OCT 20 1989

THE CANCER LETTER

P.O. Box 15189 Washington, D.C. 20003 Telephone 202-543-7665

Vol. 15 No. 40
Oct. 20, 1989

© Copyright 1989 Cancer Letter Inc.
Price $185 Per Year North America
$200 Per Year Elsewhere

DCPC Board Agrees To Commit $62 Million To Trial Of Prostate, Lung, Colorectal Cancer Screening

Physicians and screening programs currently use various techniques for screening for prostate, lung and colorectal cancer, but there has not been a definitive trial to determine

(Continued to page 2)

In Brief

Zelen To Retire As Head Of ECOG Statistical Center; NIH Organizes Genome Research Center

MARVIN ZELEN, who has headed the Eastern Cooperative Oncology Group's statistical center since 1971, will join Chairman **Paul Carbone** in retiring from ECOG leadership (**The Cancer Letter**, Oct. 6). In fact, Zelen will give up his position at ECOG's meeting in November, while Carbone must wait while the group goes through its procedure for electing a new chairman. Zelen is chairman of the Dept. of Biostatistics at Harvard and heads the Div. of Biostatistics and Epidemiology at Dana-Farber Cancer Center. "I need to get back into research," he said. . . . **NIH OFFICE** of Human Genome Research has been reorganized into the National Center for Human Genome Research. James Watson is director of the center, and Elke Jordan is deputy director. The center will assume control of all funds earmarked for NIH genome research. Until now, the National Institute for General Medical Sciences was responsible for all grants and contracts awarded under the genome program. . . . **TRAVEL AWARDS** for the 15th International Cancer Congress, to be held in Hamburg, W. Germany next August, are available in limited numbers only to Congress participants listed on the program, including poster presenters. Each award will be $1,000. Application forms are available from June Ewing, National Research Council, 2101 Constitution Ave. NW, Washington, D.C. 20418, phone 202/334-2235. Application deadline is Jan. 15. . . . **JOSEPH FRAUMENI,** director of the Epidemiology & Biostatistics Program in NCI's Div. of Cancer Etiology, has received the 1989 Gorgas Medal, awarded by the Assn. of Military Surgeons for distinguished work in preventive medicine. . . . **JOOST OPPENHEIM**, chief of the Laboratory of Molecular Immunoregulation in the Div. of Cancer Treatment, received the PharmaMedica Lecture Award for 1989 from the Danish Society of Dermatology. . . . **KEN OLSON**, retired oncologist living in New Smyrna Beach, FL, has received the American Cancer Society Florida Div.'s Distinguished Service Award. Olson, 81, was one of the first physicians to note the rising incidence of lung cancer.

Concept Approval Granted To Trial Of Prostate, Lung, Colorectal Screens

(Continued from page 1)

whether the techniques are effective in reducing cancer mortality.

The Board of Scientific Counselors of NCI's Div. of Cancer Prevention & Control has agreed to commit $62.42 million over 16 years in a multicenter randomized controlled trial to test three screening techniques. The board gave concept approval to the trial last week.

Considering that the three cancers account for 54 percent of new cancer cases and 57 percent of cancer deaths among U.S. males, "this trial is either going to save lives or money," said David Byar, chief of the Biometry Branch and co-project officer of the trial.

Other project officers are Philip Prorok, chief of the Screening Section in the Biometry Branch, and Charles Smart, chief of the Early Detection Branch.

DCPC expects to award contracts to 10 clinical centers to recruit and follow 50,000 trial participants and another contract for a data management and coordinating center.

The board also unanimously approved a concept for a project that, in its original form, was tabled at the May board meeting. The project as it was first proposed would have taken $2 million from the Cancer Center Program to fund two demonstration centers for cancer prevention among minorities. The proposal ignited a debate over cancer centers funding versus the NCI goal of reducing cancer mortality among minorities and low income groups.

As an ad hoc board committee and NCI staff were rewriting the proposal, the Cancer Centers Program was moved out of DCPC. Under its new format, the project will provide grants to approximately three centers or consortia to establish programs integrating cancer prevention, screening, early detection and treatment services for high risk minority, low income and other underserved groups. The board agreed to commit $2 million a year for five years to the project.

The board also approved a concept for a computer software services contract for the Biometry Branch.

Excerpts of the concept statements and board discussion follow.

Prostate, lung and colorectal cancer screening trial. This is a new contract concept for approximately 11 awards, for an estimated total cost of $62.42 million over 16 years.

The three major objectives of this trial are to determine in males aged 60 to 74 whether:

1. Screening with digital rectal examination plus serum prostate specific antigen (PSA) can reduce mortality from prostate cancer.

2. Screening with flexible sigmoidoscopy plus digital rectal examination can reduce mortality from colorectal cancer.

3. Screening with chest x-ray can reduce mortality from lung cancer.

Secondary objectives are:

1. To assess screening variables other than mortality for each of the interventions including sensitivity, specificity and positive predictive value, as well as incidence, stage and survival experience of cancer cases.

2. To store blood samples (20 cc per subject) for use in future epidemiologic studies concerning the etiology of prostate, lung and colorectal cancers.

The digital rectal exam is the test most often mentioned for prostate cancer screening, but recently two other tests have become available: transrectal ultrasound and prostate specific antigen. DRE has been used for many years, but careful evaluation of this modality has yet to take place. Several observational studies have examined process measures such as sensitivity as well as case survival data, but without appropriate controls and with no adjustment for lead time and length biases.

Chest x-ray and sputum cytology are the two modalities that have been suggested as screening tests for lung cancer. The uncertainty in interpretation of results from completed studies and the apparent widespread clinical perception that the annual chest x-ray is of some value lead one to conclude that a clear difference of opinion exists regarding the value of annual chest x-rays. Whether a small but important benefit exists can only be demonstrated reliably by a properly designed randomized trial.

DRE, sigmoidoscopy and occult blood testing are suggested for colorectal cancer screening. While these tests are in use, none has received a definitive evaluation and the evidence of benefit for each is at best uncertain.

The project is a two arm randomized clinical trial with 50,000 males aged 60-74 at entry, randomized to each of the two arms. One arm is controls, the other arm consists of rectal exam, PSA, chest x-ray, sigmoidoscopy and exams of the mouth, neck and skin. The frequency and duration of screening will be as follows: an initial screen and the once a year for three years for rectal, PSA, x-ray and mouth, neck, skin; initial then at three years for sigmoidoscopy.

The study will be designed to have high statistical power for detecting decreases in mortality separately for prostate, lung and colorectal cancer. Subjects with lesions suspicious for lung cancer on x-ray will receive further work up according to a protocol to be developed during the pilot phase. Subjects with colorectal polyps or suspected cancer detected by DRE or by sigmoidoscopy will undergo biopsy and removal of the polyps and biopsy of other lesions followed by further work up possibly including barium enema studies and/or colonoscopy according to the protocol worked out in the pilot phase.

THE CANCER LETTER

Editor: Jerry D. Boyd
Associate Editors:
Patricia Williams, Kirsten Boyd Goldberg

P.O. Box 15189, Washington DC 20003
Telephone (202) 543-7665
FAX No. (202) 543-6879

Published 48 times a year by The Cancer Letter Inc., also publisher of The Clinical Cancer Letter and AIDS update. All rights reserved. None of the content of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means (electronic, mechanical, photocopying, facsimile, recording or otherwise) without the prior written permission of the publisher. Violators risk criminal penalties and $50,000 damages. (ISSN 096-3917)

The examinations of the mouth for oral cancer, neck for enlarged lymph nodes due to head and neck cancer, and the skin for skin cancer and malignant melanoma are included because many physicians believe them to be good medical practice and because they cost little. The study will not have adequate statistical power to evaluate the possible benefits from screening for these sites, but it will provide information about the extra yield of cancers in the screened group.

The general timetable of the trial is as follows: protocol development and pilot studies in years 1-2; recruitment and initial screening of subjects in years 3-5; follow up and completion of screening in years 6-8; further follow up in years 9-15; final follow and data analysis in year 16.

Up to 10 centers will be recruited, each of which must be capable of randomizing 10,000 or more subjects to the study. Proposals will be solicited from military and veterans' hospitals, HMOs, cancer centers and university or other groups that can put together the necessary staff and facilities to recruit subjects, conduct the screening and follow up all randomized patients for at least 10 years after initial screening. A single contract will be awarded for a Study Coordinating and Data Management Center (SCDMC) which will be responsible for receiving and processing data in all phases of the study from the screening centers and will provide logistical support for meetings and other activities. A distributed data entry system will be used for this trial.

Subjects will be assigned using a randomized consent design. Lists of potential subjects will be prepared, then individual subjects will be randomized to screening or control groups before seeking their consent to participate in the study. Only minimal contact with control subjects will be necessary. The project officers believe that a large proportion, 80 to 90 percent, of subjects selected for the screened group will agree to be screened. If this approach is not feasible, other approaches will be tried in the second year.

Before the full scale screening trial begins, pilot studies will:

1. Test acceptability of randomization by randomizing 300 subjects per center.

2. Work out the detailed logistics by performing the screening examinations. It is assumed that all screening for any one subject will take place during a single visit to the screening center.

3. Assess background level of usage of each screening modality by surveys in each center's population catchment region and among the 300 randomized subjects at each screening center.

During the first six months of the pilot phase the investigators will develop a protocol including but not limited to: eligibility requirements, subject notification of screening results; work up of subjects with suspicious screens; mechanism for providing appropriate therapy for cancer; quality control procedures; procedures for follow up, monitoring compliance, determining cancer incidence and ascertaining cause of death.

Each screening center will identify recruitment sources and strategies. Randomization of the first 300 subjects at each center and initial screening should be done by the second six months of the study.

During the pilot phase, the SCDMC will attend all meetings of the investigators and will be responsible for documenting all decisions reached and compiling the study protocol as it is developed. The SCDMC will be responsible for developing appropriate study forms, setting up data entry and editing systems and writing a manual of operations for all procedures to be used in the trial.

At the end of the pilot phase, centers with inadequate performance will not be asked to continue with the study and will be replaced by granting contracts to the next highest applicants judged technically acceptable according to priority scores determined by the review group which selected the original awardees. Every effort will be made during the pilot phase to monitor performance and correct deficiencies to avoid replacing any centers, but this will be done if required to mantain adequate recruitment for the full scale trial. A Policy Advisory and Data Monitoring Panel will be formed consisting of outside experts with experience in mass screening, clinical trials and other appropriate disciplines.

The concept uses the following costs for the screening procedures: sigmoidoscopy $40.50; single view chest x-ray $20; PSA $10; DRE $2.50; screening of mouth, neck and skin $2.50. These costs are assumed to include salaries for medical personnel and to reflect equipment and overhead costs. Screening center costs for years 1 and 2 of the pilot phase were set at $1 million and $1.5 million. To cover other screening center expenses in years 3-16 such as data coordination, quality control, training, follow up and death ascertainments, a budget of $1.5 million a year (including indirect costs) has been set. The budget for the Study Coordinating and Data Management Center has been set at $500,000 a year for years 1-16. Blood storage is estimated to cost $2.49 million over 14 years.

Ethical concerns about the randomization of controls and subjects before seeking their consent to participate in the study were raised by several board members. "I don't think I could get this passed at my institutional review board," said board member James Holland. Smart said the design "would be unacceptable if (an institution) didn't run a health insurance program. With health insurance or an HMO you can identify people from a list, randomize, and those that are on the screening list you call in."

Holland argued that informed consent is required for investigators to use data on individuals. DCPC Director Peter Greenwald suggested that the design "is no different from SEER," in which the data is reported without informing the subject. Board member Virginia Ernster said that SEER only requires "passive follow up" while the proposed trial might require pathology reports, or other data.

Board member Edward Bresnick made a motion to approve the concept with the provision that the study must be approved by the NIH Office of Protection from Research Risks. The motion carried and the concept was approved unanimously.

Cancer prevention and clinical research in underserved populations. Estimated three grant awards, approximately $2 million a year total, duration five years.

NCI has developed several mechanisms to support and mobilize resources designed to reduce the disproportionate cancer burden among the black and other underserved populations. The missing aspect of previously funded projects is the provision of access, availability and delivery of state of the science cancer services to black and other underserved persons. These projects have been single interventions directed at specific cancer sites and small test subsets of underserved populations. This project focuses on problems related to the delivery of a broad range of quality cancer services.

This concept's goals are to:

--Reduce cancer incidence and mortality and improved survival rates for minority and underserved persons who are typified as low income/education and high risk populations.

--Demonstrate ways of increasing access, delivery, utilization and availability of quality cancer prevention and clinical services to these high risk populations.

--Conduct basic and applied research on disparities between the minorities/underserved and the general population.

This concept is intended to stimulate the establishment and implementation of a program which will integrate and deliver comprehensive cancer prevention, screening and early detection and treatment services to high risk minority, low income and other underserved persons. It should be noted that a program may be located in an urban or a rural area. Basic and/or clinical research on unexplained population disparities is encouraged and included as an option. When fully operational, this project will include the following scientific and organizational elements.:

Scientific elements:

1. An emphasis on the application of state of the science clinical and prevention methods in settings with populations at high risk for cancer, e.g., inner city or other relevant geographic locations.

2. Screening and early detection activities.

3. A program of applications and clinical trials research linked to cooperative groups and other research bases.

4. Coordination with other disease prevention efforts which are relevant to the population at risk, i.e., maternal and child

health, infectious and chronic disease programs.

5. An emphasis on cancer prevention and health promotion activities consistent with NCI's objectives.

6. Basic and/or clinical research aimed at explaining disparities in cancer rates between population subgroups in our country which are not understood.

7. An evaluation component which will measure the effectiveness of the implementation in a particular setting. Endpoint measurements of effectiveness could include an increase in the proportion of the population screened, stage shifts, or an increase in patient accrual to clinical trials programs.

Organizational elements:

1. A multidisciplinary group of public health providers, clinicians and scientists, with experience in cancer applications research, clinical trials research, basic research where appropriate, and health care delivery to minority and medically underserved persons who now have poor or limited access to quality care.

2. A collaborative effort by the appropriate organizations from universities, health providers, municipal and state health departments, voluntary organizations, community oriented or based organizations, cancer centers, insurance companies and in patient service facilities.

3. A track record of success in the implementation of intervention programs for relevant health conditions or diseases in minorities communities.

4. Specific plans for shared resources, e.g., collaborative arrangements with NCI funded cancer centers; existing cancer centers are eligible and encouraged to apply, but all applicants are encouraged to establish collaborative agreements with key institutions such as large inner city hospitals. Components of the program must demonstrate the ability to have effective organizational interactions. An application from two or more institutions (single application from multiple institutions) from a defined geographic location will be accepted.

5. An indication should be made that the costs of health services will be provided outside this project's funds.

The focus of this activity will be on determining how to meet the full spectrum of cancer needs for those segments of the population at the extreme in terms of excess risk of cancer mortality and morbidity. Consortium or consortia like arrangements of health providers, relevant health departments and cancer centers should demonstrate the extent to which state of the art comprehensive cancer care can be brought to those persons with the greatest need.

"Vastly Improved" was board member James Holland's description of the rewritten concept statement. Holland had made the motion at the previous board meeting to table the concept. "This is investigator-driven. That's the major improvement over last time," he said. He noted that the project's hypothesis is, "one can do something about cancer incidence in minority populations." The concept was approved unanimously.

Biomedical computing software services in support of the Biometry Branch. This concept seeks approval for recompetition of a contract currently held by Information Management Services, which will expire in August 1991. One award, $400,000 a year for five years for a total of $2 million. This is a 100 percent small business set aside.

DCPC's Biometry Branch is seeking a contractor to provide statistical programming, data processing and data management support for its research projects. This support includes the analysis of large sets of medical data often involving complex statistical analysis and requires the contractor to use sophisticated data handling and analytic techniques and extensive plotting by digital computer.

The facilities of the NIH Div. of Computer Research & Technology will be used for most computer processing. Computer programs will generally be written using the Fortran and Cobol programming languages, but other languages such as SAS also will be used for some applications. When appropriate, the contractor will convert existing software or write new programs to run in the PC and microcomputer environment.

The contractor's primary responsibility will be the building and editing of large and small data bases and providing adequate documentation and backup for these systems of records. This sometimes involves the transfer of medical data from paper records to machine readable form. The work scope requires that the contractor display knowledge of graphics display software and use of the WYLBUR text editor as well as other DCRT facilities, particularly the DEC-10 system or its replacement system. Although the statistical analysis of these data will be conducted under the close supervision of members of the branch, the contractor's project leader or key personnel should be experienced in the statistical analysis of medical data, and some formal training in statistics is desirable.

The Biometry Branch is composed of 16 full time professionals who perform two major functions: consultation on the development of large prevention and screening trials and the development of statistical methodology for the analysis of data resulting from such trials and related studies. The variability of the course of cancer in individual patients means that assessment of treatment differences, determination of the usefulness of diagnostic tests, or the proper interpretation of data from observational studies are often statistical problems. Members of the branch are frequently consulted for advice or collaboration on such problems.

There are numerous short term consultations dealing with specific studies, proposal reviews, site visits and review of manuscripts submitted for publication. Some consultations involve extensive trials which represent considerable efforts of the program staff. The branch represents an important resource for expert assistance in study design, implementation and statistical and computer analysis of studies being carried out by many other groups. Much of the branch's work is directly applicable to the analysis of data collected in prevention trials of cancer, analysis of data related to diagnosis and screening of cancer, and to epidemiologic studies of cancer.

Following is a list of projects for which the current contractor has provided data processing support. Although this is not a complete list and several of the projects have been completed, it is presented as a sample of the type of projects for which computer support will be needed.

1. Design, write, document and maintain interactive recode and statistical data analysis system to be operational on the DCRT computer facility's DEC-10. Convert existing programs to run on PCs. This system is comprised of user friendly and conversational program modules which can be used by NCI staff or contractors to perform statistical data analysis. Programs to assist with or provide the following are included: screening of prognostic factors, survival analysis and curve graphing, covariate modeling of survival, descriptive statistics, least squares regression analysis, power and sample size calculations, table making, data subsetting, two variable scatter plots and analysis of time dependent covariates.

2. Process and convert multiple data tapes for the 280,000 screened participants from the Breast Cancer Detection Demonstration Project to be DCRT compatible. Compute age specific breast cancer incidence rates by year.

3. Maintain and document a breast cancer screening study analysis system for the HIP screening study. The system was run using different time interval calculations to compare the study versus control groups and the study screened versus the not screened individuals.

4. Work with researchers in the branch to develop methods for identifying survival distributions in the presence of dependent competing risks when a prognostic covariate is measured.

5. Write a program to perform the paired analysis of changes after diet from baseline in phospholipids and esters for women participating in the USDA Feeding Study as part of the overall evaluation of the Women's Health Trial feasibility study.

The concept was approved unanimously. The project officer is Donald Corle.

NCI CONTRACT AWARDS

Title: Dosimetry support for studies of radiation workers.
Contractor: Tech/Ops Landauer Inc., $219,342.

DCPC Board Encourages Approval Of Dietary Fat Breast Cancer Study

The Board of Scientific Counselors of NCI's Div. of Cancer Prevention & Control last week encouraged the institute to proceed with the proposed Dietary Fat Intervention Trial in Women and suggested that NCI take a more active role in overseeing the study.

The board made its recommendation in a special workshop to consider research on the relationship of diet to breast cancer.

The RO1 investigator initiated proposal, called Diet FIT for short, was voted down 9-3 by the National Cancer Advisory Board in a recent closed session (**The Cancer Letter**, Sept. 29). However, the board may reconsider the decision at its next meeting (see below).

DCPC Director Peter Greenwald told **The Cancer Letter** that he will report to the NCAB on the workshop. Greenwald, who presented the case for funding the trial to the NCAB, was clearly disappointed when it was voted down.

At the time, he called the relation of dietary fat to cancer incidence "one of the most pressing health issues of our time," and said he did not see "any stronger alternatives" to Diet FIT.

Greenwald then took the unusual step of holding a workshop on the second day of the DCPC board meeting to discuss "Future Research Possibilities for Diet/Breast Cancer Prevention Studies." He asked the board to give him a "clear signal" on the importance of such studies, and the Diet FIT study in particular.

Diet FIT proposed to study 24,000 women aged 55-69 drawn from 12 collaborating centers. The trial design was to randomize 40 percent to a low fat diet in which fat is reduced from about 40 percent of caloric intake to 20 percent. The other 60 percent of the women, the control group, would remain on their regular diets.

The trial, expected to cost $60 million over five years, intended to test the hypothesis that over the 10 year study period there would be a drop in the incidence rates of breast, colon, rectal, ovarian and endometrial cancers, as well as coronary heart disease, in the range of 10 to 30 percent. The investigators also predict a reduction in total mortality.

The proposal was submitted by Ross Prentice, director of public health sciences at the Fred Hutchinson Cancer Research Center, and Maureen Henderson, head of the cancer prevention program at the center. Curt Furberg, director of public health sciences at Wake Forest School of Medicine is the lead investigator for the coronary heart disease portion of the study. The investigators also asked the National Heart, Lung & Blood Institute for partial funding.

The DCPC workshop included discussion of work by Richard Love, Univ. of Wisconsin Clinical Cancer Center, on antiestrogen prevention of breast cancer; Norman Boyd, Univ. of Toronto Princess Margaret Hospital, on a clinical trial of low fat diets and mammographic dysplasia; Charles Smart, chief of DCPC's Early Detection Branch, on lobular carcinoma in situ; Rowan Chlebowski, UCLA Medical Center, on dietary fat reduction for adjuvant breast cancer therapy; and a presentation by Roswell Boutwell, McArdle Laboratory and an NCAB member, on studies of dietary fat and cancer incidence in animal models. Prentice presented the case for Diet FIT.

Besides Boutwell, NCAB members Erwin Bettinghaus, Helene Brown and Irene Pollin attended the workshop.

Much of the discussion pointed to the need for a definitive study of the relationship of diet and dietary fat to breast cancer incidence.

At one point in the discussion, Greenwald interrupted a debate over the interpretation of the results of a study in China on breast cancer incidence. "I think the fact that the epidemiologists are always contradicting each other is a case for doing a trial," he said.

Besides Diet FIT, other research possibilities discussed were a trial of long term use of tamoxifen as a breast cancer preventative.

One dissenting voice on the dietary fat hypothesis was Malcom Pike, Univ. of Southern California, who argued that in postmenopausal women, estrogen levels have been shown to influence breast cancer. "You should be concentrating on the effects of hormones," he said. "I don't think we need to think in terms of all these long, long term studies."

Frank Meyskens, DCPC board chairman, said during a discussion of whether a substitute marker for breast cancer could be found, "We can go back and forth on this for a long time between the epidemiologist's versus the biologist's point of view."

Meyskens asked each DCPC board member to make a statement on the importance of going forward with Diet FIT, and to make recommendations for research.

Altogether, six board members said they were for going ahead with Diet FIT, one suggested further feasibility studies, and three other board members who attended most of the meeting left before the chance to make a statement. Five other board members did not attend the board meeting or the workshop.

Following are excerpts of the board members' statements:

James Holland: "It seemed to me the evidence is very strong that there are potential benefits of diet and potential benefits of tamoxifen. I believe that one ought to restrict the limited funds of DCPC to go to trials that relate to primary breast cancer. I think the secondary breast cancer trials are really parts of therapy. I would ask DCPC to take a stronger hand in organizing the studies with the able investigators that have made presentations, in such a way that it can be done so that the control groups are not replicated time and time again, because of the expense. Even if (the control groups) only represent 25 percent of the costs, 25 percent of 60 million bucks is still a tidy piece of change."

Donald McCormick: "I'd very much like to see a trial of some type, such as Diet FIT. It may need further fine tuning to take account of negative studies. This is an issue that will not be settled outside of a trial."

Shirley Lansky: "This has been a very informative meeting. I feel that many of the issues that have been raised need to be put to a test so we have a clear definition of how to continue. I am very excited about many of them."

Prentice, who was recently appointed to the board, made his feelings about going ahead with Diet FIT known, but also said that if the trial were to go forward, the investigators would agree to work under a cooperative agreement with NCI and NHLBI.

Edward Bresnick: "First, I strongly support a trial, or some sort of study on diet versus breast cancer incidence in postmenopausal women, and that it be really thoroughly planned to try to avoid any pitfalls. Second, I would strongly support a feasibility tamoxifen study. Third, I think this should be DCPC's major task with regard to the new (nutrition) laboratory, to understand what dietary modulations such as a decrease or increase in fat does to the pharmacokinetics of chemotherapeutic or chemopreventive agents in humans, not animals. Is biotransformation effective, if it is effective, does this mean we can now give less drugs, and therefore avoid toxicity? These are extremely important questions."

Virginia Ernster: "I'm very mixed on this one.... We really don't have answers for prevention and the dietary message has been out to the American public teasing them that diet may be responsible for breast cancer. I'm torn between what I think might be our responsibility to debunk that myth, because in some ways I think it just might do that, because the epidemiologic data and more coming down the pike are really not supportive of it, and if that's the case, we ought to be clear about it. On the other hand, this is going to haunt us for so long until we get it addressed through a trial. So for political reasons alone, not for scientific reasons, I'm prepared to go along with it. I really do not feel the data are strong enough and consistent enough to proceed with a clinical trial. If we devote $60 million to it, we're taking the money away from something else. When push comes to shove I'd say go ahead with it, once and for all, we've got to have an answer. I endorse it with mixed feelings.

Mary Madonna Ashton: "As the nonscientist on this board, I'm not in a position to judge the scientific value of the proposal, but I am extremely interested and concerned about the endpoints of these different proposals. I agree that the general public is ready to get some really good information about whether diet is important or not. And we in health departments are standing by, wishing we had some really good scientific data on which we could move our health promotion and health education activities along. It would also help our legislative effort in getting money if we had a really solid study that was broad enough and large enough to make the difference. If we could put this to rest one way or another it would be helpful to us."

Carol D'Onofrio, also a new board member: "It seems to me that...there is some room for feasibility studies.... I would caution against going forward with a very expensive trial."

Bresnick disagreed with D'Onofrio. "I want to argue against a feasibility study," he said. "We've heard three studies today, and if the question is, can we get people to stay on a 20 percent fat/calorie diet for a substantial period of time, and I consider one to two years a substantial period, we have an answer. There's no question. What are other aspects of a feasibility study? I can't think of any. It's

time to bite the bullet and go for the endpoint. Let's forget about feasibility studies."

Ernster noted that under the current plan for Diet FIT, the study would have about 80 percent statistical power with regard to the effect of dietary fat on breast cancer. "I think it would be a crying shame not to have results specific for breast cancer. As long as we're so close, we might as well make it 90 percent power for breast cancer," she said.

Prentice said that one way to accomplish that goal would be to have a longer follow up period.

Rose Kushner, executive director and founder of the Breast Cancer Advisory Center, exhorted the board to "do something. This research agenda is no longer a scientific issue, it is a political issue. These trials are not competing ideas. Let's do them all. People know they should not be eating all this stuff (fatty foods). We need to come out say, yes, the Golden Arches (the McDonald's symbol) represent x number of colon cancers or x number of breast cancers."

Cynthia Pearson, program director of the National Women's Health Network, told the board that, "Our reading of what the average woman in America would like is prevention trials in unaffected women, and the result based on a diet that leads to an overall increase in health. A tamoxifen trial is a very interesting scientific question, but it leads to widescale use of drugs. Many women are questioning long term use of drugs."

NCAB To Consider Diet Fit Trial Again During Dec. 4-5 Meeting

The National Cancer Advisory Board will consider the Diet Fit Trial again at its meeting in December, NCI Director Samuel Broder and NCAB Chairman David Korn both indicated in conversations last week with **The Cancer Letter.**

The RO1 grant application "is still actively under discussion by the board," Broder said. "There has been no final conclusion reached," Korn added. The NCAB is scheduled to meet Dec. 4-5 for the annual program review. Grant review usually is not on the agenda for the December meeting, but it appears Diet Fit will get at least one more look then, probably in closed session.

Korn said he was "outraged" that one or more persons who were present during the board's consideration of the grant disclosed details of the discussion and the vote against funding it. "That is fundamentally wrong," Korn said, although agreeing that **The Cancer Letter** had the right to publish that information once it had been obtained. "My complaint isn't with you but with whoever disclosed matters discussed at a closed meeting."

NIH policy has always been for review of grants, both by the initial review groups (study sections) and subsequent review by institute councils, or the NCAB for NCI grants, to be conducted in closed meetings. Reasons include protection of proprietary information that may be in the applications, desire to prevent embarrassment to individuals whose qualifications may be questioned, and the need to encourage full and free discussion by reviewers.

It seems obvious that Diet Fit was voted down by the NCAB primarily because of scientific issues which remain unresolved. Those issues were aired many times in public sessions, when the NCAB and the Div. of Cancer Prevention & Control Board of Scientific Counselors were considering and then killing the Women's Health Trial. Most of those discussions occurred when the concept of the trial was reviewed, and NCI's policy has been that concept reviews must be done in open meetings.

Another consideration had to be the cost: $60 million over five years, at a time when NCI's budget is under severe pressure.

The NCAB could not have been questioning the judgment of the initial review, which was done by a prestigious, ad hoc committee chaired by Henry Pitot, former NCAB chairman and director of McArdle Laboratory. Pitot's committee gave it a priority score of 152, which is in the estimated funding range.

It was not so far under the payline, however, to make it impossible for the NCAB to skip over. The payline is 154.

The application also was given a 13.2 percentile ranking, but in this case, that is meaningless. NIH wide, ROIs up to the 20th percentile are being funded, which would seem to be well over Diet Fit's ranking. Percentile rankings were adopted last year by NIH for most R01 grants as a way to "normalize" scores among study sections. That system cannot be used for special study sections, and the 13.2 given to Diet Fit was assigned by a computer without any relevance to the real ranking.

That was one of the inaccuracies in the report given to The Cancer Letter. Another

was the vote, originally reported as 6-3 (later corrected to 9-3) against funding.

Also misleading was the report that many NCAB members did not receive the grant pink sheets until the night before the meeting. NCAB member Roswell Boutwell phoned to point out that complete pink sheets are given to members assigned to specific research areas. Others get only the front pages unless they request the complete document. Those assigned to the area which included Diet Fit received the entire pink sheet; complete sets were sent to others the night before the meeting when it was realized that all members might need more details because of the controversy involved.

The Cancer Letter presented the following question to Broder, Korn, and Boutwell:

"In refusing to fund an important grant which was scored in the funding range by reviewers with unquestioned qualifications, should not the NCAB be held accountable and asked to make public its reasons for that action?"

Broder: "I do not necessarily disagree, but this grant is still under discussion. It would be inappropriate to discuss issues under review. There will be significant dissent either way the decision goes. There are strongly held, defensible views on both sides. I am impressed with the sincerity, honesty, integrity, and ability of this board, including the lay members. There is enormous strength there."

Korn: "There are serious scientific issues in this proposal that have not been resolved. There is serious concern about the feasibility, the science, and techniques. It is not a political issue. The proposal would require a major investment of federal funds, and there is much serious doubt about its value. If and when a disposition of the matter is concluded, it might be appropriate for the board to make a statement about its decision."

Boutwell: "I agree with you wholeheartedly, that ignorance breeds rumors. I spoke only about scientific issues that I know something about. In Wisconsin, we can't close the doors when scientific issues are being discussed. There may be issues here that I don't understand, but I agree that scientific issues should be on the record."

In the aftermath of the board's action, the suggestion was made in some quarters that Broder might ignore his "advisors" and fund the grant anyway. That will not happen. The NCAB's primary statutory authority is to approve funding of all grants with direct costs of more than $50,000. The board can and frequently does offer all kinds of advice to NCI directors [which they almost always follow although they do not have to], but he can't award a grant of more than $50,000 without the board's approval.

Gramm-Rudman Could Cut $85 Million From NCI In 1990; Budget In Flux

As across the board cuts in government spending went into effect this week, it was not clear exactly how much would be cut out of NCI's fiscal year 1990 budget, and for how long.

President Bush signed an order imposing cuts in defense and domestic programs as required by the Gramm-Rudman-Hollings deficit reduction law. The cuts were mandatory when Congress failed to meet the deadline for reducing the fiscal 1990 deficit below the $110 billion ceiling set by the law. Congress may rescind the cuts within a few weeks, however.

Under a conference committee bill on spending for the Depts. of Heath & Human Services and Labor, NCI would receive $1.664 billion in 1990, about $94 million above the 1989 level.

President Bush has threatened to veto the bill because it allows federal funding of Medicaid abortions for women who are victims of rape and incest.

Budget projections developed by NCI in September showed that under a 5.3 percent Gramm-Rudman-Hollings budget cut, NCI's budget would be cut by $85 million.

NCI Deputy Director Maryann Roper said last week that in addition to the Gramm-Rudman sequestration, the institute's budget would be cut in several other ways: A $4 million mandatory cut for "procurement reform"; $3 to $4 million from an NIH-wide $10 million cut in contractor salaries; some portion of an NIH-wide cut of $15 million that will go toward extramural construction; and $8 million as part of a .5 percent government-wide tap for the "war on drugs."

"It is possible that NCI's 1990 budget could end up as much as $10 million below the 1989 budget," Roper said. She said this would mean that downward negotiations for grant awards would be more severe than last year, at least 10 percent for competetive awards and 4.6 percent for noncompetitive awards.

As of presstime this week, NCI had not received word on the exact amout of cuts that would have to be taken under Gramm-Rudman.