THE CANCER LETTER

Vol. 20 No. 16
April 22, 1994

Price $225 Per Year US, Canada
$250 Per Year Elsewhere

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

NCI Apologizes For Mismanagement Of NSABP, Says Fisher Resisted Criticism

NCI officials last week acknowledged that they failed to act decisively in managing the National Surgical Adjuvant Breast & Bowel Project.

In testimony before the House Energy & Commerce Committee's subcommittee on oversight and investigations last week, NCI Director Samuel Broder said the former NSABP chairman Bernard Fisher "did not respond to constructive criticism by NCI staff" and failed to publish a new analysis of studies tainted by fraud committed in a Montreal hospital.

However, Broder said, "our staff failed to mobilize after warning signs of delay in clearing up the scientific literature and repairing inadequate compliance with auditing requirements.

"This may have occurred because of several factors: NSABP's proud reputation, the visible status of Dr. Fisher in the scientific community and as a member of our Presidentially-appointed National Cancer Advisory

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In Brief

NCI Names Rice To Head Frederick Center; NIAID Appoints Killen DAIDS Director

JERRY RICE has been appointed director of the Frederick Cancer Research & Development Center, NCI Director **Samuel Broder** has announced. Rice replaces Div. of Cancer Etiology Director **Richard Adamson**, who served as acting director of the center for 14 months following the death of **Werner Kirsten**. Rice, chief of DCE's Laboratory of Comparative Carcinogenesis since 1981, joined NCI in 1966. His research interests are in mechanisms of carcinogenesis, especially perinatal carcinogenesis. . . . **JOHN KILLEN** has been selected as director of the Div. of AIDS of the National Institute of Allergy & Infectious Diseases. He served as acting director of DAIDS since June 1993, following the resignation of Daniel Hoth. Killen joined NIH in 1980 as senior investigator in the Clinical Investigations Branch of NCI's Div. of Cancer Treatment. From 1981-84, he headed the Medicine Section of the branch. Upon leaving NCI, he was deputy chief and program officer for the Clinical Trials Cooperative Groups. From 1986-87, he was medical director of the Whitman-Walker Clinic in Washington, DC. Killen joined NIAID in 1987 as assistant director for clinical trials. In March 1988, he was appointed deputy director of DAIDS. . . . **GORDON McVIE**, scientific director of the British Cancer Research Campaign, last week was appointed president of the European Organization for Research and Treatment of Cancer.

Broder: 'We Are Very Sorry... Errors Will Not Happen Again'

(Continued from page 1)

Board, a self-consciousness in asserting authority over an independent researcher, or a mistaken belief that somehow the lapses by a senior research group were temporary.

"We are very sorry that this has happened, and we assure you that such errors will not happen again," Broder said to the subcommittee.

Fisher, 75, is credited with revolutionizing the treatment of breast cancer. NSABP came under attack last month, following the disclosure that surgeon Roger Poisson of St. Luc Hospital in Montreal was found guilty of scientific misconduct after submitting falsified data to NSABP's studies. Complying with NCI's demand, Fisher resigned from his post at NSABP in March.

The controversy prompted NCI to make major changes in its clinical trials monitoring and auditing procedures, Broder said.

Fisher, who had been expected to testify, did not attend the hearing, citing illness. He issued a statement attributing the cooperative group's lag in auditing to underfunding and an increase in workload caused by the 1992 launch of the Breast Cancer Prevention Trial.

The publication of reanalysis of the pathbreaking lumpectomy study and studies of tamoxifen in breast cancer were planned but were not given high priority, Fisher said. *(Fisher's statement appears on page 11).*

Representatives from consumer advocacy groups and breast cancer survivors testified that they had lost faith in NCI due to the Institute's slow response to the problems and lack of public disclosure of the fraud. They called for more consumer representation on scientific oversight and advisory committees as well as on study sections.

As the hearing concluded, Rep. John Dingell (D-MI), subcommittee chairman, said he was satisfied with NCI's action to remove Fisher as principal investigator and to tighten the monitoring of clinical trials. He said he will ask Fisher and other representatives from the Univ. of Pittsburgh to testify at a second hearing to discuss the management of the cooperative group.

Also certain to come under scrutiny is the controversy over the risk of uterine cancer death from the drug tamoxifen, Dingell said. Under Dingell's questioning, Broder said NCI should have been told in early 1992 of the first uterine cancer death of a patient taking tamoxifen in NSABP's B14 study of the drug as prevention for recurrence of breast cancer.

That information could have affected the status of the Breast Cancer Prevention Trial which is testing tamoxifen's potential to prevent breast cancer in healthy women at high risk of developing the disease, testified Cindy Pearson, program director of the National Women's Health Network.

In a related development last week, the NIH Office of Research Integrity has begun an investigation into potential fraud discovered at another hospital in Montreal, St. Mary's Hospital Center. In a statement, ORI said that the investigation has uncovered five instances of potentially falsified data involving three patients entered in the Breast Cancer Prevention Trial.

The April 13 hearing signaled the determination by Congress to play an increasing role in the managing—and, in the process, politicizing—biomedical research. "Many in the scientific community have resisted outside scrutiny, and others have sought to minimize the problem," Dingell said. "Scientific misconduct is a very real problem that requires an aggressive response by the scientific community and the federal government.

"The case before us is a vivid reminder of how poor the response of the scientific community can be, and how serious the consequences may be when the scientific community and the federal government fall down on the job," he said.

Loss of Public Trust

Members of Congress, women's health advocates and breast cancer survivors said they were shocked to learn—one year after the fact—that the NIH Office of Research Integrity had found that Poisson had

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Subscription $225 per year North America, $250 elsewhere. ISSN 0096-3917. Published 48 times a year by The Cancer Letter Inc., also publisher of The Clinical Cancer Letter.

falsified data involving patients enrolled in 14 NSABP studies, including the B06 trial of lumpectomy and radiation versus mastectomy (**The Cancer Letter**, March 18).

"I cannot understand why a medical doctor would falsify data in a study intended to guide thousands in making what could be a life or death decision, and why the people given the responsibility to oversee the study did not publicize the fraud immediately," Jill Lea Sigal, diagnosed with breast cancer six months ago at age 32, said to the subcommittee. Sigal said she based her decision to have a lumpectomy on the results of the NSABP B06 study.

"The discovery that officials at NCI and NSABP not only knew about the fraud, but that they did nothing to make this important information readily available to the public and the scientific community is the most disturbing fact," Fran Visco, president of the National Breast Cancer Coalition and a member of the President's Cancer Panel, said to the subcommittee.

"While we appreciate the fact that it appears as though this time women with breast cancer were not placed in great jeopardy by the deceit and negligence of the scientists involved, we are outraged that the information was kept from the public, from women with breast cancer, other institutions, and from physicians who were advising women," said Visco, a breast cancer survivor.

Since its inception, Visco's group has advocated more involvement of breast cancer advocates and patients in setting research priorities.

"I recently read in [The New York Times, March 27] a quote from a top official at NCI [Michael Friedman, director of the Cancer Therapy Evaluation Program] who said, if a year or two ago he had been able to 'intuit' women's concerns about the NCI and NSABP behavior, NCI would have acted differently," Visco testified.

"Had a consumer advocate, a woman with breast cancer, been part of the process, the public's peace of mind in women's lives would not have been left to the uncertainties of an individual's intuitive ability.

"It should be policy of the NIH and NCI that when federal money is being spent, consumer representation belongs at the table at study sections, data monitoring committees, oversight committees.

"When you are handing out money on a Congressional level, on the NCI level, you certainly have the power to make as a condition, to be eligible for that money, the fact that a consumer representative must be involved," Visco said.

Patricia Schroeder (D-CO) and Olympia Snowe (R-ME), co-chairs of the Congressional Caucus for Women's Issues, supported Visco's proposal.

"I think it's time we say to these researchers: There's only one reason I vote for money for medical research, and that's because I think good medical research is going to help us find a new treatment, it's not to give them a little sandbox they can play in and not be accountable to anybody," said Schroeder. "I'm sure you all are going to work together to find some way we finally do give them the message or shut off their money. One or the other."

Snowe (D-ME) asked Visco whether Congress should consider legislation to that effect. "It would be much harder for [NIH] to contravene public law."

Snowe and Schroeder, who are not members of Dingell's subcommittee, were invited to take part in the inquiry.

"Top NCI Officials Ignored The Director"

Outlining the chronology the investigation of fraud at St. Luc, Dingell said NCI Director Broder was first briefed by ORI on July 3, 1991.

"Dr. Broder concluded that the fraudulent St. Luc data should be removed and all previously reported studies should be reanalyzed and the results published," Dingell said.

Fisher later submitted 13 papers for publication that contained the St. Luc data. Seven of these papers have been published, Dingell said.

NSABP presented an oral reanalysis to NCI and ORI staff in 1992 showing that the conclusions remained unchanged. NCI and ORI insisted on a "news blackout" for the following year, pending the conclusion of the investigation, Dingell said.

Between 1992 and 1994, NCI "sporadically and only half-heartedly encouraged NSABP to complete a manuscript reporting the reanalysis," improve the group's audit procedures, and establish a data safety and monitoring committee, Dingell said.

"One of the reasons we are here today is that no one followed the direction of the director of the NCI," Dingell said. "Top NCI officials ignored the director's instructions and Pittsburgh ignored the directions of its funding institution.

"In fact, top NCI officials have complained to the subcommittee staff that they could not even get Dr. Fisher to return their phone calls, let alone take any direction from the NCI," Dingell said.

Broder did not dispute Dingell's assessment.

"The NSABP did not respond to constructive criticism by NCI staff," Broder testified. "The NSABP failed to publish its reanalysis, inform its membership of the incident, reassure the public, notify scientific journal editors and other grant-support organizations of the fabrication, publish accurate papers that clearly disclose what Dr. Poisson did, and in a larger sense, adhere to NCI's guidelines for management of the group's operations office and quality assurance functions."

Despite requests, NCI failed to compel the group to reanalyze and publish the data, and to bring operations into compliance with the group's guidelines, Broder acknowledged.

"We also did not adequately overcome our reluctance to demand that an independent investigator--who himself was not a respondent in a misconduct case--turn over his data files in their entirety, to have others reanalyze the results," Broder said. "We are trying to learn from this experience to ensure that our response to episodes of fraud in clinical trials is prompt and effective."

Under questioning by Brown, Broder elaborated on Fisher's response to NCI's requests to strengthen auditing procedures.

"Dr. Fisher's response to us was quite disrespectful of the role that government employees play, and quite disrespectful of the status and function that we have," Broder said. "Basically, he said words to the effect that, 'Who are you to criticize me? I know how to do clinical trials, I've been doing them since before you were a doctor.'"

NIH Director Harold Varmus and ORI Director Lyle Bivens said the institutes plan to publicize misconduct findings more widely.

"There are profound tensions between the public's need for access to information that could affect people's health and the right of someone accused of fraud to be protected by due process," Varmus said. "The public does not want to be frightened by false accusations or deprived of knowing the consequences of accurate ones. For these reasons and others, the prompt resolution of allegations of fraud and the rapid dissemination of findings of fraud in clinical research are matters of great importance."

Another Fraud Investigation

ORI has begun an investigation into more potential fraud discovered by NCI at St. Mary's Hospital Center in Montreal. In a statement last week, ORI said the investigation has uncovered five instances of potentially falsified data involving three patients entered in the Breast Cancer Prevention Trial.

"The possible falsifications involve changes in dates of tests required either to establish eligibility for the trial or to follow-up patients," ORI said. "In one instance, a laboratory value appears to have been altered to meet eligibility criteria.

"Based on the available information, neither the ORI nor the NCI believe the identified misstatements affect the results of the prevention trial," ORI said. "They appear to be limited to the Breast Cancer Prevention Trial, no results from which have been published, and do not affect treatment trials carried out at the same hospital.

"The ORI is continuing the investigation to determine the full extent of the problem and who is responsible for the data falsification."

According to the statement, ORI does not usually comment on investigations until they are closed. "However, because of prior publicity involving this investigation and concerns from the patient community regarding the validity of the NSABP studies, the ORI believes that this public statement is needed to provide accurate information to the public and the scientific community," ORI said.

Tamoxifen, Uterine Cancer and the BCPT

Sources on Capitol Hill and at NCI said that in the long run the controversy over the trial of tamoxifen in healthy women who are at an increased risk of developing breast cancer seems likely to eclipse the issue of scientific misconduct.

NCI and the NSABP began in April 1992 the Breast Cancer Prevention Trial, a $65 million, 10-year study to determine whether administering tamoxifen to high-risk, asymptomatic women could reduce by one-third their risk of developing breast cancer. The informed consent documents and the risk-benefit profile for the trial were based partly on results of the NSABP's B14 study of the drug as prevention for recurrence of breast cancer.

About 10,500 women enrolled in the study until accrual was suspended to all NSABP trials earlier this month, Barnett Kramer, director of the Early Detection & Community Oncology Program in NCI's Div. of Cancer Prevention & Control, said to **The Cancer Letter**.

Consent forms told women that the risk of contracting uterine cancer was three times higher from taking tamoxifen than not taking the drug, Pearson said to Dingell's subcommittee last week.

"If the most up-to-date information had been given to women, they would have been told that the risk of uterine cancer was not three times as likely, but four to five times as likely," Pearson said.

The first tamoxifen-related uterine cancer death in the B14 study occurred June 25, 1991, but Fisher said it took two years to determine the cause of death of the patient, according to Dingell. Fisher told the subcommittee staff that "he was unable to obtain the autopsy analysis from the hospital in his study," Dingell said.

"By October 1993, Fisher was aware of at least four uterine cancer deaths attributed to tamoxifen," Dingell said.

Two weeks ago, FDA and the manufacturer, Zeneca Pharmaceuticals, warned doctors about the risk of death from uterine cancer associated with tamoxifen (**The Cancer Letter,** April 15).

"The company has told the subcommittee staff that it first learned of uterine cancer deaths caused by tamoxifen when it was informed by NCI, not Dr. Fisher, in December 1993," Dingell said.

Broder testified that NSABP also did not inform NCI or FDA of the deaths promptly. "It is my professional judgment that we should have received information on certain facts, and particularly it would be possible to have information on endometrial cancer early in 1992, possibly earlier," Broder said. "That information was not provided to us until substantially later than that."

The Institute found out about the endometrial cancer deaths at an NSABP meeting in October 1993, Broder said.

"Serious Ethical Questions"

"I believe the NCI decision to proceed with a prevention trial involving the administration of a potentially toxic drug to otherwise healthy women raises serious ethical questions," said Rep. Henry Waxman (D-CA). "Hard questions need to be asked about the adequacy of the informed consent process. We need to carefully scrutinize the planning process used by the NCI in initiating this trial."

The Women's Health Network called attention to other issues in the original consent forms, including the risk of blood clots requiring hospitalization, and the risk of liver cancer.

In addition, a review by the staff of the late Rep. Ted Weiss (D-NY) found that of 268 consent forms used by the same number of centers, 26 percent provided "inadequate information about the need to use birth control and the types of birth control which were appropriate to be used in the study," Pearson testified. The forms deemed inadequate by the network were from Catholic hospitals involved in the study, she said.

Before his death, Weiss planned a hearing of the Committee on Government Relations, Human Resources and Intergovernmental Relations Subcommittee. The hearing was chaired by Rep. Donald Payne in October 1992.

"Because of Dr. Healy's resistance to that committee's oversight, we have no information about whether or not those 26 percent of the participating centers have fully complied with the need to give women all the appropriate information," Pearson said.

"Mr. Chairman, that may be something we may be able to find out," Schroeder said. "We should stop the trial immediately—that's outrageous—if there are women who are not getting the full consent."

NCI's Kramer said the Institute is considering "a lot of modifications to the trial design" of the BCPT, including increasing the level of breast cancer risk a woman has to have in order to enroll. The risk is determined using a statistical model developed by NCI's Mitchell Gail, and is based on several probable risk factors for breast cancer.

In an interview with **The Cancer Letter** last week, Kramer said women over 60 who had the risk factor of 1 were eligible to enroll in the study. However, women over 60 who actually enroll have the average risk of about 3.5.

"We may modify the risk eligibility beginning at age 50 or 55," Kramer said.

The DCPC Board of Scientific Counselors will be asked to review the trial at its meeting the first week of May, he said. Consumer advocates are involved in the trial's data safety monitoring committee, he said.

The new Clinical Trials Monitoring Branch in the Div. of Cancer Treatment will oversee the regulatory issues and quality assurance of the BCPT, in addition to clinical treatment trials conducted by the cooperative groups, Kramer said.

Fisher-ICI Pharmaceuticals Chair?

Another issue the subcommittee raised was the issue of a donation by Zeneca Pharmaceuticals for an endowed chair at the Univ. of Pittsburgh in Fisher's honor.

Varmus testified that after learning that the "Who's Who" directory listed Fisher as the chair

holder, he asked NCI Div. of Cancer Treatment Director Bruce Chabner to investigate the matter.

"It seemed to me not to pass my own smell test," Varmus said.

In a letter to Varmus dated March 25, Thomas Detre, senior vice chancellor for health sciences at Univ. of Pittsburgh, wrote that ICI Pharmaceuticals Group (now Zeneca Pharmaceuticals) made a $600,000 grant to the university in 1989 to establish a Bernard Fisher-ICI Pharma Professorship.

"Discussions with the donor were conducted by a faculty colleague who thought of this as a way of honoring one of his esteemed colleagues," Detre wrote. "At the time, Dr. Fisher expressed to me his personal dislike for this type of recognition, but the university continued these discussions in spite of Dr. Fisher's objections."

The university received additional $100,000 for the endowment from other sources, but fell short of the $1 million the university requires to establish an endowed chair, Detre wrote. "Neither Dr. Fisher nor any other person has ever been appointed to this chair, nor have any proceeds from the endowment been used to support Dr. Fisher's research or any other activity."

Varmus said he was told the "Who's Who" listing was a secretary's mistake in writing Fisher's biographical listing.

"I think it is difficult to maintain an appearance of propriety and the practice of propriety if one's own department has received a large endowment for a professorship by the company that has supplied the drug that is being used in a clinical study being carried out by that investigator," Varmus said.

Fisher has been a member of the Univ. of Pittsburgh faculty since 1947, and a professor of surgery since 1959. In 1986, Fisher was awarded the title of Distinguished Service Professor of Surgery.

Changes At NSABP

Officials at NCI and NSABP said the cooperative group is undergoing a complete overhaul.

"In the past, rather than having an audit where investigators go to the site where the research is being conducted and to examine records from that site and look for supporting information, the way the NSABP conducted their audits was to have individuals [photocopy] records and bring them back to Pittsburgh," Friedman said to Dingell's subcommittee.

"In contrast to how our other cooperative groups operate, the number of charts sampled at each of these research sites was relatively small," he continued. "Instead of having a large number or a larger number of charts sampled from a larger enrolling institution, they had a small, fixed number of charts examined at each institution. Although it was defended by the NSABP, this was not a system that we felt was entirely appropriate."

Under the newly instituted auditing system, NSABP will send researchers to the site to "actually look at the primary data, an x-ray or EKG form, or whatever, to confirm the reliability and truthfulness," Friedman said.

In addition, due to NCI's concern about the lumpectomy trial, the Institute independently examined more than 850 research records of patients enrolled in the trial to examine them for fraud, Friedman said.

NCI also examined about 1,400 charts from different studies to try to detect any systematic problems.

Scientific Post for Fisher?

Ronald Herberman, NSABP's new principal investigator, said the group has developed a draft plan in response to the NCI letter describing NSABP deficiencies (**The Cancer Letter**, April 8).

The plan was to be sent to NCI this week. "We are optimistic that this plan will sufficiently address the concerns of NCI," Herberman said to **The Cancer Letter**. This would enable accrual to NSABP trials to continue. Accrual was suspended as of April 4.

The accrual suspension has created difficulties for NSABP institutions that rely on regular funding from the group. "This has created widespread concern among institutions and investigators, because they have regular staff who are dedicated to NSABP trials," Herberman said. "For the time accrual is stopped, a large proportion of the funding they would ordinarily be getting has been ceased.

"Our response is that we are doing everything we can to get the plan in place and approved by NCI so this interim in minimized," he said.

Under the plan, NSABP would create the position of scientific director for Fisher, Herberman said. This would enable the group "to avail itself of Dr. Fisher's scientific expertise and unique insights into breast cancer, but to have his role in the reorganization focused on the scientific leadership," he said.

"A major element of the plan is to restructure the group to empower a broader range of the membership in protocol development and various other aspects of running the group," Herberman said.

This includes new standing committees responsible for protocol development and implementation.

Another area for "significant change" will be "more open and regular communication between the group and the public at large," he said.

Cancer survivors and advocates will be invited to serve on several committees and will be involved in membership meetings and protocol development, Herberman said.

"We are also proposing something novel to help avoid any repetition of the kinds of fabrication that Dr. Poisson was associated with, namely to have the dates that are important eligibility, such as times of surgery, be part of the informed consent process," Herberman said.

Patients would be asked to sign a form that includes these dates and agree to their accuracy.

NSABP's newly formed oversight committee includes Charles Coltman, chairman of the Southwest Oncology Group; Clara Bloomfield, chairman of the DCT Board of Scientific Counselors; Barbara Parker, medical oncologist at Univ. of California at San Diego; Stephen George, head of biostatistics for the Cancer & Leukemia Group B; Larry Norton, of Memorial Sloan-Kettering Cancer Center; Susan Love, surgical oncologist at Univ. of California at Los Angeles; Amy Langer, executive director of the National Alliance of Breast Cancer Organizations; and Dorothy Raizman, a Pittsburgh lawyer.

The committee met April 12-13 in San Francisco to review the draft plan for restructuring of NSABP.

Hearing Highlights: 'Science Does Not Exist In A Vacuum'

The following are the highlights from the April 13 hearing of the House Energy and Commerce Committee's Subcommittee on Oversight and Investigations.

The hearing examined the issues related to fraudulent data in the clinical trials conducted by the National Surgical Adjuvant Breast & Bowel Project, the issues of management of the cooperative group as well as the adequacy of informed consent forms used in the group's tamoxifen trials.

Visco: Trials Need Consumer Representation

From testimony by Fran Visco, president of the National Breast Cancer Coalition and member of the President's Cancer Panel:

I have received a number of telephone calls over the past week from members of the scientific community. They want to make certain that we, activists, understand that we must not throw the baby out with the bath water...

I've been told not to overreact. Not to question too much...

I'm sitting here, I'm a member of the President's Cancer Panel, I'm a breast cancer survivor, I lead a national breast cancer organization, and I found out about [the fraud in the lumpectomy study] by picking up The New York Times.

And I still don't know what happened.

What was reanalyzed, when it was, who did it? Who's involved?

Public trust in the system has eroded. And we're going to get it back through hearings like this, and by letting consumers be a part of the decision-making process.

This sorry story reveals a system overly concerned with professional reputation and institutional ego, both public and private institutional ego.

And while the participants shuffle to position themselves to best protect themselves and to point a finger at someone else, I ask them to stop, and to look at me, look at all of the women in this room, all the women in your lives. It is my life, it is our lives, that your decisions impact. It is my money, it is public money that you spend. We, women with breast cancer, consumer advocates belong at the table.

We must be a part of the decision-making, of data monitoring committees, of oversight committees and study sections...

Science is not a concept that exists in a vacuum. It is performed, too often in isolation, insulated from the public by individuals, by imperfect people with biases and shortcomings. That is why we need a strong system of checks and balances, oversight, different perspectives that will allow science to proceed unimpeded by ego, fraud and erosion of public trust.

And that will occur if consumer advocates are given an informed, meaningful, seat at the table.

Broder: NCI Kept in the Dark on Tamoxifen Risks

John Dingell (D-MI), chairman of the subcommittee: Last Friday, FDA and Zeneca [the manufacturer of tamoxifen] issued a new warning label based in part on the findings of at least four cancer deaths associated with the administration of tamoxifen in the trial.

The subcommittee recently obtained from Dr. Fisher a chronology of events related to the deaths of these women, and submitted it to NCI for review. What conclusions did NCI draw from your review and the analysis of the timeliness of the disclosures of the deaths of those patients?

Samuel Broder, director of NCI: It is my professional judgment that we should have received information on certain facts, and particularly it would be possible to have information on endometrial cancer early in 1992, possibly earlier.

That information was not provided to us until substantially later than that. This speaks to the issue of us wanting to hold the IND for such studies, which we did not have. I believe that early in 1992, certain information about endometrial cancer death could have been provided to us.

DINGELL: So it would be fair to say one of the deaths should have been reported early in 1992...

BRODER: This particular patient initially was signed out as a pulmonary embolism. And since the diagnosis had pulmonary embolism as a cause of death, I believe there was some legitimate basis for not making a decision.

But personally, I feel early 1992 would be fair.

DINGELL: Is it fair to say that NCI and the manufacturer should have been notified in 1993 about a second death?

BRODER: That's fair.

DINGELL: Now, the notification of the third death should have occurred by at least January 1993, is that so?

BRODER: I believe that that's fair.

DINGELL: They have three, and then the fourth death, there should have been notification by at least August 1993, is that right?

BRODER: Sir, I believe that's correct.

DINGELL: Now, when were you notified, doctor?

BRODER: We received our notification through an NSABP meeting that was held toward the end of October 1993.

DINGELL: Substantially later than you should have been notified.

BRODER: You are correct.

DINGELL: Doctor, is it your testimony that the American public should be informed about the deaths associated with tamoxifen, as well as increased cancers associated with tamoxifen in 1992, not 1994?

BRODER: I believe that the appropriate communication should have started early in 1992.

DINGELL: The testimony so far indicates that [the trial participants] may not have been properly and adequately advised to give their full and adequate consent, based on fair exposition of the facts and the data available to the examiners.

Is that a fair statement?

BRODER: I believe that the situation has a complexity, because the very first informed consent did disclose to patients the possibility of the lethal outcomes.

They were related to embolic, thrombolytic cardiovascular [events], so patients were on notice that death was a possibility, and patients were on notice that endometrial cancer was a possibility, but you are quite right, and your point is well taken, that the issue of endometrial cancer which should have been brought up to current state was not provided.

DINGELL: The risk with regard to endometrial cancer was either not stated or was significantly understated.

BRODER: The risk of death from uterine cancer most assuredly was not properly and adequately provided.

DINGELL: As a matter of fact, was there any information at all with regard to possible fatalities resulting from this?

BRODER: The death due to uterine cancer, no. But death due to other causes, patients were put on notice of the possibility of lethal outcome.

DINGELL: Is there any requirement now in the protocols or in the rules and regulations of either NCI or NIH that would require women to be properly notified in connection with the risks?

BRODER: We are re-examining and will, as a condition of a grant, require the same kind of notification that the grantee would owe to the IND holder. Now we can be in the information loop immediately, not as an afterthought. And we are prepared to not fund proposals where that is not possible.

In a community-based study which is far-flung, and, by definition, has a number of sites in multiple areas, and also has central pathology services and other things that need to be done, one has to accept a certain amount of delay. Also, there is a need to make sure that if an alarm is sounded, that it is based on very valid information, so that the meaning of the alarm would be preserved.

I think our processes need to be improved, and we are taking steps to make sure that the grantee understands that. We will also strongly discourage

either the private companies or the individual grantees from holding the IND, which in effect was the case with tamoxifen.

Tamoxifen Trial Participants Not Notified

DINGELL: Have all of the women who were put at risk by the failure to adequately disclose the risk of death of uterine cancer been informed of the new level of risk?

BRODER: The answer is no.

DINGELL: The answer is no?

BRODER: The process in a large far-flung community-based study requires several steps. While we could theoretically provide notice of some type, a local institutional review board not responding to the government must approve and endorse any changes in informed consent. We have tried to make the information as publicly available as we can, but I cannot assure you that every single woman has signed a new informed consent.

DINGELL: We have many questions here, one of which is a simple moral question: Shouldn't these women be informed that they have been put at additional risk which was not disclosed to them at the time they agreed to participate in study?

BRODER: Yes, that process is going on now, and will be completed. [If] your question is, will every single woman be notified, the answer is yes.

DINGELL: When will that occur, because they are now all at additional risk with regard to uterine cancer, some also with regard to blood pressure, and possibly other matters. When will they receive notice?

Harold Varmus, NIH director: Mr. Chairman, all the 206 sites for the tamoxifen prevention study have been informed of the recommendations to change the consent forms to be in accord with the newly available evidence.

And now, it is the responsibility of those who are charged with the study at each of those sites to respond and inform the patients. The NCI itself cannot inform patients directly, we are informing them through the sites participating in this multi-institutional study.

DINGELL: You told me that all of the women have been informed, or just the sites have been informed?

VARMUS: All of the sites have been informed, and we hope, I mean, we trust, I mean, we will enforce—

DINGELL: Ah, the three great terms—the three great virtues...I'm curious, how are we to say the sites have informed the women? We cannot say so, can we?

BRODER: Mr. Dingell, you are quite right to raise this issue. The trial is currently suspended.

We have taken our process of how one informs women of newly evolving side effects to the Office of Protection from Research Risks, which advises us in that process.

Perhaps you might also take into account the fact that in any study, there will be an ongoing process of new risks, some of them acute, some of them long-standing, and some of them chronic, there is always going to be an updating process, so this is not the only time we are going to have to continuously modify informed consent.

The Office of Protection from Research Risks advised us that upon their evaluation, this process did not require an immediate call-back notification, but [that the notification] could be done in the normal cycle in which women would [return] to the clinic.

However, we have chosen not to take that option, and we will be calling women back. In addition, we will have a process to ensure that sites have notified all women before that site can reaccrue women in the process when the current suspension is over..

Broder: "I Hope His Health Improves..."

DINGELL: Where is NIH with regard to your ability to notify participants [in clinical trials]?

VARMUS: It is a regulation that all patients in the study be informed through the institutional review boards. You are raising a legitimate question of whether we should have proper rules to follow up on the notification process, and you can rest assured that we will look into that very vigorously.

BRODER: I'd like to second that, because I want to assure you that we take your concerns and criticisms very seriously to heart and believe they are valid. And we will look to see if there is a structural problem that we can repair. And we will also explore whether the NCI has some direct access to patients. I believe that we will probably told that we have limited...

DINGELL: I think it would be useful if you had direct access, but I think it is even more useful that you simply require that the patients do be informed.

BRODER: That is a requirement.

VARMUS: Whether I know that all patients have been informed or not, I cannot say that I know that.

BRODER: Also, we have limited rights of access to grantees files, names and addresses, but we will

certainly review that as well.

DINGELL: Now the deaths should have been reported in 1992, before any of the patients entered the prevention study, should they not?

BRODER: That is correct, there was —

DINGELL: That was not done.

BRODER: That was not done as far as I can tell, that was not done even to the FDA.

DINGELL: Thank you. Can you tell us why?

BRODER: I would have to speak for Dr. Fisher, and I would prefer not to do that.

DINGELL: As the record shows, we have invited Dr. Fisher to appear here and he has indicated that his health prevents him from being with us. Perhaps we will be affording him another opportunity, but as I have indicated, we will be asking the university to come before us.

BRODER: I hope his health improves.

DINGELL: Well, I do, too. At least enough that he can appear here before us.

"Who Are You to Criticize Me?"

Rep. Sherrod Brown (D-OH): We have the director of NCI telling subordinates to have the Univ. of Pittsburgh reanalyze the data, republish the analysis, not publish further studies using this falsified, fabricated data, yet every single directive was disobeyed, ignored, taken too lightly. Why?

BRODER: I believe that is in part a function of Dr. Fisher's formidable reputation, and I believe that the staff were attempting to negotiate a collegial, non-confrontational way of dealing with a highly regarded figure.

I believe there was an excessive level of collegiality and a higher level of tolerance than is now the case. Staff simply did not wish to confront and order Dr. Fisher, who after all had a great deal of status in the scientific community, and I believe that that is in part responsible for what happened.

BROWN: It sounds a little bit like Congress.

Collegiality, protecting people, people protecting themselves. That sounds like the criticisms people sometimes level at this institution.

What's the rationale beyond that for why Dr. Fisher and his colleagues would continue to submit and publish papers that are known to contain that false data?

VARMUS: These are questions that should be addressed to Dr. Fisher, but there are some potential explanations that have to do with his desire to publish the findings of studies that had been carried out.

I cannot myself condone the inclusion of data from St. Luc Hospital once fraud had been ascertained. The information from that hospital should have been excluded from any further publication, so I don't want to pretend to understand how that came to be.

BROWN: Subcommittee staff found that as early as July of 1992, NCI officials were admonishing Dr. Fisher to upgrade and strengthen auditing procedures. What was the response of Dr. Fisher to those repeated requests from NCI?

BRODER: I would say that Dr. Fisher's response to us was quite disrespectful of the role that government employees play, and quite disrespectful of the status and function that we have.

Basically he said words to the effect that, "Who are you to criticize me? I know how to do clinical trials, I've been doing them since before you were a doctor."

That's not literally what he said, but that's my editorial response.

Dingell's Parting Promise: More Hearings

DINGELL: I want to make it clear to you, Dr. Varmus, and to you, Dr. Broder, that I have immense respect for you both.

The comments you have made today ... have been most helpful and important.

There has long been an effort on the part of this subcommittee to see to it that government money is properly spent, that protection of participants in trials and tests and studies is adequate, the information available to them is at a level that you and I would like to see them have.

This is not just an isolated question in which science will rectify the falsification with regard to improprieties... Human lives are at stake.

We sense that there is great awareness on your part, Dr. Varmus and Dr. Broder, and I am content to work with you and to see to it that the kind of efforts that you are making—which is significantly different and better than your predecessors, including one of your most immediate predecessors, Dr. Varmus—to see to it that you succeed in your efforts to make this system work better for the benefit of all of us.

That the taxpayers' money be better spent, that the protection be afforded to participants, that the information be such as to give an honest appraisal so that people can make proper judgments with regard to their personal activities.

You and I look forward to a time when we can

work together. If things have happened today which caused you distress, you have my expression of sorrow and apology, and I want you to understand that we are going to try to work with you, and we expect good things from you.

You are currently engaged in a difficult task. The potential wrongdoing of a colleague, a scientist, particularly a well-known and influential figure in science, is always difficult. It's fraught with peril to you, possible lawsuits and other difficulties.

We understand, it takes time to refine procedures so you can do this thing properly, and we will work with you to give you both the time and the climate in which you may do these things with minimum peril to yourself and greatest success from the standpoint of the great undertaking of which you are a part.

Fisher, In Statement, Admits Mistake On Publication Delay

In a statement last week, Bernard Fisher acknowledged that it was a mistake to delay publication of discovery of fraudulent data in the lumpectomy trials.

Since the fraud did not affect the study's conclusions, "we did not feel that submitting the reanalysis for publication was as urgent as pursuing some of the other significant projects we were working on," the former chairman of the National Surgical Adjuvant Breast & Bowel Project said in a written statement dated April 13.

According to the document, NSABP's auditing capabilities were stretched thin because of the launching of the prevention trial. "We hope that this will now be remedied," Fisher wrote.

Though the statement did not address the controversy over informed consent in the breast cancer prevention trial, the controversy that dominated the Dingell hearing, Fisher wrote that the question of whether the drug tamoxifen can prevent breast cancer will only be determined in clinical trials.

The text of Fisher's statement follows:

Having directed the National Surgical Adjuvant Breast & Bowel Project for over 25 years, I am now engaged in a comprehensive evaluation of the issues raised by recent disclosures.

In that effort, I continue to work closely with Dr. Carol Redmond, an internationally renowned statistician who has long been director of the Biostatistical Center of the NSABP.

But even before our evaluation can be completed, I have provided an overview of my thoughts to my colleagues at the Univ. of Pittsburgh and the NSABP, as well as to the NCI and the staff of the House Oversight and Investigations Subcommittee.

During the past 25 years, the NSABP has conducted many clinical trials to determine the best treatment of breast cancer. The findings from our trials have revolutionized the treatment of this dread disease by demonstrating that a lumpectomy followed by radiation therapy, rather than a disfiguring radical mastectomy, is the preferable treatment for most women with breast cancer.

The findings also demonstrated that the use of postoperative chemotherapy, as well as the drug tamoxifen, is of substantial value in preventing the recurrence of breast cancer.

Conducting a randomized clinical trial requires the collaboration of patients, researchers and clinicians from many different institutions.

By involving patients from many institutions, we ensure the generalizability of the findings across diverse populations and we minimize the possibility that flawed data from a single site can affect the outcome of a study.

In 1991, we found that an investigator at St. Luc Hospital in Montreal had deliberately altered data relating to patient eligibility for clinical trials. We immediately informed the NCI and federal regulatory officials and the investigator was suspended. We promptly reanalyzed the studies in which patients from St. Luc Hospital participated.

These reanalyses, which were shared with NCI, demonstrated that excluding the St. Luc data did not result in any change in the outcomes or conclusions of our studies. Others are independently reanalyzing the findings from our clinical trials, and we are confident that they will confirm our original conclusions.

These conclusions, I should add, have also been confirmed in clinical trials conducted by others.

Had there been the slightest evidence that the conclusions of our studies were affected by the St. Luc data alterations, we would have reported these findings immediately. Moreover, the NCI, as it has done in the past, would have issued a "clinical alert."

But because there were no changes in the study conclusions, we did not feel that submitting the reanalysis for publication was as urgent as pursuing some of the other significant projects we were working on. In retrospect, this proved to be a mistake. The lack of publication raised unnecessary fears among breast cancer patients.

My colleagues and I, who are dedicated to discovering and disseminating reliable information about breast cancer, should have been more sensitive to this possibility and published our reanalyses more promptly.

We repeat, however, that breast cancer patients have no reason to fear that they are receiving inappropriate therapy because of the St. Luc data alterations.

In the past 18 months, our work has expanded enormously. A newly-initiated breast cancer prevention trial recruited more patients in one year than were recruited in any year in all of the treatment trials combined.

Because of underfunding, our auditing capabilities were stretched thin. We hope that this will now be remedied. But, in any event, there is no reason to believe that undetected error or fraud will undermine the validity of our pathbreaking studies.

The NSABP is presently conducting both treatment and prevention trials involving tamoxifen. We are carefully monitoring for side effects, including uterine cancer, and will continue to make certain that physicians and patients are promptly informed of what we learn. We believe, based on all that is now known, that tamoxifen is an appropriate treatment to prevent recurrences of breast cancer.

The NCI and the FDA concur. Whether the use of tamoxifen can safely and effectively prevent the initial onset of breast cancer will only be determined by findings from clinical trials.

I have dedicated my professional life to demonstrating that clinical trials are a powerful tool for determining how to treat and prevent disease.

I am committed to using this tool to fight the scourge of breast cancer, and will work with Dr. Ronald Herberman, interim chair of the NSABP, and NCI in every way possible to assure that the NSABP continues to play its cutting edge role in the conduct of clinical trials.

Mysterious Group Urges Letter Campaign Supporting Fisher

What is the Coalition in Support of Breast Cancer Research?

Earlier this month, in a mailing to cancer researchers nationwide, the mysterious coalition urged a letter-writing campaign in support of Bernard Fisher, the recently removed chairman of National Surgical Adjuvant Breast and Bowel Project.

Many researchers who received the mailing said they were jarred to find it unsigned. In effect, a person who chose to remain unknown was urging them to stand up and be counted.

However, sources said the campaign generated about 100 letters to NIH and about 40 letters to Rep. John Dingell (D-MI), whose subcommittee on oversight and investigations conducted a hearing on NSABP April 13.

An investigation by **The Cancer Letter** found that the group is operating from a misleading address and that its telephone number, though available through directory assistance, cannot be traced to a valid address. The nature of the group could not be determined since it did not identify itself as a business and was not listed at the Bureau of Charitable Organizations of the Pennsylvania Department of State.

"The university is aware of the letter, and we cannot determine that anyone who speaks for the university—or even anyone in the university—is connected with it in any way," said Lewis Popper, general counsel for the Univ. of Pittsburgh.

"We are particularly concerned about any appearance that the university is using this organization as a stalking horse, which is far from the case. The controversy over NSABP should be resolved on its merits, and not through a letter-writing campaign."

The coalition's mailing, dated April 5, urged cancer researchers to contact House and Senate members, President Clinton, HHS Secretary Donna Shalala and NIH Director Harold Varmus.

Enclosed in the mailing was a model letter that called for the following actions:

- The reappointment of Fisher as chairman of NSABP "to enable him to continue his scientific research and to plan an orderly transition to a new chairman at an appropriate time, with the advice and guidance of the NSABP executive committee."
- "An investigation of NCI officials responsible for Dr. Fisher's unjust treatment."

After several attempts to contact the coalition by telephone, **The Cancer Letter** retained a private investigator to go to the address on the stationery, suite 240, 3520 Forbes Avenue in the Oakland section of Pittsburgh, close to the Univ. of Pittsburgh campus and the headquarters of NSABP.

The investigator reported that suite 240 did not exist at that address. However, there was a location of Mailboxes Etc., which had a box numbered 240.

It could not be determined whether the owner of the box was describing it as a "suite" on the stationery. It is illegal in Pennsylvania to represent mail boxes as suites or apartments, law enforcement officials said.

"If a person is representing a mail box as a suite or an apartment, they are violating the state unfair trade practices law," Renardo Hicks, director of the Bureau of Consumer Protection in the Office of Attorney General, said to **The Cancer Letter**.

Hicks said the penalties under the law could be as high as a $1,000 fine for every letter sent.