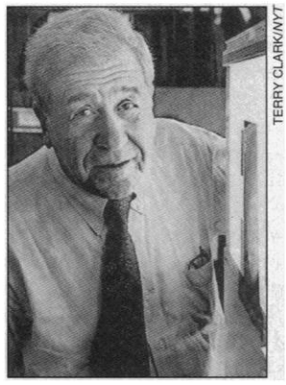
BREAST CANCER

Reanalysis Confirms Results of 'Tainted' Study

Women with breast cancer received mixed reports from the research establishment in the past week. The good news is that lumpectomy (minor surgery) has been shown to be just as much a lifesaver as mastectomy in treating small tumors. This result was first announced a decade ago, on the basis of a major clinical trial, but it had been clouded by reports that some data in the trial were tainted by fraud. Now a detailed reexamination of the untainted data leaves no doubt that the original conclusion was valid. But a major, and surprising, disappointment has come from another study: A long-term clinical trial of tamoxifen—a drug used to treat breast cancer—has been canceled, and physicians have been notified that tamoxifen appears to lose therapeutic value after 5 years' use (see box).

The data comparing lumpectomy with mastectomy come from a huge study of more than 2000 patients, orchestrated by Bernard Fisher of the University of Pittsburgh. His 89-center collaborative group—known as the National Surgical Adjuvant Breast and Bowel Project (NSABP)—found in studies published in 1985 and 1989 that lumpectomy, lumpectomy with radiation, and mastectomy were all equally effective in extending the lives of women with small (4 cm or less) tumors. The results have now been shown valid for an average patient follow-up of 12 years. Although cancer reappeared at a high rate among women who had lumpectomy alone—about 35%, compared to 10% among women who underwent mastectomy or lumpectomy-plus-radiation—it did not significantly increase mortality in this analysis.



TERRY CLARK/NYT

Untainted. Fisher says new analysis vindicates his work.

After churning out such data for 18 years, NSABP ran into trouble in 1994. A surgeon at one of the participating hospitals—St. Luc's in Montreal—was discovered to have falsified the records of six patients in the lumpectomy study, also known as the B-06 trial. The *Chicago Tribune* ran an exposé of the case, and Representative John Dingell (D–MI) held an investigative hearing at which he raked Fisher and the National Cancer Institute (NCI) over the coals. Because the validity of NSABP's data had been questioned, the government conducted a massive audit of B-06 patient records. Fisher and NSABP staffers also reanalyzed the data independently. After 18 months of fencing among the NCI, Fisher, and the *New England Journal of Medicine*—which had published the original study and was upset not to have heard about the tainted data sooner—*NEJM* published a reanalysis last week. It also published an audit by NCI and a 36-trial meta-analysis by a large collaborative group confirming Fisher's initial results.

"We are very pleased to see this come out at last," Fisher said in a telephone interview. NCI's audit of the study, by Michaele Christian and colleagues, found discrepancies in the NSABP data but judged them to be "uncommon" or not significant enough to affect the study's conclusions. The NCI team audited only 86% of the patients in the study because, a staffer says, it would have been prohibitively expensive to track down every last one. Of the 1554 audited cases, NCI reported that 4.4% contained "at least one discrepant item," and 7.3% had one or more unverified item.

The most striking defect, according to biostatistician John Bailar of the University of Chicago, writing in the same issue of *NEJM*, was the failure of NSABP physicians to "be meticulous about informed consent" before patients were assigned to a treatment group. Only two thirds of the patient files contained consent forms that had been signed before surgery. Documented consent was obtained after surgery in 210 cases; consent forms were undated in 137 cases; and consent was not verified in 71 cases. Bailar wrote that he found this record "unjustifiable."

Asked to rate the trial today, Fisher said, "It was impeccably run. ... It emancipated the scientists and clinicians from concepts that governed breast cancer surgery for the major part of this century."

–Eliot Marshall

Long-Term Tamoxifen Trial Halted

The demand for tamoxifen, a synthetic hormonelike drug, has been growing steadily since the 1980s, when it was found to help prevent the recurrence of breast cancer. The drug locks onto estrogen receptors in tumors that contain them, blocking the growth stimulus that estrogen provides. But last week, preliminary results of a major clinical trial indicated that this effect may fade with prolonged use; in fact, the findings prompted concern that long-term tamoxifen use may even increase cancer risks for some women.

As a result, managers of a major cancer research project—the National Surgical Adjuvant Breast and Bowel Project (NSABP) in Pittsburgh—immediately canceled a long-term tamoxifen therapy experiment known as the B-14 trial. The National Cancer Institute (NCI) also sent a bulletin to 22,000 physicians on 30 November advising them that there is "no advantage" for women with "node-negative, estrogen-receptor-positive breast cancers" to take tamoxifen for more than 5 years. NCI added that there is a "troublesome possibility" that using tamoxifen for more than 5 years "might actually be detrimental."

"This is very big news; it's a surprising result," says Lauren Schnaper, an oncologist who directs a breast cancer study involving older women at the University of Maryland, Baltimore. She had planned to give tamoxifen to patients in one arm of her study for an indefinite period. The trial is now being redesigned. But while patients in clinical trials will get the new warning on tamoxifen, it may be more difficult, she says, to change use by physicians not in trials. "Many people in this country feel that tamoxifen is just a wonder drug," Schnaper says. According to one NCI staffer, as many as 1 million U.S. women may be taking tamoxifen, perhaps 20% of them for longer than 5 years.

The news on tamoxifen comes from a special review conducted last month by members of NSABP's data and safety monitoring committee. They found that 92% of those who had taken tamoxifen in the B-14 trial for 5 years were disease-free for 4 years after they stopped taking it, versus 86% in the group that had taken it longer than 5 years. The long-term group had six new endometrial cancers compared to just two in the 5-year group; six new contralateral breast cancers versus five; and 12 other new primary cancers versus nine. These findings matched results from a soon-to-be published Scottish study.

Jeff Abrams, the NCI official who monitors NSABP, says animal studies have suggested theories why tamoxifen doesn't work well after 5 years—such as that tumors exposed to the drug for long periods adapt and begin responding to it as they do to estrogen. But Abrams notes it will take more basic research to get the complete answer.

–E.M.