BREAST CANCER RESEARCH ON TRIAL

Congress hears a tale of false data, delays, and doubts

By KATHY A. FACKELMANN

An uncharacteristic hush fell over the hearing room as 32-year-old Jill Lea Sigal described her fight with breast cancer: "The fear that arises from facing one's own mortality at my age can at times be paralyzing," she told members of Congress at a recent hearing.

Now, Sigal's dread of a deadly return of cancer is compounded by fear that she chose the wrong treatment for the disease.

Sigal told the House Subcommittee on Oversight and Investigations that she had received a diagnosis of breast cancer 6 months ago. At that time, her doctor told her about a landmark 1985 study that compared lumpectomy (excision of the tumor and a small amount of tissue surrounding it) to mastectomy (a more extensive procedure in which surgeons remove the entire breast and some of the lymph nodes). The study revealed that women in the early stages of breast cancer who opted for the breast-conserving lumpectomy plus radiation treatments lived just as long as those who underwent the more disfiguring procedure.

After consulting with her doctor, Sigal decided to undergo a lumpectomy. Last month, Sigal learned that the 1985 study contained fraudulent data.

"I thought I had made an informed decision," she told the panel. "Now I must wonder every day if I really have done everything to maximize my chances of survival."

At the hearing, designed to explore the federal government's response to this case of fraudulent breast cancer data, representatives of women's groups and government officials also testified in front of the standing-room-only crowd of lobbyists, scientists, and journalists. Rep. John D. Dingell (D-Mich.), chairman of the subcommittee, contends that key researchers and federal officials knew about the bad data for years yet failed to inform the public in a timely manner.

"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," Dingell says.

At stake: the public's trust not just in the lumpectomy study, but in several other important breast cancer trials as well (see sidebar). For example, this case has raised questions about the Breast Cancer Prevention Trial, a controversial study in which healthy women at high risk of developing breast cancer take the drug tamoxifen in hopes of staving off the disease (SN: 4/16/94, p.247).

The imbroglio began with Roger Poisson, a surgeon at St. Luc's Hospital in Montreal and one of the investigators in the National Surgical Adjuvant Breast and Bowel Project (NSABP). Poisson was one of about 5,000 physicians contributing data to NSABP, a multicenter U.S. and Canadian research group working on nearly two dozen cancer studies supported by funds from the National Institutes of Health.

In June 1990, staffers at the NSABP central office, located at the University of Pittsburgh, noticed in a routine review of data that Poisson's group had submitted two breast cancer reports that appeared identical except for the date of surgery. This oddity led NSABP to order a more extensive, on-site audit of the records at St. Luc's. The review, conducted in September 1990, revealed additional discrepancies in at least 20 cases.

NSABP Director Bernard Fisher and his chief statistician, Carol Redmond, traveled to Montreal in December 1990 to meet with Poisson and coinvestigator Sandra Legault-Poisson. Fisher and Redmond told the pair that the irregularities in recruiting patients must stop. They also informed Poisson that NSABP would conduct a more extensive audit of the St. Luc records.

But it wasn't until Feb. 12, 1991, 8 months after the initial finding of suspicious data, that Fisher alerted the National Cancer Institute (NCI) to the "irregularities" discovered at St. Luc's. NCI then notified the Food and Drug Administration, which had approved one of the NSABP protocols involving the anticancer drug tamoxifen. Also in February 1991, NIH's Office of

Research Integrity (ORI) started its own probe and put the St. Luc medical records under lock and key.

From the outset, Poisson admitted to a loose interpretation of the NSABP rules for entering patients into the various clinical trials. "I'm not ashamed of having done my best to enter as many patients as possible in the various protocols," Poisson wrote in a Feb. 9, 1991, letter to NSABP.

Indeed, as early as May 15, 1991, the FDA had an admission of guilt signed by Poisson that he had falsified data in violation of FDA's regulations governing investigational drugs. At that time, FDA barred Poisson from performing research that involved U.S.-approved experimental drugs.

Meanwhile, the ORI fraud squad decided that the irregularities appeared widespread enough to warrant an audit of the entire lot of St. Luc's cases included in NSABP trials since 1975. ORI pulled the original hospital records for all of the 1,511 St. Luc's patients and used that information to check the data submitted to NSABP's Pittsburgh office.

On June 21, 1993, ORI declared in a notice in the Federal Register that Poisson had "fabricated or falsified data related to laboratory tests and dates of procedures in 115 separate instances dating from 1977 through 1990." That notice followed from an April 1993 ORI report.

The investigators discovered a number of cases in which key dates had been changed to make a patient appear eligible for a trial. In others, a crucial laboratory test, such as a hormone receptor value, had been altered. Finally, Poisson's group appeared to have entered patients into various studies without obtaining the proper consent.

In at least one case, a patient refused several times to join a trial. The patient signed the original "consent" document on the line that reads, "I refuse to participate in the protocol." On the same piece of paper, there appears a handwritten note saying, "Patient made a mistake." The hospital records indicate that even after she was being treated under the protocol, this patient again indicated she did not wish to participate.

Poisson told federal investigators that this patient kept changing her mind: "The fault here is that I thought she would accept, but obviously she did not."

In another serious breach of accepted medical practice, a patient with a history of congestive heart failure was entered into a protocol that specifically excluded heart patients. The study called for chemotherapy with a drug that can damage the heart muscle. The ORI report states: "Patient eligibility for the study was falsified by providing negative answers to questions on NSABP forms about cardiac disease history."

The ORI investigators found that in most cases, staff at St. Luc's recorded the faulty data on NSABP forms. "The data staff admitted to making the changes or entering fabricated values at the request of Dr. Poisson, who assured them the changes were trivial, that they were done for the good of the patient, and that they would not affect the outcome of the studies," the report notes.

Furthermore, "As non-professional staff with generally a high-school level education . . . they followed the instructions of their physician supervisor, and should not be held responsible. . . ."

The report concludes by charging Poisson with scientific misconduct. As a result of that finding, Poisson was barred from obtaining U.S. government funds to conduct research for 8 years.

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From the start, Poisson admitted to fabricating data. Many scientists believe that his admission of guilt and the ORI final report should have ended the case.

Yet Dingell's panel believes the NSABP's handling of the St. Luc problem illustrates serious deficiencies in its response to scientific misconduct.

"The fact is that the Pittsburgh audit procedure failed to detect any fraud at St. Luc's for over a decade," says a subcommittee staffer. NCI officials also believe that NSABP was remiss in its oversight of the multi-million-dollar project.

NSABP had been auditing St. Luc's data at the rate of eight records every 3 years. NCI officials noted that the Pittsburgh staff might have discovered the faked data much earlier had they adopted a more rigorous audit schedule.

"The circumstances relating to NSABP Institution 97 [St. Luc's Hospital] indicate that a change is required in the NSABP audit program," says an Oct. 29, 1992, letter to Fisher from NCI's Joan K. Mauer.

When Fisher ignored that request, NCI repeated it—this time more forcefully: "In view of the impending release of the Office of Research Integrity's report of the investigation of Institution 97, again we urge NSABP to review and revise its audit procedures," states Mauer's Jan. 7, 1993, letter to Fisher. "We feel the NSABP audit procedures will be under close scrutiny and open to possible criticism, since the data alteration problems from Institution 97 went undetected for more than a decade."

NSABP still didn't comply. Fisher didn't even return NCI Director Samuel Broder's phone calls.

At the hearing, Broder told the panel that Fisher "rejected out of hand" repeated attempts by NCI to get NSABP to tighten its audit procedures. When asked why Fisher would ignore NCI's direction, Broder said: "I would say that Dr. Fisher's response was quite disrespectful of the role that government employees play."

Broder admitted that NCI staffers appeared reluctant to take stronger action against NSABP because of Fisher's reputation as a pioneering researcher. Broder said that Fisher told NCI, Who are you to criticize me? or words to that effect. "No one will ever tell us that again," Broder promised Dingell's panel.

Fisher was excused from testifying before the subcommittee because of ill health. However, NSABP leaders say they are working on a revised audit policy.

Government officials also knew that Fisher's tardiness in reporting the problem with Poisson's data could have hindered the subsequent federal investigation. "The delay in NSABP's reporting their finding of altered data to [ORI] afforded [Poisson] and his staff the opportunity to destroy or alter evidence," says a Feb. 10, 1993, confidential memo from ORI Director Lyle W. Bivens to Broder.

Bivens refers to the fact that NSABP first discovered serious discrepancies in the St. Luc data 8 months before reporting the problem to NCI. No one, however, has offered evidence that Poisson did destroy any documents.

Fisher's reputation was further tarnished when a second case of falsified data surfaced on March 28, 1994. This case involves several instances of allegedly faked data involving three patients at another Canadian hospital enrolled in the Breast Cancer Prevention Trial.

On the day of the congressional hearing, the Department of Health and Human Services released a statement outlining ORI's ongoing investigation into the second case. To date, these falsifications involve alterations in laboratory results or changes in the dates of tests conducted on study participants.

ORI does not believe the changes will affect the results of the trial. The alterations took place at St. Mary's Hospital Center in Montreal. Bivens told the panel that ORI has not released the name of the

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doctor involved but added that Poisson played no part in this case.

After learning of the St. Mary's case, NCI halted NSABP recruitment of patients. "NSABP may not resume adding more patients until NCI completes an intensive review of all records and quality assessment and control procedures at NSABP," according to an NCI statement issued on March 29, 1994.

At the same time, NCI ordered Fisher to step down as director of NSABP. On April 1, the University of Pittsburgh announced the appointment of cancer researcher Ronald B. Herberman as interim head of NSABP. Herberman, together with Pittsburgh's Donald L. Trump, will manage the project. Fisher will stay on as NSABP's chief scientific adviser.

Poisson's misconduct continues to haunt the research community because it contributed heavily to a trial designated B-06—the 1985 comparison of lumpectomy to mastectomy.

When Fisher stepped down from NSABP, he tried to calm fears that the fraudulent data might threaten the conclusions of B-06 or any of the other NSABP protocols. His group has reanalyzed B-06 and several other studies without the St. Luc data. The results have been submitted to the NEW ENGLAND JOURNAL OF MEDICINE.

"I assure the public that the published conclusions from NSABP's breast cancer studies remain valid and are not compromised by any of the recent developments," Fisher says.

The day before Dingell's hearing, NCI released an independent assessment of the lumpectomy study. The Emmes Corp. of Potomac, Md., used computerized files provided by NSABP to analyze the study without the data contributed by Poisson's group. The Emmes analysis indicates that the conclusions of the trial remain valid.

Other studies have also shown the value of lumpectomy in the treatment of early breast cancer. Indeed, a report in the April 20 JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION (JAMA) confirms the benefits of breast-conserving surgery for some breast cancer patients.

Despite such reassuring news, doubts about the validity of the data collected by the other NSABP centers remain. In fact, NCI has ordered an extensive audit of all such data.

"My personal view is that this is an unmitigated disaster for American women," says Harmon Eyre, a deputy vice president at the American Cancer Society (ACS) in Atlanta. "We're concerned that the public's confidence in clinical trials will erode," adds ACS spokeswoman Joann Schellenbach.

Indeed, in her testimony before Dingell's committee, Sigal said she wasn't ready to accept NCI's conclusion that the study findings remain valid. "I don't take their word for it," she said. In addition, she voiced a basic mistrust of the way clinical trials are policed.

Rep. Patricia Schroeder (D-Colo.) concurred. "We're told the fraudulent data didn't affect the results of this and other studies," she said. "Even if that is true, it is unforgivable that women's health and well-being should have been treated so cavalierly or that women should have been so needlessly frightened." Schroeder serves as cochair of the Congressional Caucus for Women's Issues.

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As for blame, there's plenty to go around. There's no doubt about Poisson: He admits he faked data. NSABP, under Fisher's leadership, clearly delayed in telling NCI about the fraud. NSABP's refusal to fix the audit process or to conduct an appropriate reanalysis of the data certainly hurt the reputations of NCI, Fisher, and the University of Pittsburgh. NCI officials now admit they should have taken swifter action against Fisher.

A Dingell staffer says NCI staff allowed Fisher to put them off for far too long: "It's clear there was arrogance [on Fisher's part]." Indeed, Fisher may have fallen victim to the same mind-set that felled Poisson—the belief that his work was so important, he could ignore the red tape of federal requirements.

Ironically, this case will surely lead to even more paperwork for researchers as NCI starts to require clinical investigators to comply with tougher auditing procedures.

Will more rigorous auditing suffice? "This stuff often exists as a data tape; if somebody wanted to go in and change the data and it was done in a subtle way... you'd probably never figure it out," says Howard I. Morrison, a cancer epidemiologist at Health Canada in Ottawa. □

Fraud takes its toll

The NSABP trials that have fallen under the shadow of the fraudulent St. Luc data include:

- B-06: This trial compared the removal of a cancerous tumor (lumpectomy) to surgical removal of the entire breast and some of the lymph nodes (mastectomy). The results suggested that women who receive lumpectomy and radiation therapy for treatment of early breast cancer survive as long as women who undergo the more radical (and highly disfiguring) mastectomy (SN: 3/16/85, p.165). Those results dramatically changed the way surgeons treated women with early breast cancer, leading to far greater use of the breast-conserving lumpectomy procedure.
- B-13: In this study, NSABP researchers recruited women with early breast cancer whose tumors did not contain estrogen receptors. Patients received mastectomy or lumpectomy plus radiation as their primary treatment. Some got additional treatment with cell-killing chemotherapeutic drugs; others received no such adjuvant therapy. The findings suggested that adjuvant chemotherapy increases the survival chances of such women (SN: 3/4/89, p.135).
- B-14: In this trial, related to B-13, NSABP researchers studied early breast cancer patients whose tumors did contain estrogen receptors. Such receptor-positive tumors were thought to respond to hormone treatments such as tamoxifen. After primary therapy, women received either tamoxifen or an inactive substance. The trial showed that tamoxifen significantly boosts the survival odds for such women.
- B-16: NSABP researchers published the results of another study in the April 6 JOURNAL OF THE NATIONAL CANCER INSTITUTE. That study found that tamoxifen treatment for invasive breast cancer increases slightly a woman's risk of endometrial cancer. Yet the NSABP investigators conclude that the anticancer benefits of tamoxifen therapy outweigh this risk.
- P-1: The Breast Cancer Prevention Trial, which has stirred up considerable controversy (SN: 9/25/93, p.207; 9/18/93, p.181), involves giving the drug tamoxifen to healthy women at high risk of breast cancer in order to prevent the disease. The trial is designed to determine whether tamoxifen can prevent breast tumors in these women.

—*K.A. Fackelmann*