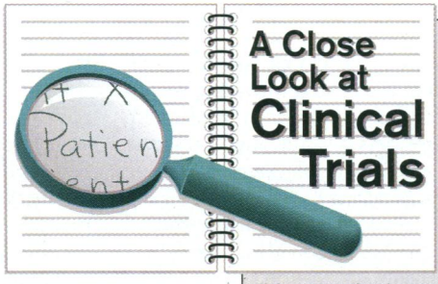
Tamoxifen: Hanging in the Balance

A major clinical trial to determine if tamoxifen can help prevent breast cancer in healthy women is on hold; researchers are again debating whether the benefits justify the risks



SPECIAL NEWS REPORT

Recent revelations of tainted data in a major breast-cancer study have focused attention on clinical trials. The article beginning on this page looks at a study that has been caught in the fallout. An eight-page special report beginning on page 1534 examines problems in ensuring the validity of data in large-scale clinical trials.

In March, the roof caved in on Bernard Fisher, the renowned surgeon and cancer researcher at the University of Pittsburgh, when it was revealed that a major study Fisher headed had been contaminated with falsified data and that he had dragged his feet in publishing a corrected version. Buried under the rubble was another project, one National Cancer Institute (NCI) director Samuel Broder has called "probably the most important study we are doing right now." It is a clinical trial, begun by Fisher's group in May 1992, to test whether the drug tamoxifen—a hormone-like compound synthesized in 1966—can cut the incidence of breast cancer in healthy women who are at high risk of getting the disease. This $68-million trial, one of the most ambitious and controversial NCI has ever undertaken, has been put on hold as the agency scrambles to repair the damage caused by the fraud scandal.

The revelation of the tainted data, first publicized by the *Chicago Tribune*, prompted NCI to launch a massive audit of all studies run by the National Surgical Adjuvant Breast and Bowel Project (NSABP), the unit Fisher headed at Pittsburgh from 1969 until March. NSABP has been coordinating landmark trials of surgical and drug treatments for breast and bowel cancers, involving tens of thousands of patients and more than 400 collaborating clinical centers across North America. Representative John Dingell (D–MI) began to investigate NSABP, and other federal agencies started their own probes. When audits turned up signs of lax administration, NCI forced Fisher and his deputy, Carol Redmond, to resign as leaders of NSABP and suspended all the clinical trials they were running, including the tamoxifen study (*Science*, 25 March, p. 1679).

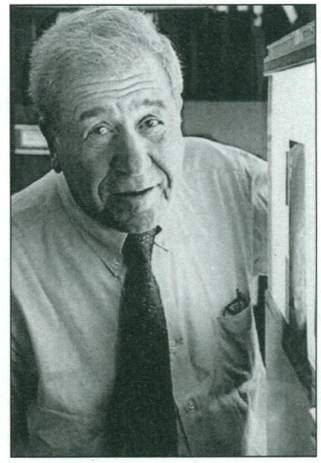
For the tamoxifen study, this enforced hiatus has come at a critical time. Some 11,000 healthy women aged between 35 and 78 years had already been recruited when the trial was halted, and NSABP was hoping to sign up another 5000 by the end of 1994. Half were to be given tamoxifen for 5 years; the other half, a placebo. The plan was to follow them for 7 years to determine whether the treated group had fewer breast cancers than the control group. But the researchers conducting the tamoxifen trial worry that the scandal could interfere with these carefully laid plans. Unless the trial gets moving again quickly, says Donald Trump, NSABP's current administrative chief, "the enthusiasm of investigators may wane," and it could become difficult to recruit patients.

The suspension of the study has also rekindled a fierce debate about the risks of giving a powerful drug like tamoxifen to healthy women. Before the trial began, critics charged that the drug had never been adequately studied. They noted that its mechanism was not understood, and that toxicology studies suggested its use might lead to lethal tumors (see box, next page).

A handful of recent deaths from endometrial cancer among breast-cancer patients taking tamoxifen in a separate trial have raised these concerns anew. Since the critics think the risks and benefits weren't considered carefully enough before the trial began, it's not surprising that epidemiologist Trudy Bush of Johns Hopkins University in Baltimore, a leading skeptic, says the NCI-ordered hiatus offers a "golden opportunity" to conduct a full risk-benefit analysis before resuming the study.

So far, however, the critics haven't made much of an impression on NCI's top scientific advisers. On 5 May, an independent NCI Board of Scientific Counselors agreed unanimously that the trial should be resumed. But the panel did ask NSABP to give participants more detailed information about risks and to add a new safeguard—annual endometrial cancer tests for all participants. At a meeting on 1 June, the National Cancer Advisory Board (NCAB) added its voice to those calling upon NCI to get the project restarted "as soon as possible." Broder assured the NCAB that he was doing all he could to get the research going again this summer, and that he felt there was "substantial cause for optimism."

But whether there really is cause for optimism about the fate of the tamoxifen trial will be determined by decisions that are to be made over the next few weeks. The NSABP is installing a new data auditing system and preparing to elect new leaders, acts that the group hopes will demonstrate it has a new management style. At the same time, NSABP has been told it will undergo a more formal review next year, for NCI has decided to "recompete" the contract for management of the trial. Meanwhile, the Food and Drug Administration (FDA) will re-analyze data on risks and benefits of tamoxifen during a public session on 7 June. Dingell has scheduled another hearing on Fisher's management of NSABP on 15 June, which could affect NCI's plans. But NCI's manager of the tamoxifen trial, Leslie Ford, insists that the congressional inquiry "has nothing to do with the *science* of the prevention trial." She expects NSABP will get the green light to resume data analysis this month.



TERRY CLARK/NYT

Tamoxifen pioneer. Under Bernard Fisher's leadership, breast-cancer trials bloomed, but management problems arose.

Tamoxifen, the good and the bad

Although many of the problems now confronting the trial can be traced to Fisher's management, Fisher is also widely perceived as the force that got the trial started in the first place. It was he who led the way with almost two decades of testing of tamoxifen on breast-cancer patients. Some of the most

Delayed Reaction

For more than a year, women enrolling in a massive clinical trial to test whether tamoxifen lowers their risk of getting breast cancer signed a consent form stating that other clinical studies have indicated that the drug increases risks of uterine cancer. But the consent form went on to note that "[n]o deaths from uterine cancer were reported. The uterine cancers that have occurred have been at an early stage and are thought to be curable." Several months before the consent form was changed, however, the researchers running the prevention trial apparently had evidence in their files that these reassurances were erroneous: A handful of breast-cancer patients participating in another tamoxifen study they were managing (the B-14 trial) had died after being diagnosed with uterine cancer. The first death occurred before the prevention trial got under way in 1992—yet none of the deaths were reported to the National Cancer Institute (NCI) until October 1993, and the consent forms were not changed until January 1994 (*Science*, 18 February, p. 910).

These delays have caught the attention of Representative John Dingell (D–MI), who asked NCI officials at a hearing in April to explain what happened. Dingell is expected to grill the former leader of both the B-14 and the prevention trials—Bernard Fisher of the University of Pittsburgh—on the matter at a hearing scheduled for 15 June. And NCI director Samuel Broder said at the April hearing and in an interview with *Science* that he considers the delays unacceptable.

According to NCI, 23 women in the B-14 trial who were assigned to tamoxifen use were diagnosed with endometrial cancer in the late 1980s or early 1990s; six died, but only four cases were associated with tamoxifen use. Testifying before Dingell's subcommittee on oversight and investigations on 13 April, Broder said NCI "should have received information" about endometrial cancer "early in 1992." Dingell asked, "So it would be fair to say that one of the deaths should have been understood and reported in early 1992; is that fair?" Broder replied: "That's correct." He agreed that the National Surgical Adjuvant Breast and Bowel Project (NSABP)—the Pittsburgh organization that was running the trials—should have reported at least four of the deaths by August 1993. Instead, NCI learned of all of the deaths in late October 1993.

Fisher responded through an attorney, Joseph Onek of Washington, D.C., that it was "absolutely untrue" that he knew of endometrial cancer deaths before reporting them to NCI in October 1993. Onek claims that for a period of 2 years, NSABP officials were unable to determine the cause of death in the first endometrial-cancer victim, and that they had similar, though less severe, problems in determining the cause of death in the second, third, and fourth patients.

If Fisher seemed slow to report information on endometrial cancers, it was not for lack of prodding. *Science* has obtained internal NSABP memos—first reported in the newsletter *Cancer Letter*—indicating that tamoxifen's British manufacturer, ICI Pharmaceuticals, and its subsidiary, the Zeneca Pharmaceuticals Group of Wilmington, Delaware, had long been pushing for an analysis of tamoxifen's side effects. ICI research official P.L. Walton began asking Zeneca for NSABP's hard numbers on endometrial cancer in July 1992. By July 1993, Zeneca had obtained enough information from NSABP to conclude that patient advisory forms would have to be revised to include stronger warnings. By August 1993, NSABP staffers themselves had become concerned enough about endometrial cancers that Fisher's deputy, Carol Redmond, sent him a memo strongly recommending that an annual gynecological exam be made mandatory for all subjects on tamoxifen.

In November 1993, after Broder learned about the first uterine-cancer death, he asked that NSABP rewrite consent forms immediately. NCI and NSABP began work on the new wording in December 1993, incorporating it into consent forms the following January—2 years after the first death had occurred in the B-14 trial.

–E.M.

convincing data came from a massive test of tamoxifen therapy, coordinated by NSABP, called the B-14 trial, involving a dozen major collaborating institutions and nearly 3000 patients. This clinical trial was limited to women whose cancer showed no signs of spreading and whose tumors appeared to be hormone-responsive because they included estrogen receptors. In 1989, Fisher published early results indicating that women in the B-14 trial treated with tamoxifen had a 40% reduction in new breast cancers compared with women in a control group.

There were also hints from various studies that tamoxifen might provide additional side benefits. The drug appears to change the balance of serum lipids in postmenopausal women as estrogen does, apparently lowering cholesterol and possibly reducing the risk of coronary artery disease. Tamoxifen prevents bone loss, and some think it could reduce osteoporosis and hip fractures among older women. The data from B-14 have not established the heart or bone benefits, however. For that reason, investigators hoped the prevention trial might come up with some hard data on these points.

But tamoxifen is also known to pose several hazards. Investigators' chief concern was that, like estrogen, the drug might promote endometrial cancer. A half-dozen studies, including B-14, have shown that using tamoxifen at least doubles this risk. The drug has also been associated with an increased rate of deep-vein thrombosis and rare cases of ocular degeneration. Toxicology studies also found that tamoxifen induces liver tumors in rats.

Nevertheless, tamoxifen looked so promising that Fisher and others, such as surgeon Michael Baum of the Royal Marsden Hospital in London, argued for a massive trial to test whether it could be effective in reducing breast-cancer incidence among healthy, high-risk women. In Britain, Baum led a relatively small trial of tamoxifen for cancer therapy, sponsored by the private Cancer Research Campaign. But Britain's Medical Research Council so far has declined to heed Baum's appeals that it sponsor a large prevention trial because it remains concerned about possible hazardous side effects. In the United States, on the other hand, NCI decided the risks were worth taking, and it backed Fisher and NSABP as managers of the world's largest prevention trial. Statisticians calculated that 16,000 women would need to be studied to yield a significant difference between the treated and untreated groups of women—a difference of just 62 fewer expected cases of breast cancer.

The risk intensifies

The trial continued without major incident until late 1993, when NSABP began to realize that patients on tamoxifen in the B-14 trial were developing endometrial cancer at a higher rate than expected and that four had died. NSABP statistician Joseph Constantino argues, however, that the increased rate of endometrial cancer hasn't changed the bottom line of the risk-benefit calculations for women entering the trial.

Constantino and NCI's Ford have presented this argument at several review panels since last November. And as *Science* went to press, they were preparing to present the data backing their argument to the FDA. The rate of endometrial cancer incidence among tamoxifen users in the B-14 trial, according to Constantino, is now three times the rate seen in the general population—greater than

the twofold increase in risk NSABP originally assumed. This translates into about 46 additional cases of endometrial cancer among the entire treated population over 7 years of monitoring.

NSABP's data safety and monitoring board, chaired by epidemiologist Theodore Colton of Boston University, met to review this analysis at a special session in Washington, D.C., on 4 May. At the meeting, the panel also heard from Trudy Bush, who, with her colleague Kathy Helzlsouer, came to challenge the NSABP forecast as too optimistic. These two critics had already published a paper arguing that NSABP had overstated tamoxifen's power to protect against heart attacks. They pointed out that only a few studies out of more than 30 had found this positive effect, and they argued that if these questionable benefits were removed from the calculations, the trial would no longer appear to offer any net benefit. They wrote that a more realistic assessment raises the question "of whether the trial should continue as designed."

NSABP's Constantino responded by ripping apart the Bush-Helzlsouer paper, saying it was based on erroneous data assumptions. Some of the assumptions, it turned out, were taken from less-than-fully-documented tables in the NSABP protocol, however. But Constantino's trump card was a recalculation of the anticipated breast-cancer benefits. After analyzing the details on women actually enrolled in the trial, NSABP had found that their risk of getting breast cancer was twice as high as anticipated. "We had [initially] used a conservative assumption about the breast-cancer benefit," says Constantino. The new numbers mean that many more women—132, not 62, out of the 8000 treated—are likely to avoid cancer by taking the drug (see table). Bush, though conceding that some of her assumptions were wrong, argues that her conclusions still hold. She says the debate has become so "emotional" that an outside arbiter should step in and resolve it. The FDA may perform that task in a review of tamoxifen begun this week.

Colton, the panel chairman, cut off the debate between Bush and Constantino at this point. He told *Science* he and other members found NSABP's data persuasive. Members of NCI's board of scientific counselors expressed similar views. For example, Robert Greenberg of the University of California, San Diego, said that while "there were some good points" in Bush's paper, he heard "no new information that would lead us to advise against continuing the trial."

The panel did impose two new conditions, however. It asked that participants be given age-specific information about their risks. And it asked NCI to agree to pay for annual endometrial testing for all participants. The NCI's Board of Scientific Counselors met on 5 May and unanimously adopted these recommendations, also urging NCI to restart the trial as soon as possible. Broder has accepted the changes, which Ford says could cost an extra $3 million to $5 million per year.

Members of the safety panel and the Board of Scientific Counselors feel that the trial is on firm ground now. "Obviously, there needs to be endometrial monitoring of all participants in the trial," says Barbara Hulka, an epidemiologist and expert on estrogen studies at the University of North Carolina who serves on NSABP's independent safety panel. "I'm not critical of the original plan because...there wasn't much data in the literature on risk to the endometrium." But now, Hulka believes, "NCI should put up the money," help train medical staffs, determine the best type of aspirator to use in sampling, and set national standards for endometrial testing. "It will require work," she notes, but "even if there were some potentially more aggressive cancers" caused by tamoxifen, says Hulka, "we ought to be able to pick up precursors" and catch them early.

BALANCING TAMOXIFEN'S RISKS AND BENEFITS

Assumptions		Number of Predicted Events							
		Detrimental				Beneficial			
Liver Cancer	Pulmonary Embolic Death	Endometrial Cancer	Liver Cancer	Pulmonary Embolism	Total	Breast Cancer	Coronary Heart Disease	Total	Net Benefit
No Increase	No Increase	83	0	0	83	133	44	177	**94**
	Twofold	83	0	4	87	133	44	177	**90**
	Fivefold	83	0	17	100	133	45	178	**78**
Twofold Increase	No increase	83	2	0	85	133	44	177	**92**
	Twofold	83	2	4	89	133	44	177	**88**
	Fivefold	83	2	17	102	133	45	178	**76**

*3 years of accrual; 7 years of follow-up; 30% reduction in breast cancer; 20% reduction in coronary heart disease; threefold increase in endometrial cancer.

Positive balance. This new risk-benefit analysis, prepared by the NSABP, was presented to an FDA advisory committee early this week. Benefits are numbers of cases prevented; detriments are numbers of endometrial- and liver-cancer cases caused, plus deaths from pulmonary embolism.

Political hurdles

The changes recommended by Colton's panel are already being put into effect, says NSABP's Trump. In a matter of weeks, he predicts, the Pittsburgh center will be ready to resume recruiting patients. Broder and Bruce Chabner, NCI's chief of cancer treatment, also expect recruitment to resume this summer. But NSABP still faces several major hurdles, some of them political. Most significant is the question of credibility. Can NSABP convince the research community—and more to the point, can it persuade Representative Dingell—that its risk estimates are solid and that it has corrected the apparent administrative weaknesses that led to the crisis in March?

As for NSABP's leadership, it is due for a significant change. Members of the organization are now attempting to rewrite NSABP's constitution to permit an executive committee to elect a new permanent leader. It's important that the collaborative move quickly and carefully, says Chabner, because NCI has decided to put the contract up for bidding, and the new leader will have to present a convincing argument for keeping the project at Pittsburgh. NCI's goal is to subject the management of NSABP to outside peer review and to obtain the community's seal of approval on the new management team, wherever it is located. This will be a big challenge for the staff now at Pittsburgh, since it must gear up to write a grant proposal while trying to make changes in the protocol and responding to audits and investigations from Washington.

Proponents of the trial argue that it's important to finish the work begun in 1992 because doctors are already prescribing tamoxifen for women with a high risk of breast cancer, even in the absence of proof that it works. The purpose of doing large clinical trials, says Charles Hennekens of Harvard University, is to find out whether a controversial regimen is effective. And the only way to resolve the debate is to finish collecting the data. Otherwise, says Hennekens, "we have to assume that any time there's a hazard, we shouldn't be using something, and I don't think that that assumption is tenable."

–Eliot Marshall

With reporting by Lisa Seachrist.