Advisory Board at this meeting in October, 1986 (See attachment.). For various technical reasons, related primarily to obtaining PHS approval for restricting eligible offer or institutions to HBCUs, actual awards did not take place until June of 1989. At that time, two contracts were awarded for a five year period.

ISSUE:

The Statement of Work for these contracts included three phases, the first of which, "Planning and Study Design", has been considerably protracted in time (> 2 years as opposed to a projected 9 months) in the case of both awardees. In large part, this occurred because of the requirement that clearance by the Office of Management and Budget must be obtained for the various survey instruments which are essential to the conduct of the second phase of the contract activity. Retaining the institutional staff and infrastructure put in place for this activity, during the extensive revision and reformatting of these documents, has necessitated repeated extensions of Phase I, as well as continued fiscal support at a maintenance level, in anticipation of eventual OMB clearance.

We are now given reason to expect that OMB approval of both the contractor institutions' submissions will be cleared by OMB before the end of calendar 1992. At that point, we propose to extend the period of performance as well as add additional funds so that the contractors might immediately implement Phases II and III. However, we have been advised by our Research Contracts Branch that "concept review...is required when extending the contract six months or more...[and] whenever the estimated cost of the contract is to be increased by 50% or more of the annualized funding level." This concept review must be conducted by the cognizant Advisory Board (or Board Subcommittee).

NATIONAL CANCER INSTITUTE
DIVISION OF EXTRAMURAL ACTIVITIES
COMPREHENSIVE MINORITY BIOMEDICAL PROGRAM

Concept Review - July 1992

Project Title: Cancer Prevention Awareness: The Black College as a Resource

Type of Award (Check):

_____ New Contract
_____ Re-competition
_____ JOFOC
_____ Interagency
__X__ Extension

Research/Resource (Check):

__X__ Research
_____ Resource

Current Contract Number/Title: N01-CO-94393
N01-CO-94394

Current Contract Expiration: June 30, 1995
Contract Expiration with Extension: June 30, 1997

Total Dollars Obligated by Phase

	Number of Years	Funding
Phase I	2.5	2,233,667
Phase II	4.5	3,803,444
Phase III	0.5	248,889

New dollars requested by Phase

Current Negotiated Funding Amount **	Proposed Funding Level *	Difference
Phase II		
3,803,444	5,056,771	1,253,327
Phase III		
248,889	342,004	93,215

Total estimated increase: 1,346,542

ACTION:

Action:

We are requesting approval for an extension of this initiative by members of this subcommittee for a period of two years (from July 1, 1995 to June 30, 1997).

* The dollars in the proposed column are derived from the recent budget estimates received from the subject contractors.

** The dollars in the current negotiated represent dollars already set aside for these contracts.

The total estimated increase represents dollars in addition to the set aside for the prospective fiscal years.

September 21, 1992

SUBCOMMITTEE
ON
MINORITY HEALTH, RESEARCH AND TRAINING

NCI staff presented an overview of all NCI minority health, research and training programs, activities and initiatives. This included specific minority programs such as the MARC, MBRS, supplements to research project grants, the Science Enrichment Program, and the new Predoctoral Minority Fellowships.

Other research training programs with minority components were also presented such as the minority recruitment plan which is a required component of all institutional research training awards, and several cancer education programs directed at minority students and populations.

The Subcommittee also discussed the Minority Health Professional Training Initiatives aimed at developing and strengthening faculty and infrastructure at minority health professional schools.

The recent NCI sponsored workshop on **NATIVE AMERICAN TRAINING OPPORTUNITIES: STRATEGIES FOR THE FUTURE** was summarized and the subcommittee was informed of NIH committees currently conducting an evaluation of all NIH minority programs.

The committee discussed the need for more directed outreach activities to specific minority populations with the goal of achieving equity for minority research and training activities in the mainstream NCI programs. The following recommendations were made:

1. Interaction and coordination with other NCAB subcommittees, e.g. Information and Cancer Control, to disseminate health, and research training information to minority populations.

2. Early release of information on NCI initiatives giving a listing of objectives, budget, etc. once or twice a year.

3. Information on all research training mechanisms and cancer education programs should be given to all appropriate minority schools and leaders.

4. Ongoing outreach initiatives should be used as effectively as possible to specifically identify minority students and researchers using a series of national conferences and other means.

National Cancer Advisory Board

Subcommittee on Planning and Budget
Minutes of Meeting

September 21, 1992

The meeting was called to order at 1:00 PM by the Chairman, Dr. Erwin Bettinghaus. The following subcommittee members were present: Drs. John Durant, Bernard Fisher, Samuel Wells, Jr., Paul Calabresi and Ms. Deborah Mayer. Subcommittee members Drs. David Bragg and Howard Temin were unable to attend. NCAB members Drs. Walter Lawrence, Jr., Sidney Salmon and Charles Wilson, President's Cancer panel member Dr. Henry Pitot, Dr. Broder, members of the NIH P01 Working Group, and other NCI staff were also in attendance. Ms. Cherie Nichols served as Executive Secretary.

NIH Strategic Plan

Ms. Nichols presented an update on NIH Strategic Plan activities and distributed the current "framework document" containing the mission, goals, philosophy and objectives of the Plan, and Dr. Healy's article from the July 17 issue of Science. The Chair asked Ms. Nichols to keep the Subcommittee informed of any further developments.

Innovative Research Grant Mechanism

Ms. Bynum announced that the NIH draft document that adapts the R21 grant mechanism to support innovative research, which Dr. Healy supports and planned to use part of the NIH Director's discretionary funds to make awards, has been tabled. Further consideration of an innovative research mechanism may be addressed by the Subcommittee at a future meeting.

1993 Budget

Hard copies of Dr. Broder's slides on the 1993 budget were made available to the Subcommittee members.

P01 Grant Mechanism

At the previous Board meeting, NCI staff were requested to gather data and review the use of the program projects by the NCI. Dr. Kalt presented slides which provided the fiscal information relevant to the Board's concerns--the use of NCI P01 grants for translational and basic research and the overall use of P01s at the NIH. As of June 1, 1992, 72% of P01 dollars were awarded for translational project grants. Of the 151 grants awarded, 73% are funded in rank order and 27% by exception. It was noted that, within P01s, the individual project grant average unit cost is about the same as a R01. Responding to a question about

capping the number of projects in the P01, Dr. Broder emphasized that peer reviewers will be asked to consider the appropriateness of the number of projects to the scope of the proposal. He advised investigators to chose the number of projects with great care and to scientifically defend it. At present, there continues to be no specified cap, but peer review will take the number of projects into account, where appropriate. After discussion of the data presented, Dr. Bettinghaus asked the Subcommittee members to consider Dr. Broder's earlier request to provide advice to the NCI on: the percent of dollars to be allocated for P01s from the RPG pool; the mix of basic and translational dollars in the P01 portfolio, and the provision of a monetary cap for program project grants. The NCI working group will present its review and recommendations on the operation of the program project grant mechanism at a future meeting.

There being no further business, the meeting was adjourned at 2:00 PM.

Erwin Bettinghaus, Ph.D
Chairman

NATIONAL CANCER ADVISORY BOARD
SUBCOMMITTEE ON WOMEN'S HEALTH AND CANCER

September 21, 1992 Minutes

The meeting was called to order at 2:05 p.m. by the Chair, Mrs. Johnson. Ms. Schneider introduced the speaker, Kathy Albain, M.D., who is a medical oncologist at the Loyola University Medical Center in Chicago and Chair of the Committee on Women's Health (CWH) of the Southwest Oncology Group (SWOG).

Dr. Albain stated that the SWOG CWH focuses on cancers that are unique to women; are more prevalent or are an increasing problem; and on cancers for which there are different risk factors, interventions or outcome in men and women. The CWH pays particular attention to accrual of women to trials, representation of minority and disadvantaged or underserved women in trials, and technology transfer to all women, as well as broader public health issues. CWH made a presentation in May 1992 as part of the site visit for the SWOG grant renewal application.

Statistical analyses of SWOG data to identify gender and racial/ethnic differences have produced some interesting findings. For example, women smokers with Stage 1 lung cancer are more likely than men to stop smoking and black women with ovarian cancer have a shorter survival than white women, controlling for stage at diagnosis and treatment.

CWH links SWOG members from committees for specific diseases, cancer control, nursing and data management with the public health arena. It has external and internal advisory

boards with active participation by the CWH. CWH members can chair a study, co-chair a study, or participate in a large statistical study with a disease-specific committee and the statistical center. Dr. Albain described activities in four areas:

A. Monitor accrual to trials and propose strategies to remedy any deficiencies. New standard face sheets have been developed for trials that include information on socioeconomic status (SES), insurance, and gynecologic history.

B. Investigate special problems of gender-specific cancers, such as initiation of a new study on the treatment of chemotherapy induced menopause and examination of the black/white survival differences for ovarian cancer.

C. Sponsor studies of gender differences in cancers that affect both men and women.

D. Undertake new initiatives in the public health arena such as developing new approaches to technology transfer as exemplified by improving recruitment to trials, and by care for underserved women.

The involvement of lay women who have had an experience with cancer in the activities of the group is also being explored.

Dr. Albain described other plans and objectives of the CWH and stated that resources are needed to carry these out. The CWH did receive one supplement this year from the Office of Research on Women's Health (ORWH) for a project that will pay salary for a data manager for one year. The Chair thanked her for a very interesting presentation and opened the meeting for questions.

The suggestion was made that through its therapeutic breast cancer trials, SWOG has an opportunity to reach the relatives of breast cancer patients and encourage them to have screening mammograms. It was noted that there are some indications that such women are less compliant with screening recommendations, perhaps out of fear.

A question was asked about how SWOG is interacting with breast cancer patients since the NCI Cancer Therapy Evaluation Program is looking at ways to involve cancer patients in NCI activities. Dr. Albain described two approaches:

- Involvement of SWOG staff, data managers and others, who have had a personal experience with breast cancer and participated in a clinical trial.

- Inclusion of lay cancer patients in this capacity as well.

In both cases, patients would be asked to participate in meetings, could see the protocol concepts, and comment on the informed consent document.

A suggestion was made that the CWH consider studies of the effects of implants in breast cancer patients who have them for reconstruction. There is a strong interest in studying the health effects of implants in breast cancer patients. Because the numbers are small (80% of implants are for augmentation), it is very hard to do the research.

Dr. Becker advised the CWH to focus on topics not being adequately studied by others. Many investigators are studying genetic markers, but many fewer are looking at the important public health issues, the effects of socioeconomic status, and minority issues.

Mrs. Brown commended the CWH for involving patients in writing protocols. Many informed consent documents scare people, particularly patients at lower educational and SES levels, leading to decreased accrual of these patients. She also commented that minority patients are more likely to trust information received from a person of the same racial/ethnic background. There is a need to coordinate information efforts and get the information out in a way that people will volunteer rather than having to be recruited. Dr. Albain commented that a lot of networking is required and she has been learning a lot this year from talking with people from fields other than her own.

Ms. Schneider asked whether, apart from resources Dr. Albain indicated were needed, there were other things NCI could do to facilitate the networking needed. Suggestions were made regarding contacts with the Black, Hispanic and Appalachian Leadership Initiatives on Cancer. Dr. Becker advised that support for early program development for socially

valuable activities might be more likely to come from a private foundation and that the development offices at the participating institutions should be consulted for recommendations. Mrs. Johnson again thanked Dr. Albain and introduced Dr. Vivian Pinn, Director of the NIH Office of Research on Women's Health. Dr. Pinn said that accrual of women to trials will be a major focus for her office in 1993.

Mrs. Johnson then asked for suggestions for the agenda for future meetings. It was announced that the report of the 1991 conference on Research Opportunities in Women's Health was released today. The Executive Secretary was asked to send copies of the malignancy chapter to the Subcommittee members. The recommendations of the malignancy panel will be scheduled for future discussion.

The meeting adjourned at 2:55 p.m.

Brenda Johnson

Mrs. Brenda Johnson
Chairperson

Subcommittee Members Present:
Mrs. Brenda Johnson, Chair
Dr. Fred Becker
Mrs. Zora Brown
Iris J. Schneider, Executive Secretary
Mrs. Marlene Malek

Others Attending:
Nancy Rhodes, Nova Research
Edward Trimble, NCI
Mary McCabe, NCI
Lea Sekely, NCI
Michael Friedman, NCI
Elizabeth Moore, NCI
Carol Curtiss, ONS
Elizabeth Anderson, NCI

Susanne Haynes, NCI
Daniel Ihde, NCI
Faye Austin, NCI
Gretchen Hascall, NCI
Astrue Bader, consultant
Vivian Pinn, ORWH

R. Davilene Carter, AACE
Ruthann Giusti, NCI
Elaine Lee, NCI
Carrie Hunter, ORWH
Sheri Douphe, ORWH

Minutes

Subcommittee on Environmental Carcinogenesis
The National Cancer Advisory Board

September 21, 1992

Members Present

Dr. Frederick Becker (Chairman), M.D. Anderson Cancer Center
Dr. Erwin Bettinghaus, Michigan State University

Dr. Richard H. Adamson (Executive Secretary), NCI

Other NCAB Members Present

Dr. Lakshmi Mishra, Consumer Products Safety Commission
Dr. Ralph Yodaiken (Department of Labor)

Guests

Dr. James Felton, Lawrence Livermore National Laboratory
Dr. David Howell, NCI
Dr. Robert Scheuplein, Food and Drug Administration
Dr. Susan Sieber, NCI
Dr. Elizabeth Snyderwine, NCI

The Subcommittee on Environmental Carcinogenesis, National Cancer Advisory Board (NCAB) met on September 21, 1992, in Conference Room 9, Building 31, National Institutes of Health, Bethesda, Maryland.

After opening the meeting and welcoming those present, Dr. Becker announced that any members of the public wishing to express views regarding any items to be discussed could do so by writing to the Executive Secretary of the Subcommittee, Dr. Adamson, within 10 days after the meeting. He added that any statements by members of the public would receive careful consideration.

Dr. Becker noted that laboratory and epidemiologic studies continue to provide evidence strongly suggesting that dietary factors contribute to a substantial portion of human cancer. The epidemiologic evidence is from variations in cancer incidence and mortality rates between countries, within a country, and among migrants to a new country whose cancer rates become progressively more like those of the indigenous population as they become increasingly assimilated into it.

Dr. Becker pointed out that laboratory studies have identified compounds in foods that are tumor promoters, others that are carcinogens, and still others that inhibit carcinogenesis. The subject of this meeting, heterocyclic aromatic amines, attracted attention several years ago when Dr. Sugimura and

his colleagues in Japan found that mutagenic compounds were found in broiled foods. Since that time, further studies by Dr. Sugimura, Dr. James Felton and colleagues at the Lawrence Livermore Laboratories, scientists in Europe, and several scientists at the NCI have helped clarify this field. Today, about 17 heterocyclic amines have been isolated and identified from cooked fish, beef, fowl, and from beef extract, and some studies have been performed on their biological and carcinogenic activity.

After Dr. Becker concluded, Dr. Adamson introduced Dr. Elizabeth Snyderwine of NCI's Division of Cancer Etiology Laboratory of Experimental Carcinogenesis, who presented an overview of heterocyclic amines occurring in cooked foods. Dr. Snyderwine said that there are many dietary components which may influence cancer. These include such macroconstituents as total caloric intake, fats and other lipids, protein, dietary fiber, and alcoholic beverages; and microconstituents, such as vitamins, minerals, food additives and contaminants; and mutagens/carcinogens in food. The latter include naturally-occurring carcinogens and those introduced during cooking.

Dr. Snyderwine said it has long been known that cooking produces mutagens. These fall into two large categories; the benzpyrenes, resulting from exposure of fats to very high temperatures, and the heterocyclic amines, resulting from cooking of proteins and their constituents. After she identified a number of heterocyclic amines and their sources, Dr. Snyderwine observed that heterocyclic amines in cooked food fall into several groups: the nonimidazole-type heterocyclic amines, including the amino acid pyrolysates and the protein pyrolysates, and the imidazole-type heterocyclic amines, including the quinolines, the quinoxalines, and the pyridines. The imidazole-type heterocyclic amines are found in a wide variety of cooked beef and fish commonly consumed in the United States, while the nonimidazole-type are not commonly found in the Western diet, because they are formed at temperatures higher than those ordinarily used in most Western cooking. The imidazole-type heterocyclic amines have been detected in fried ground beef; broiled sardines; broiled salmon; smoked, dried mackerel; beef extract; fried codfish; and a number of other foods.

There are several critical factors in the formation of heterocyclic amines in cooked foods. Of great importance is the composition of the food (muscle-derived meats generate the highest quantity), including the specific proteins, peptides, amino acids, creatinine, and reducing sugars found in it. Also extremely important are the cooking conditions, including the temperature, duration of cooking, water content, and method of cooking. Broiling and frying, which usually involve the highest temperatures, create the highest quantities of heterocyclic amines, and a substantial number of these are created by the high-temperature reaction between creatinine and certain amino acids.

Dr. Snyderwine pointed out that the mutagenic activity of most of the heterocyclic amines in the Ames assay is substantially higher than many typical carcinogens such as aflatoxin. In addition, many of the imidazole-type heterocyclic amines have proven to be highly carcinogenic in rats and

mice, usually affecting the liver, but also affecting the small and large intestine, the lung, the mammary gland, the skin, the lymphatics, and other organ sites. One of this class of heterocyclic amines, a quinoline known as IQ, has also been found in ongoing studies to be a potent liver carcinogen, inducing hepatocellular carcinoma in Cynomolgus monkeys. Also of interest, another compound called PhIP, 2-Amino-1-methyl-6-phenylimidazo [4,5,b]pyridine, produces only colon and mammary gland tumors in rats.

Dr. Snyderwine explained that the carcinogenicity of the heterocyclic amines depends upon metabolic activation in the body and outlined some of the molecular pathways by which this activation takes place. She also summarized work elucidating the adducts formed by the interaction in the monkey between metabolites of the heterocyclic amines and the animal's DNA.

Dr. Snyderwine concluded her talk by noting that there are several methods by which the formation of heterocyclic amines can be minimized when cooking food. They are:

1. Stew, boil, and poach meat more often.
2. Vary the method of cooking meat and fish.
3. Microwave fish and poultry more often.
4. Eat beef cooked medium instead of well done.
5. If microwaving chicken or pork, microwave before barbecuing, and pour off the juices resulting from microwaving before placing the meat on the barbecue.
6. If making gravy, do not allow meat drippings to become dry before preparing the gravy.

The next speaker was Dr. James Felton of the Lawrence Livermore National Laboratory, who discussed preliminary risk assessment of heterocyclic amines. Dr. Felton explained that epidemiologic studies have shown a correlation between the intake of red meat and the incidence of colon cancer in many countries, noting that both fat intake and the intake of heterocyclic amines may be influential in this connection. Dr. Felton pointed out that cooking of beef, poultry, and fish at the same temperature produces essentially the same specific heterocyclic amines at the same times during a 10-minute cooking period; and at the end of 10 minutes, most of the heterocyclic amines that will be formed have been formed. However, the generation of heterocyclic amines is not always linear over all times and temperatures; high temperatures, such as 230 degrees, may produce 3 nanograms of heterocyclic amines per gram of meat after 6 minutes and 21 nanograms after 10 minutes; 190 degrees may produce 2 nanograms after 6 minutes and 5 nanograms after 10 minutes; and 150 degrees may produce 0.5 nanograms after 6 minutes and 1 nanogram after 10 minutes.

Dr. Felton presented data showing the dramatic decrease (90%) in the mutagenic activity of meats to be grilled or fried if they are first microwaved and the resultant juices discarded. He explained that this gets rid of some of the meat's fats and creatinine, which would otherwise contribute strongly to the

formation of heterocyclic amines at high temperatures. In addition, less fat is available to drip on the coals and form benzpyrene.

Dr. Felton said that emerging evidence of mutagenic activity in certain bread products led him and his colleagues to investigate the effects of heating time on the mutagenic activity in a variety of fried, baked, and toasted non-meat foods. Among these were white bread, pumpernickel, bread sticks, croissants, pizza crust, pancakes, and graham crackers. In some cases, notably pumpernickel and bread sticks, there was a six- to eightfold rise in mutagenicity if the foodstuff was cooked about 50% longer than usual but at the usual temperature. This rise seems to be attributable largely to the effect of long baking times on wheat gluten in these cases. Similar effects are seen when patties made of certain commercially-available meat substitutes, most of which are high in wheat content, are fried at 210 degrees for 6 minutes on a side. The presence of arginine and, perhaps, threonine seems to be important in the formation of many of the heterocyclic amines in wheat-based products.

Dr. Felton stressed that the quantities of heterocyclic amines in these foodstuffs were much smaller than those found in similarly-cooked meats, but observed that they contribute to the overall intake of heterocyclic amines in the average diet and must therefore be taken into account.

Finally, Dr. Felton pointed out that since cancer bioassays use very high quantities of the compound being tested, it is particularly important to determine the risk of such compounds to humans, who are exposed to much lower levels. He indicated that sophisticated tests done at his laboratory with an accelerated mass spectrometer suggest that a linear extrapolation from high doses to low doses of certain heterocyclic amines may be reasonably valid for determining the risk to humans of these specific compounds in the diet. However, Dr. Felton strongly stressed that even in a <u>worst case</u> scenario--that is, an individual who consumed over a lifetime a maximum quantity of foods prepared in a way that maximized the formation of heterocyclic amines--the excess risk of developing cancer would be approximately 1 in 1,000 in a lifetime.

The final speaker of the session was Dr. Robert Scheuplein of the Food and Drug Administration (FDA), who discussed the FDA position on heterocyclic amines. Dr. Scheuplein said that the research findings cited during this meeting probably represent only the tip of the iceberg as far as "natural" carcinogens are concerned, but noted that the FDA has only been given regulatory authority over adulterated foods, not natural foods. Moreover, although it has been estimated that the lifetime risk of developing cancer from ingesting food is roughly 1 in 15, it is not known how much of that risk is due to heterocyclic amines, or to promoting activity of proteins and fats, or to other carcinogens, just as it is not known how much of that risk is negated by anticarcinogens in foods, whether naturally-occurring or added. However, the FDA does have authority over, and is investigating, the addition of flavoring substances which are derived by thermal processing: "artificial smoke," flavorings which impart a meaty flavor to foods, and so on.

Dr. Scheuplein pointed out that not only do Americans consume about 20 billion pounds of red meat, poultry, and fish per year, but they also consume about 17 million pounds of "processed flavors" with these meats in their various forms, as well as in many other foods.

Dr. Scheuplein said that there are 23 companies making some 600 formulas of these processed flavors, and that for the past two years the FDA and these companies have been trying to determine where the flavors are used, how they are used, the components in them, and the toxicity of the materials. Although there is an attitude of cooperation between FDA and industry, the FDA finds itself confronted with a host of analytical and legal problems, and Dr. Scheuplein said that he expected the process of determining the risk of such materials to be lengthy. He expressed the hope, however, that the flavoring industry may be able to make analogues of the aforementioned flavors synthetically and cleanly, i.e., free from heterocyclic amines and similar compounds.

Dr. Adamson concluded by pointing out that regulatory agencies such as the FDA have banned synthetic chemicals such as Alar upon the revelation that they pose a 1 in 1 million lifetime risk of cancer to humans, and that since a worst-case scenario of ingesting heterocyclic amines in cooked foods poses a 1 in 1,000 lifetime risk of cancer, it would therefore seem prudent to follow the methods for safe preparation of meats outlined by Dr. Snyderwine. He added that ingestion of foods thought to possess anticarcinogenic activity, such as the cruciferous vegetables and other vegatables and certain fresh fruits, would also seem wise.

After these remarks, Dr. Becker thanked the participants for their contributions and adjourned the meeting.

Richard H. Adamson, Ph.D.
Executive Secretary

Approved

NATIONAL CANCER ADVISORY BOARD

AGING AND CANCER SUBCOMMITTEE

SUMMARY MINUTES, September, 1992

The Aging and Cancer Subcommittee, chaired by Ms. Deborah Mayer, met in open session from 2 to 3 PM on Monday, September 21, 1992 in Conference Room 9, NIH Building 31. In addition to the chair, the NCAB members in attendance were: Drs. Lawrence, Wilson, Durant, Bettinghaus, Fisher, Salmon, Pitot and Calabresi. Dr. Marvin Kalt, DEA, NCI, was Executive Secretary.

The new Chair opened the meeting by reviewing the charge to the Committee, in order to help define its future objectives. Dr. Calabresi provided insight into the historical context of the need for the group, by reminding the attendees that, as other causes of death decrease, the resulting extension in lifespan will mean that age-associated prevalence of, and mortality from cancer will increase dramatically unless improvements are found.

Dr. Kalt presented to the Subcommittee data on the current aging-specific research in the NCI extramural portfolio, and NCI staff identified several current initiatives in ovarian, breast and prostate cancer. The Committee identified several immediate areas of need, including research on the attitudes of health care providers to elderly patients; attitudes of patients themselves to cancer and to health in general; defining "elderly" and the appropriate points in the life course for research on, and interventions in, various cancers; possible physiologic differences in elderly subjects that may influence treatments; and fundamental studies on the relationship of carcinogenesis to cellular aging.

Actions were suggested on several fronts. First, the Subcommittee will arrange a series of presentations by NCI Divisional staff responsible for cancers that affect the elderly, to provide an overview of the Institute's activities, and to identify where additional cross-divisional activities may be warranted. Second, a liaison will be invited from the National Institute on Aging to explain their programs, and to help explore how areas of potential overlap can be shared on a common basis. Third, discussion encouraged consideration of a conference to highlight the potential for research and international cooperation.

Finally, members were encouraged to review the application portfolio each round to identify specific applications of potential relevance, or areas that seem to be chronically under-represented by competitive applications.

There being no further business, the meeting was adjourned at 3 PM.

DRAFT

SUMMARY

Cancer Centers Subcommittee
National Cancer Advisory Board
National Cancer Institute

September 21, 1992

Attendees

NCAB Members

Dr. Salmon, Chairperson
Dr. Calabresi
Dr. Becker
Dr. Bettinghaus
Ms. Mayer
Dr. Wells
Dr. Wilson
Dr. Chan
Dr. Lawrence
Dr. Durant

NCI Staff

Dr. Kimes, Executive Secretary
Dr. Ihde
Dr. Rabson
Dr. Holmes
Dr. Maslow
Dr. McCormick
Dr. Muul
Ms. Waldrop
Ms. O'Neill
Dr. Browning
Dr. Yang
Ms. Hubbard
Dr. Kalt

Public - none

The Subcommittee convened at 4:10 p.m. and adjourned at 5:45 p.m. The following topics were discussed:

1. Progress of the Cancer Centers Program in assessing the need for Clinical Research Cores on Cancer Center Support Grants (CCSG).
Dr. Kimes reviewed the many factors that are currently creating problems for the clinical oncology research community ranging from the tightening of policies of third party payers to pay for clinical trials to the lack of adequate access of clinical researchers to investigator-initiated sources of research support. He then described the changes that have already been implemented in the Cancer Centers Program to stimulate innovative clinical research with the CCSG and the current status of evaluating clinical research cores, promising to resolve the major issues within the next two to three months. Dr. Salmon and others reiterated the vital need of cancer centers to have core resources in the form of data managers and research nurses that can be used to stimulate and stabilize the conduct of short-term, small pilot Phase I/Phase II studies. Dr. Kimes noted that it is likely that clinical research cores will be linked to the submission of RO1 applications. Dr. Salmon agreed that linking these cores to the submission of applications is reasonable but not to funded applications until the NCI/NIH has established a reliable investigator-initiated peer review and funding process. Dr. Durant noted that there should be a way to

evaluate the quality of clinical research from publications in well-respected, peer reviewed journals if the investigators have no independent, traditional grant support.

2. Use of CCSG funds outside the "primary" area served by the clinical/comprehensive center. There was considerable discussion on the above topic, there being agreement that CCSG grant resources should not be used to expand the research activities of a cancer center outside its normal catchment area. In the case of cancer centers expanding their activities well beyond their primary area and using the NCI Comprehensive Cancer Center designation to attract patients, the NCI name should not be used to promote these activities. Other types of expansions that overlap and interfere with the research activities of other NCI-designated cancer centers having primary responsibility for the area should be discouraged. NCI staff were advised to consult the Executive Committee of the NCI and submit a draft policy statement to the subcommittee at the next meeting.

3. Information being requested of cancer centers. Dr. Kimes noted that the NCI has two different issues to consider in how it requests information: (a) what is needed to conduct a thorough peer review evaluation of a CCSG which focuses entirely on the research of a cancer center and (b) what is needed to be responsive to the requests of the public and Congress in terms of their perception of cancer centers which focus on health care delivery, quality of life issues, and responsibility to communities.

   Dr. Kimes indicated that after the review process has been tested more thoroughly, the Centers Program will reevaluate the information that is being requested and streamline wherever possible. In addition, NCI staff will work closely with those centers having particular difficulties to ensure that they are not placed under any undue hardships.

4. The Subcommittee was offered the opportunity to provide additional comments on the new CCSG Guidelines, but there were none. It was agreed that the guidelines had been discussed very thoroughly and that any further revisions would be small ones for staff to make relating to clarity, etc.

5. Quality of life issues and responsibilities of NCI cancer centers. The NCI deals with quality of life issues (e.g., pain management, rehabilitation, psychosocial services) in many areas throughout the NCI (i.e., DCPC programs, the Cancer Training Branch R25 initiatives, OCC programs, and the Cancer Centers Program). It has been the policy of the NCI with regard to cancer centers to encourage "NCI-designated Comprehensive Cancer Centers" to become more committed to activities and promoting the facts associated with quality of life issues. Comprehensive cancer centers should be striving to be the best and set the example for state-of-the-art care, research, information, and education activities that benefit their communities/regions. The Subcommittee believed that these issues are important and should be

stated in the comprehensive guidelines in a broad fashion but not so specifically that every center is expected to be good at everything. This is an unreasonable expectation but is a goal for all centers to work towards.

The Subcommittee discussed future agenda items, and it was agreed that at the next meeting the comprehensive guidelines and a draft policy statement as discussed in 2. above would be on the agenda.