THE CANCER LETTER

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HHS System Of Misconduct Investigation Not Suited For Clinical Trials, Broder Says

The system for investigating and punishing scientific misconduct was designed for single institutions and is inadequate for confronting wrongdoing in multi-institutional clinical trials, NCI Director Samuel Broder said to an HHS advisory panel earlier this week.

"The original model has been to identify, detect and [discipline] individual scientists who commit acts of scientific misconduct, primarily at a specific institution," Broder said to the HHS advisory Commission on Research Integrity at a meeting Nov. 7. "This model, in my opinion, is not

(Continued to page 2)

In Brief

Schilsky Succeeds McIntyre As CALGB Chair; UC Irvine Awarded New Cancer Center Grant

RICHARD SCHILSKY was elected chairman-elect of the Cancer & Leukemia Group B at the cooperative group's board meeting last week. Schilsky, director of the Univ. of Chicago Cancer Center, will become chairman of the group next April 1. He succeeds **Ross McIntyre**, the James J. Carroll Professor of Oncology, Dartmouth-Hitchcock Medical Center, who will have served the five-year term. The CALGB central office will move from Dartmouth to Chicago. . . . **UNIV. OF CALIFORNIA** at Irvine Clinical Cancer Center was the only new NCI-designated cancer center in FY94, receiving a P30 Cancer Center Support Grant of about $3 million over three years. The center is one of 54 NCI-designated cancer centers in the US. "We are proud and thrilled about this national recognition for the UCI Cancer Center," said center director **Frank Meyskens Jr**. Co-PI on the support grant is **Hung Fan**, director of the UCI Cancer Research Institute. The center is recruiting for a chair in the new Dept. of Radiation Oncology. Contact Meyskens, who is chairman of the search committee, Tel: 714/456-6310, FAX 714/456-5039. . . . **SAMUEL BRODER**, NCI director, was awarded the Jeffrey A. Gottlieb Memorial Award by M.D. Anderson Cancer Center this week. The award recognizes physicians and scientists who have made contributions to research in cancer therapy. Broder was honored for his understanding of "the significant role of therapeutic research, recognizing the essential interaction between basic biology, therapeutic research, prevention research, and all related disciplines," said Emil Freireich, professor of medicine at M.D. Anderson. . . . **BREAST CANCER WORKSHOP** sponsored by NCI titled "An Appraisal of Clinical Research for the Treatment of Early Breast Cancer" is scheduled

(Continued to page 8)

Wanted: New Way To Handle Misconduct In Clinical Trials

(Continued from page 1)

easily transplanted when one is dealing with multi-institutional clinical trials."

The commission was created to examine the HHS policies on scientific integrity.

Opening with the caveat that he was speaking for himself rather than for his Institute, Broder said the existing system was incapable of handling scientific misconduct in clinical trials and suggested that scientists be forced to report misconduct on informed consent forms, in a manner identical to reporting of drug toxicities.

Broder's views appeared to be at odds with those of the NIH Director Harold Varmus, who told the advisory group that, by-and-large, the system of handling scientific misconduct functioned adequately.

"On the whole, [the HHS Office of Research Integrity] has succeeded in many ways," Varmus said at the same meeting.

One area of concern was the slow conduct of investigations, he said. In particular, the allegations related to the controversy over the National Surgical Adjuvant Breast & Bowel Project have taken too long to process, he said.

"It has been said that justice deferred is justice denied, and when cases take many months, or even years to reach satisfactory conclusion, that serves no one well," Varmus said.

Fraud, falsification and plagiarism by scientists is "neither rare nor common," Varmus said. "It occurs frequently enough to be of serious concern, but not so frequently that we should feel that the fabric of science is unraveling before our eyes," he said.

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The list of remedies suggested by Varmus was limited to adjustments to the existing system: placing a greater emphasis on ethics in the education of young scientists and a clear elaboration of the circumstances when ORI should take over an investigation being conducted by an institution.

Broder: Clinical Trials Present A Special Case

By contrast, Broder said scientific misconduct in multi-institutional clinical trials presented a special challenge and required special standards for investigation, special authorities for NCI, and—ultimately—a higher standard of accountability to participants of trials and the entire society.

"We must have the ability to investigate and audit that may go outside the specific determining roles of a particular ORI investigation," Broder said. "The public may frequently say, Don't give me a statement that you don't know. And the only way to answer that is to conduct our own audit."

In cases where ORI is called in to undertake an investigation of scientific misconduct in multi-institutional trials, the office should be obligated to provide a plan or a time table for completion of its work, Broder said.

"The ORI should give special deference to the request of a granting agency for expeditious handling of the matter or for assistance in identification of failure of compliance," Broder said. "They should give this matter extreme gravity. In one sense, ORI and [the HHS Office of Protection from Research Risks] is providing a function on behalf of the grantor."

As ORI conducts investigations of misconduct in clinical trials, it operates in a setting radically different from an investigation involving a small number of people at a single institution, Broder said.

Multi-institutional clinical trials may frequently involve 500 sites or more," Broder said. While it is difficult enough to deal with misconduct issues at a particular institution, "it is exponentially more complicated if you now want to ask an individual grantee to monitor and conduct inquiries and validating at multiple sites."

Even in cases where no scientific misconduct is found, NCI should have the authority to withdraw funding from institutions that are found to be performing poorly, Broder said.

An Adverse Event

"At least as far as multi-institutional clinical trials

are concerned, scientific misconduct must be viewed as an adverse event," Broder said.

As such, scientific fraud would have to be reported in informed consent forms, brought to the attention of data safety monitoring boards, and noted in publications.

"There is very low threshold for notifying individuals about adverse events," Broder said. "There are also established mechanisms for dealing with adverse events.

Reinventing NCI

Intramural Clinical Research Could Lose "Critical Mass"

NCI's intramural clinical research should not be downsized further, or the Institute will lack a "critical mass" of patients and physicians to carry out worthwhile investigations, an NCI official said to an advisory committee recently.

NCI can downsize without harming its best research by eliminating some duplication, but its clinical research programs should be protected from budget cuts, NCI Div. of Cancer Treatment Director Bruce Chabner said to the DCT Board of Scientific Counselors last month.

"I am very concerned about the future of clinical research at NIH," Chabner said to the board. "We are rapidly approaching the point where we will not have a critical mass of clinical activity, both patients and physicians, to create an effective clinical facility."

Less than 200 inpatients per day are using the NIH Clinical Center, Chabner said. About half of the patients are participants in NCI research programs.

"If our clinical programs downsize significantly, the Clinical Center will cease to be viable as a clinical care facility," Chabner said.

Chabner, who announced at the meeting that he plans to leave NCI next May, also warned against the consolidation of the Institute's intramural research programs. A working group of the National Cancer Advisory Board met earlier this month to begin a review of NCI's internal programs (**The Cancer Letter**, Nov. 4).

"There Is Some Duplication"

"NCI can and must downsize without sacrificing its most valuable research programs," Chabner said to the DCT board. "There is some duplication and there are projects that do not meet the highest standards. In the process of downsizing, it will be important to examine resources across divisions to achieve economies and consolidations.

"However, I believe it would be virtually impossible to consolidate all intramural programs under one person and maintain informed and effective leadership," Chabner said. "The basic and clinical programs are simply too diverse and too specialized to incorporate under a single scientific leadership.

"I believe it would be a mistake to separate the intramural and extramural programs across the board," he said. "While separation might have minimal negative impact for certain grant-related programs, for other undertakings such as drug discovery and development, the intellectual life-blood flows from intramural research.

"Drug discovery for cancer and AIDS cannot be separated from the intramural biology and pharmacology laboratories, and from the clinical services, without depriving the effort of its connections to basic research," Chabner said.

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NCI grantees may have to assume services that the Institute traditionally has done internally, NCI Director Samuel Broder said to the DCT board last month.

Services such as helping companies file Investigational New Drug applications for the FDA or aiding cooperative groups with monitoring of clinical trials may have to be done by grantees—with additional funding from NCI, Broder said.

"[HHS Secretary] Donna Shalala gave us reassurances that biomedical research will grow, but the Federal workforce is going to fall," Broder said. "Some functions that we have traditionally done centrally are going to have to be decentralized."

The "reinventing" and "streamlining" of the Federal workforce in response to Vice President Gore's report will force NCI to make major changes, Broder said.

"If we attempt to do business as we have done in the past, we will end up with problems," he said.

NCI staff and the extramural community must be "unshackled from prior conventions" in order to cope with the 19 percent cut expected in the Institute's workforce between FY 1993 and FY 1999, Broder said. He invited advice from the board.

It may not be effective simply to ask Congress for more money, Broder implied in his remarks to the board.

For the 1995 appropriations, Congress gave NCI

and NIH less than the amount requested by President Clinton. NIH received the largest dollar increase of any program in HHS.

In addition, NCI has not been "severely restricted in comparison to our sister institutes," Broder said. NCI and the National Heart, Lung and Blood Institute have had an 8 percent growth rate compared to 11 percent for NIH overall.

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Downsizing of NCI "flies in the face" of the recommendations made by a special committee of the National Cancer Advisory Board, said DCT Board member Paul Sondel, professor of pediatrics, oncology and genetics at the Univ. of Wisconsin Comprehensive Cancer Center.

The Subcommittee to Evaluate the National Cancer Program, in a report two months ago, said the US was not reaping the full benefit of the past 23 years' investment in cancer research due to serious funding gaps in basic and translational research. The report identified other problems, including lack of coordination of federal programs, and lack of access to quality health care (**The Cancer Letter**, Oct. 7).

The report called for a $60 million increase in funding for translational research, and an increase of $180 million for investigator-initiated grants.

"That recommendation in the current world cannot be met," Broder said to the DCT board. "It is an illusion" to think that expansion can take place without cuts in other areas, he said.

"We will have to think of novel ways for contractors to take on additional responsibilities," he said. For example, the monitoring of clinical trials could be done by grantees by using funds in the research project grants pool, he said.

Board Chairman Clara Bloomfield asked whether that meant DCT's new Clinical Trials Monitoring Branch would be eliminated.

The branch was created in response to the "emergency" NCI faced with the National Surgical Adjuvant Breast & Bowel Project, Broder said. "What one does in an emergency situation is not what one would do normally," he said.

If he were to see a restaurant patron choking on food, Broder said, he would perform the Heimlich maneuver. "That's not the normal way to greet people," he said.

"We don't want emergencies," Broder continued. "Cooperative groups that cause emergencies for us may not be funded in the future. We won't have the luxury to rehabilitate them."

New AIDS Clinical Trials Group Approved In Concept By BSC

Advisors to the NCI Div. of Cancer Treatment approved in concept a new grant program to establish a consortium of institutions conducting clinical trials of AIDS-associated malignancies.

The proposed Request for Applications would make $2 million available in the first year to fund about 10 grants. The new grants will be administered by the Cancer Therapy Evaluation Program.

The DCT Board of Scientific Counselors also gave concept approval to two program announcements by the Developmental Therapeutics Program inviting AIDS-related research proposals, and a CTEP program announcement for the Clinical Trials Cooperative Groups.

Also approved was the recompetition of two contract programs. Concept statements follow:

DCT Clinical Trials Cooperative Groups. Program announcement, planned announcement date January 1995, review by Cancer Clinical Investigations Review Committee. Cancer Therapy Evaluation Program.

NCI is reannouncing its intention to accept applications from institutions interested in conducting multi-institutional clinical trials in a Cooperative Group setting. Awards shall continue to be made using the cooperative agreement mechanism (U10). Potential applicants will be encouraged to contact the Cancer Therapy Evaluation Program staff to discuss and/or clarify any issues or questions regarding this announcement. The "Guidelines, Clinical Trials Cooperative Group Program" and the "Cooperative Group Terms of Award" are available upon request from CTEP.

The Clinical Trials Cooperative Group program was conceived in 1955, when Congress appropriated $5 million to NCI to establish the Chemotherapy National Service Center. By 1958, 17 groups were operated under research grants from NCI; their main activity was the testing of new anticancer agents from the NCI drug development program. The program has evolved into one that places major emphasis on definitive studies of combined modality approaches to the treatment of cancer.

During 1980-81, the mechanism of support for the Cooperative Group program was converted from grant support to a cooperative agreement. The purpose of this change was to define the involvement of NCI program staff in the coordination of group activities.

There are ten NCI-funded groups. These groups accrue approximately 20,000 new patients onto treatment studies each year, with many times that number of patients in follow-up. Thousands of investigators participate in Cooperative Group protocols, and over $75

million is awarded annually by NCI in support of Cooperative Group research.

NCI's Cooperative Groups consist of researchers who jointly develop and conduct cancer treatment clinical trials in multi-institutional settings. Each group is supported to generate new trials compatible with its particular areas of interest and expertise, as well as with national priorities for cancer treatment research. While a wide variety of investigational efforts are therefore appropriate, this program does not overlap with or replace funding mechanisms for more narrowly focused, Research Project Grant activities.

The goals of the DCT Clinical Trials Cooperative Group program are:

1. Improved Therapy—Therapeutic research aimed at improving the survival and quality of life for persons with cancer is of highest priority to DCT. Emphasis is placed on definitive, randomized Phase III studies and the developmental efforts preliminary to them.

2. Adjunct Studies—The database of patient information accumulated in the course of treatment research, including the possibilities for large-scale collection of tissue samples with subsequent correlation of biologic features with patient outcome, provide the groups with unique opportunities to address scientific questions about genetics, epidemiology, pathology, and other cancer-related topics.

3. Cancer Control—Groups supported by DCT may serve as research bases for treatment and cancer control research performed by Community Clinical Oncology Program cooperative agreement awardees supported by NCI's Div. of Cancer Prevention and Control.

4. Clinical Trials Methodology—The program provides a unique framework for research in clinical trials methodology. While CTEP encourages development of and experimentation with new study designs within the Cooperative Group framework, purely statistical research is appropriately funded through other mechanisms.

AIDS-Associated Malignancies Clinical Trials Consortium. Proposed RFA, first year award $2 million, total four years, special review committee. Cancer Therapy Evaluation Program.

Individuals infected with HIV have a marked increase in the appearance of intermediate and high-grade B cell non-Hodgkin's lymphoma (NHL) and Kaposi's sarcoma (KS), and show trends for an increased incidence for Hodgkin's disease, anogenital dysplasia and cancer, as compared to age-matched controls.

NCI is encouraging investigators to apply novel therapies or innovative approaches in pilot or Phase I and II clinical trials.

Although there is clinical trials research in AIDS malignancies in the currently funded NIH clinical trials cooperative groups, none of the groups place AIDS malignancies as a top priority. This may be due to the relatively small proportion of AIDS-related malignancies compared to the general population with cancer, and the major emphasis on controlling the underlying HIV infection and opportunistic infections in the AIDS clinical trials. The result is a small number of patients with AIDS-associated malignancies in all trials, and/or a very slow accrual rate. This may also be due, in part, to inadequate referrals to trial investigators.

The accrual targets for trials in AIDS-associated malignancies may best be achieved through a multicenter Consortium through a cooperative agreement award (U01) in which prioritization of studies is made, and the patient volume is large and accessible. NCI would now like to strengthen the therapeutic trials process by establishing a multicenter Consortium to hasten the development of exploratory, Phase I and Phase II clinical trials using novel agents or innovative approaches, with the goal of moving towards Phase III testing. The clinical trials' objectives and approaches will be investigator-initiated, but consistent with the program aims of improving the survival and quality of life for persons with AIDS-associated malignancies and providing fundamental insights into the biology of these tumors. Collaborative interactions between clinicians and laboratory scientists are essential features of these types of investigations.

The project will use the cooperative agreement (U01) to fund approximately 10 applications to design and develop clinical trials with novel agents or using innovative approaches in patients with AIDS-associated malignancies. NCI is seeking talented scientists from academic and nonprofit research organizations who will interact with other members of the Consortium, and with CTEP to conceive, create, and evaluate new approaches to therapy of AIDS-associated malignancies. Scientific approaches should be broad and reflect the creativity and capabilities of team participants. Each application may consist of one institution or multiple institutions.

Eligible institutions may apply for one or more of the following types of awards: (1) Clinical Trials Member, and (2) Operations, Statistical and Data Management Center. Separate applications must be submitted for each type of award. One consortium, called the AIDS-Associated Malignancies Clinical Trials Consortium, will be developed out of the separate, U01-funded awardees. One statistical, operations, and data management center will be funded through a U01, to coordinate the statistical, operational, and data management issues for the Consortium. The potential exists for expanding to Phase III studies should the initial efforts with this project prove successful, and relevant Phase III questions are appropriate.

Cancer Therapy Evaluation Program Computer Support. Recompetition of contract held by Capitol Technology Information Services. Estimated $2.54

million per year, total five years.

This contract supports the computer systems of CTEP. These systems include: the CTEP Information System (CTEP-IS), the PMB Inventory Management System (PMB-IMS), the Adverse Experience Reporting System (AERS), Annual Data Updates (ADU), Quarterly Data Updates (QDU), CTEP-LAN, PMB-LAN, the Clinical Trials Monitoring Branch-Information Management System (CTMB-IMS) and the Regulatory Affairs Branch (RAB) Cooperative Research and Development Agreements (CRADAs) and Clinical Trials Agreements (CTAs) Data Base systems.

The existing CTEP-IS and PMB-IS databases will be maintained and future development will include their full integration and standardization. The QDU, PQDU, and ADU systems will be fully integrated within the CTEP-IS. The development of a Therapeutics Development Clinical Trials Information Management System for the Investigational Drug Branch will need to be continued. Full development and optimization of the RAB databases will be required.

To complete and maintain each of these new systems, significant additional programmer and technical staff will be required beyond the current contract. Projected staffing to maintain and refine PMB-IMS, CTEP-IMS, BRB, and AERS includes one principle investigator, one project manager, four programmers, two documentation specialists, one LAN manager, one systems analyst, and one hardware specialist. Additionally, six data clerks and one courier will be required to support these systems. Development of the IDB database will require two programmers, two technical support/trainers, and two data clerks. The RAB database will require a programmer, two technical support/trainers and two data clerks. Requirement definition and then system development, implementation, and training for the CTMB will require two programmers, two technical support/trainers, and three data clerks.

Synthesis of Bulk Chemicals and Drugs for Preclinical and Clinical Studies. Recompetition of contracts held by Ash Stevens Inc., Pharm Eco Laboratories, and Starks Associates. Estimated $3 million a year, total three years, with two additional one-year options. Developmental Therapeutics Program.

The chemical preparation laboratories are service laboratories designed and selected to prepare known chemical and bulk drugs that are needed by the program for preclinical and clinical studies.

During the past three years, the contractors have collectively produced an average of 85 individual preparations per year. The following are a few examples of compounds prepared under these contracts: 9-aminocamptothecin (NSC 603071, 200 gm), CAI (NSC 609974, 9 kg), pyrazoloacridine (NSC 66140, 6 kg), 6-O-benzylguanine (NSC 637037, 1.7 kg), penclomedine (NSC 338720, 20 kg), temozolomide (NSC 362856, 15 kg), BE4/4 (NSC 640506, 1 kg), breflate (NSC 656202, 750 gm), cosalane (NSC 658586, 100 gm), protease inhibitor (NSC 654021D, 120 gm), quinobene (NSC 638352, 500 gm), B-F-DDA (NSC 613792, 2 kg), calanolide A (NSC 650886), and others.

In the past, each organization held two or more contracts with identical work scope, but the contracts were segregated according to whether the compounds were related to AIDS or cancer. We propose to combine all six contracts into one contract to save administrative expenses and time. The combined capacity will enable us to undertake 60-100 synthetic projects annually depending on complexity and size of the project. The "AIDS only" contracts, in force until 1997, will be negotiated to close in 1996. The estimated annual amount of $3 million reflects a 13% reduction from the FY 1995 levels.

Modulators of Apoptosis for Treatment of AIDS and AIDS-Related Malignancies. Proposed program announcement. Planned announcement date December 1994. Developmental Therapeutics Program.

It is proposed that R01/R29 grants be established for discovering new approaches and agents to modulate apoptosis in AIDS-related malignancies. Possible examples include, but are not limited to, altering gene expression or gene products which regulate apoptosis, i.e., p53, c-myc, bcl-2 or bax, DNA repair mechanisms, stimulation of oxidative damage or stress, and growth factor action in regulation of apoptosis. Applications should be focused on discovery of agents for modulation of apoptosis and not on new approaches designed solely to understand basic principles of the apoptotic process. Development of in vitro and in vivo model systems for discovery of apoptotic modulators is encouraged. Applications could include discovery and biological evaluation of active agents using these models.

Models for AIDS and AIDS-Related Malignancies. Proposed program announcement, first year award $2 million, total three to five years, announcement date December 1994. Developmental Therapeutics Program.

The goal of this proposed program announcement is to solicit the development of useful and predictive biochemical, cellular, and in vivo models for evaluation of new therapies against HIV and AIDS-related malignancies. Some examples are listed below:

•Biochemical Assays. Rapid, resource efficient, and cost effective assays to evaluate new agents that block events in HIV virus replication are encouraged. Models for well-studied targets such as reverse transcriptase and proteases are not encouraged. For those AIDS-related cancers in which a putative cofactor may be involved, approaches are sought to identify and define the precise role of the cofactor in the specific malignancy and to

exploit this information for therapeutic advantage.

•Cell Culture Assays. It is desirable that new cell culture models be developed for HIV replication and AIDS-related malignancies that more closely simulate the in vivo state. Models that mimic the three dimensional, multicell-environment or those based on single cycle replication kinetics would be of utility. For AIDS-related cancers, cell culture systems predictive of in vivo events that allow for studies of the mechanism(s) of action of specific cofactors and that would be useful for evaluating potential therapies are highly encouraged.

•In Vivo Models. Models that reflect the state of knowledge of AIDS pathogenesis, are simpler and less expensive than available models are needed. Novel approaches using transgenic and gene knockout animals are especially encouraged. Other animal models can be proposed. Non-lentivirus models are not encouraged.

Letter to the Editor

NCI Mammography Pamphlets Little More Than Propaganda

To the Editors:

The House Subcommittee on Government Operations report critical of NCI's decision to change its guidelines for breast cancer screening (**The Cancer Letter**, Nov. 4) confirmed the contrived sequence of events leading to the change, the lack of objective analysis behind the decision, and NCI's failure to provide women and their physicians with a balanced review of the data.

Of particular concern was the fact that the NCI Executive Committee, for the first time in its history, had disregarded the near unanimous advice of the National Cancer Advisory Board, and yet there is no record of a meeting or a vote by that committee. Beyond the director, there is no clear responsibility for this major change in "NCI" policy.

Your readers may be interested in knowing that NCI has continued to promote a one-sided and incomplete analysis of the data with the recent publication of two NCI pamphlets that purportedly explain the use of mammography, but do little more than try to buttress NCI's screening recommendations.

The pamphlets are "Understanding Mammography," July 1994, NIH Publications #94-3836, and "Screening Mammograms," July 1994, NIH Publications #94-3835.

Having obtained copies of the printed pamphlets, breast imaging experts identified significant factual errors in the material, and urgently requested that NCI withdraw and revise the brochures. This has apparently resulted in the withdrawal of the pamphlet aimed at physicians, but the pamphlet for the public is still being distributed.

In addition to providing incomplete information and an outdated analysis of the screening data to bolster NCI's position on screening, the pamphlets contain factually incorrect information:

1. The brochure for the public states, "All major cancer and health organizations agree that screening every 1 to 2 years with mammography can reduce cancer death rate by about one-third for women ages 50 and older."

In fact, the majority of the organizations recommend screening every year for these women, and do not advise an interval of 2 years.

2. The physicians brochure has a heading, "What are the Pros and Cons for Screening Women ages 40-49?" yet none of the "Pros" are provided.

3. The pamphlets are misleading when they suggest that since 80% of cancer occur in women ages 50 and over, cancers in women under the age of 50 are not important. The Institute continues to repeat this comparison of women ages 40-49 with *all other women* despite having been shown how this biases the interpretation of the data.

The fact is that in 1993, 16% of breast cancers occurred in women ages 40-49, but the Institute continues to ignore the fact that only 17% of cancers occurred in women ages 50-59. The same rationale could be used to suggest that breast cancer is not important for women ages 50-59 because 83% of cancers occurred among women who were not in their fifties.

A similarly specious argument could be used to avoid screening women ages 60-69 since 76% of cancers occurred among women who were not in their sixties. NCI is well aware of these figures. The Institute's perpetuation of this type of analysis can at best be termed deceptive.

4. The results from the Malmo trial, showing a 49% mortality reduction for women under the age of 50, were not included in a table that summarizes the data from the clinical trials.

5. The pamphlets provide incidence data, but are worded in such a way as to suggest rates that are an order of magnitude too low. The pamphlet suggests there will be "only 159 cancers that develop among 100,000 women in their forties." These are annual incidence figures, but the wording suggests that they are for a whole decade. Each year there will be 159

new cases. There will be 1,590 over the decade.

6. The brochures provide numbers for the sensitivity of mammography that are simply incorrect. The pamphlets state that mammography fails to detect 40% of breast cancers in women ages 40-49. The figure is extrapolated from outdated mammographic techniques and one screening trial that used single view mammography. Single view mammography alone has been shown to result in missing more than 10% of breast cancers. Furthermore, far more cancers are missed by clinical examination than by mammography at all ages, yet NCI urges clinical breast examination. Modern screening programs detect the same percentage of small cancers among women in their forties as among women in their fifties.

7. The pamphlets continue to reinforce the myth that there are abrupt changes at age 50. They suggest that the detection rate and positive predictive value (PPV) of mammography suddenly improve at age 50. This is simply not the case and is a misrepresentation resulting from faulty analysis. NCI bases much of its argument on a publication that arrived at spurious conclusions because the authors artificially grouped their data using the age of 50 as their point of analysis (Kerlikowske, K. et al., Positive Predictive Value of Screening Mammography by Age and Family History of Breast Cancer, JAMA 1993;270:2444-2450).

There is a steady increase, with increasing age, in the detection rate and PPV of mammography that merely reflects the steady increase with age of the prior probability of cancer in the population. By analyzing data that actually change steadily with increasing age, but using artificial grouping and age 50 as the point of analysis, these data are made to appear to change abruptly at that age. NCI has continued to ignore the basic scientific facts that the data, when analyzed by individual ages, show that any parameters that change with age (breast density, detection rate, etc.) change gradually and steadily, with no abrupt change at age 50, or at any age.

8. The pamphlets discourage the use of mammography for screening women ages 40-49, yet continue to support the use of clinical breast examination. If NCI disregards data that show a benefit for mammography, it is unclear how it can continue to suggest that clinical breast examination has any value in reducing the death rate from cancer. If recommendations are to be based on "evidence," this recommendation is insupportable. No study to date has "shown conclusively" that clinical breast examination has any benefit, particularly, as stated in the pamphlets, for "women of all ages."

The pamphlets state that there is "no evidence from empirical studies...available to evaluate the efficacy of...a clinical breast examination." That is simply false. The Health Insurance Plan of New York, the Edinburgh trial, and the National Breast Screening Study of Canada all screened their younger women with both clinical breast examination and mammography. The results of these trials have been used to disparage mammography, despite the fact that two out of the three have demonstrated a benefit for women under the age of 50. If NCI rejects the benefit from mammography shown by these trials, the Institute also must interpret the trials as showing no benefit for clinical breast examination for women ages 40-49. NCI persists in a total lack of scientific consistency and honesty.

9. The pamphlets persist in the unsupported distinction between "screening" and "diagnostic" mammography. NCI continues to perpetuate an incorrect emphasis on diagnostic mammography. The value of diagnostic mammography and screening mammography have been detailed in a previous letter to **The Cancer Letter** (March 11, 1994).

The lack of scientific integrity and accuracy displayed in these pamphlets is astonishing. The credibility of NCI already is in question with regard to the issue of breast cancer screening. These pamphlets are little more than propaganda to promote the Institute's position.

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SPORE Briefing Is Nov. 30

(Continued from page 1)

for Nov. 15, 8 a.m., at the Holiday Inn Bethesda. Contact Carmen Warren, Tel: 301/907-3844. . . . **SPORE BRIEFING:** NCI has planned a briefing session for those who plan to submit a letter of intent in response to the RFA for SPOREs in prostate cancer (**The Cancer Letter**, Sept. 23). The briefing is scheduled for Nov. 30, 8:30 a.m., Bethesda Marriott. Contact Andrew Chiarodo, Tel: 301/496-8528. . . . **BREAST CANCER SONGS:** Bristol-Myers Squibb Co., the National Alliance of Breast Cancer Organizations, Hammer & Lace Records, and Hearst Publications have sponsored a recording of female vocalists. One dollar from each sale of the recording, Women for Women, will benefit NABCO. The recording, which is not available in stores, may be ordered by calling 1-800-877-SONG.