

# Mammography Trial Comes Under Fire

While reports that a large study has shown that mammography might increase breast cancer deaths for some women were unfounded, the study remains controversial

Early this month, a slew of news stories suddenly propelled a debate that had been simmering in the cancer community for several years into the public eye. At issue: the question of whether women between the ages of 40 and 50 should have annual mammograms to detect breast cancer. The news reports by and large told of a startling—and frightening—finding: The National Canadian Breast Screening Survey (NBSS), one of the most ambitious clinical trials of mammography ever attempted, had apparently found that regular mammograms actually increased breast cancer mortality in the 40-to-50 age group.

These reports, which turned up on at least one major U.S. television network and led to headlines such as “Is Mammography Bad for Your Health?” in the 18 May issue of *Time*, sowed alarm and confusion among women already deluged with bad news about the rising incidence of breast cancer. Both the National Cancer Institute (NCI) and the American Cancer Society (ACS), for example, have recommended that women in their 40s have a mammogram at least every 2 years. And the reports also put physicians in a difficult spot, for they cannot evaluate the results of the Canadian study themselves before advising their patients. The reason? The study has not yet been published—and it is unlikely to be for at least several months.

Ironically, however, reassurance is coming from the researchers who have been carrying out the NBSS, who say that the news stories that reported an increase in mortality were wrong. In telephone interviews, the study leaders, epidemiologists Anthony Miller and Cornelia Baines of the University of Toronto, declined to discuss their unpublished results in detail, but they told *Science* that the NBSS's current results do not show a statistically significant increase in mortality in 40-to-50-year-old women who had regular mammograms. Reporters were apparently led astray by rumors circulating about the NBSS results at a recent conference on breast cancer sponsored by the American College of Radiology (ACR).

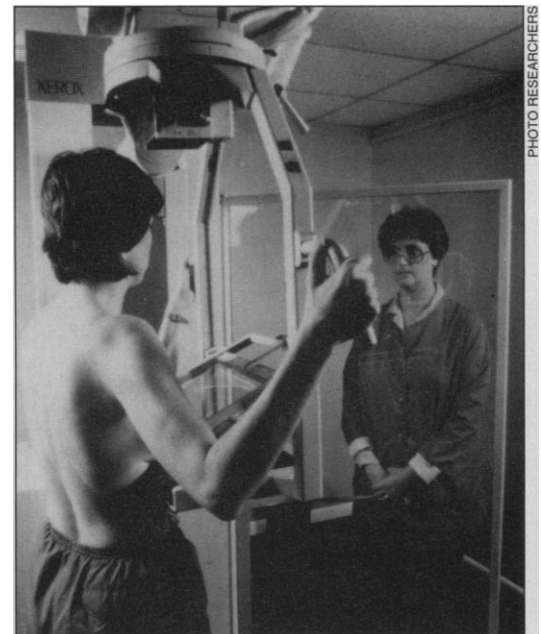
But that does not mean the controversy about the NBSS's findings can be put to rest, for the researchers did not deny that the study showed no benefit of mammograms in either the younger age group or in women over 50. Many researchers are not ready to buy that idea—even though they haven't seen the complete data—and they are publicly attacking the way the NBSS was carried out. Indeed,

shortly after the Boston meeting ended, the ACR put out a press release detailing that group's objections to the study. The fear, says one of the study's critics, radiologist Daniel Kopans of Massachusetts General Hospital in Boston, is that the NCI and the ACS will withdraw their recommendations because of the NBSS results. “It would be a tragedy if younger women were dissuaded from having mammograms because of mistaken results from a flawed study,” remarks another study critic, Steven Feig of Jefferson Medical College in Philadelphia.

Miller and Baines, meanwhile, are incensed that their study is under attack, even before the results have been published so that they can be fully and fairly evaluated. They are even accusing their critics of having an anti-Canada bias. “Results from the back door [Canada] have to be discredited even before they are released,” Baines grouches, pointing out that studies in Europe, which have also found either no benefit or increased mortality in screened younger women, have not drawn such fire. However, none of these studies was even close to the size of the NBSS, which included 90,000 women in their 40s and 50s, and thus weren't expected to carry the same significance.

**A tough goal.** Indeed, criticisms of the NBSS began practically as soon as it was launched in 1980. At best, the study, which was funded by Canada's National Cancer Institute, the Canadian Cancer Society, and the Department of Health and Welfare, was aiming at a difficult goal. While several studies have shown that regular mammograms can save the lives of women over the age of 50, researchers have had trouble evaluating the potential benefits of mammography in women between the ages of 40 and 50 for several reasons. Their breasts are denser than those of older women, for example, and that makes it more difficult to see very small tumors. What's more, the incidence of breast cancer is much lower in the younger age group, so that a very large study would have to be done to obtain statistically significant results.

Women recruited for the Canadian study were randomly assigned to either a mammogram or control group. The 40-to-49-year-old women in the mammogram group had four to five mammograms, each accompanied by a physical breast exam, during the



**Efficacy challenged.** For women under 50, mammography may not save lives, according to the NBSS.

roughly 7-year duration of the study, while the controls had only a single physical exam. (Women in their 50s had annual mammograms and physical exams and their controls had annual physicals.) The women were then followed to see how many in each group developed breast cancer and how they fared.

But even as the first mammograms were being taken in the early 1980s, complaints began to surface. Radiologist Wendy Logan-Young, who's in private practice in Rochester, New York, was supposed to help oversee the quality of the NBSS's mammograms, but she resigned after only a few months, claiming she had never seen a single mammogram and that her recommendations for standards were being ignored. Jefferson Medical's Feig succeeded her, but after almost 2 years, he, too, left frustrated and dissatisfied. Then, in the wake of these defections, an external review board of four radiology experts was convened to assess the technical quality of the NBSS mammograms. Massachusetts General's Kopans was one of its members, and he also came away convinced of the inadequacy of the Canadian screenings.

In particular, Kopans and Feig claim that because of bad equipment and poor instruction of radiologists and x-ray technologists, the vast majority of the mammograms from

the study were of such low quality that they were useless for detecting the very small cancers that would be the easiest to treat successfully. Contributing to this problem, says Logan-Young, was the Canadians' decision to use very low radiation doses because of worries that too-high doses might increase breast cancer development. In addition, Kopans and Feig contend that many more women who eventually proved to have advanced breast cancers were accidentally randomized into the mammogram group, thereby skewing the study results so that the death rate would appear higher in that group.

For their part, Miller and Baines are em-

phatic in their defense of the study's design and results. Miller says that the U.S. researchers saw only early mammograms and results that were not representative of the entire study. "They were looking at small samples from a large study," he notes. As the study progressed, he maintains, the quality of the mammograms improved, a reflection of the general trend toward better mammograms throughout Canada. Miller's defense of the study is supported by David Beatty, the executive director of Canada's National Cancer Institute, one of the study's major funding sources, who describes Miller as a "good investigator."

Grumbles about the study were largely con-

fined to the radiology community—until April of last year. That's when NBSS researchers presented some preliminary findings at the Second International Cambridge Conference on Breast Cancer Screening in England. They reported that the breast cancer mortality rate among screened women aged 40-to-49 was 50% higher than among controls. This information found its way into the press—each camp blames the other for the leak—and women across the UK were soon greeted by the headline, "Women Who Have Breast Scanning Are More Likely to Die of Cancer," in the Sunday *Times* of London, a theme that was repeated in several other news stories.

## New Clue Found to Oncogene's Role in Breast Cancer

While epidemiologists have been arguing over how effective mammography is in preventing breast cancer deaths (see accompanying story), more molecularly inclined researchers have been buzzing over a flurry of new results on an oncogene, called HER2, that appears to play a key role in the progression of some breast cancers. Several groups have recently reported results that should help explain how HER2 works, and these findings may point the way toward improved breast cancer therapies. The reason for the excitement is that about 5 years ago women whose tumors have an overactive HER2 gene were found to be more likely to relapse and die than women without the abnormality.

Researchers have known since 1984 that HER2 codes for a protein with all the characteristics of a growth factor receptor, but they've had trouble finding its ligand, the molecule that binds to the receptor and activates it. That's where the new work comes in, as researchers are at last getting their hands on the HER2 ligand. And that should help clear up some mysteries about the way HER2 activity affects cell growth and other responses, says molecular biologist Stuart Aaronson of the National Cancer Institute, whose own work includes HER2 studies. Until the ligand was identified, he points out, "we couldn't know whether it would turn up the receptor activity or whether it might in fact turn it down." And without that information, researchers don't know whether they should try to design anticancer therapies to block the ligand-receptor interaction or enhance it.

The immediate task, however, is to sort out competing claims concerning who identified the HER2 ligand. Indeed, the work is producing something of an embarrassment of riches, as at least four different groups claim to have found candidate ligands. Some, but not all, may be identical, and it will take some time to determine just how they are related to one another and what each one does. And, to complicate matters even further, there are signs that a priority dispute is brewing between two of the groups.

One group, led by William Holmes and Richard Vandlen of Genentech Inc. in south San Francisco, reports its results on page 1205 of this issue. These researchers found that a line of cultured human breast cancer cells secretes a family of proteins, which they named "heregulins," that not only bind to the HER2 receptor protein but also stimulate its biological activity. That follows hard on the heels of a report in *Cell* earlier this month in which Yosef Yarden and his colleagues at the Weizmann Institute of Science in Rehovot, Israel, along with co-workers at Amgen Inc., in Thousand Oaks, California, and Cell Analysis Systems in Illinois, describe the purification of a protein that binds the rat HER2 receptor. Both of these groups have cloned the genes for

their HER2 ligand candidates, and the sequences reveal that the Yarden group's protein is the rat equivalent of heregulin.

But even though Genentech's Holmes says heregulin constitutes the "first identification and DNA sequence of a human ligand for HER2," it's not clear that this is the first sighting of that particular protein. Two years ago, Ruth Lupu and Marc Lippman of Georgetown University in Washington, D.C., found two proteins that are secreted by breast cancer cells and also bind to the HER2 receptor. Lupu, who has worked with the Genentech group, and in fact sent them the cancerous tumor cell line from which they isolated the heregulins, says, "I don't have any doubts that the proteins [derived by her group and the Genentech group] are the same or very similar." Holmes says that he cannot confirm that contention until the Georgetown group's DNA sequence is available for comparison with the Genentech sequence.

**Many HER2 ligands.** In addition, last year Mark Greene and colleagues at the University of Pennsylvania Medical School came up with still another HER2 ligand from the rat that differs from the other reported proteins, a situation that he says was to be anticipated. "There seems to be a number of these ligands floating around, and that's not uncommon." He suggests that the HER2 receptor may be analogous to that for epidermal growth factor, which is activated by several agents. That possibility is supported by recent work by Robert Bast's group at Duke University. They've shown that there may be at least three different ways of activating the HER2 receptor, only one of which seems to require the ligand provided him by the Georgetown group.

While Genentech's Holmes is quite confident that the heregulins will prove to be the primary activator of the HER2 receptor, the matter is far from settled. And equally confusing are the results the different groups obtained when they tested their ligands' effects on cells. When the Genentech group exposed cells to heregulins, they found that the cells divided and proliferated. In contrast, the rat version of the protein caused some cell types to do the opposite—they matured and stopped dividing. And the human ligand isolated by the Georgetown group did both, depending on the concentration used.

But as perplexing as the HER2 ligand situation is, it should not take long to settle the questions regarding the identities of the ligands and their role in the cell, says Dennis Slamon of the University of California School of Medicine in Los Angeles, who first noted that HER2 gene activity correlates with a poor prognosis. "Now that these molecules are available, there will be a flurry of activity. It will be fairly clear within 6-12 months," he says.

—Michelle Hoffman

That set the stage for the Boston breast cancer conference, which was held during the last week of April. Although NBSS researchers did not present their data there, Kopans and Feig were freely detailing what they see as the study's unforgivable flaws. Meanwhile, Associated Press reporter Daniel Haney quoted Samuel Shapiro, a professor emeritus at Johns Hopkins University School of Hygiene and Public Health and an NBSS scientific adviser, as saying that the study had found a "differential in that direction [higher mortality]." And finally, the American College of Radiology topped things off by issuing its press release. The result: The story broke into the U.S. press in a big way, with numerous stories raising the issue of mammography's safety.

No one was more shocked by the news accounts than Miller and Baines, who say that in the year between the Cambridge and Boston meetings, they and their colleagues had collected and analyzed additional data, which made it clear that mortality of the younger women who had mammograms was not significantly higher than that of the controls. They also didn't find any benefit of mammography in women older than 50, however—a surprising finding in view of the several previous studies showing that it does save lives in that age group. Feig, for one, says that this proves that the Canadian study is flawed.

Although Miller isn't conceding any flaws in the NBSS design, he does say that the study probably doesn't give the definitive word on mammography's potential value to women under 50. "No study has found a benefit in younger women within a follow-up period of up to 10 years, and that's as far as we've been able to go," he explains, adding that the women might have to be followed for 15 to 20 years to see an effect.

Since Miller and Baines are now in the final stages of preparing the manuscript of the paper describing the NBSS results for submission to the *Canadian Medical Association Journal*, it's unlikely to appear before the end of the year. It will be eagerly awaited. "NCI is championing at the bit to evaluate the Canadians' final results," says Edward Sondik, deputy director of the institute's division of cancer prevention and control.

And while it's still too early to say whether the paper will change any minds about recommendations for mammograms in the younger age group, it might if researchers find the results persuasive. Indeed, Kopan's fears that the NCI will backtrack on its recommendations may not be unfounded. The institute will be "evaluating all available data," Sondik says. "But when you have that many women in a study, it will certainly weigh heavily."

—Malory Allison

Malory Allison is a free-lance writer based in Boston.

## AIDS

# CDC Closes the Case of The Florida Dentist

For almost 2 years, it has been a medical horror story that has captivated the nation—even the world. Nearly everyone who reads newspapers figured they knew the perpetrator: Florida dentist David Acer, who had apparently infected Kimberly Bergalis and four other patients with the AIDS virus, and one after another they were coming down with the disease. But, while there has been strong epidemiological evidence supporting that conclusion, proving it—either to the satisfaction of the scientific community or to a jury—has been extraordinarily difficult.

Now, scientists at the Centers for Disease Control (CDC) in Atlanta, where the case has been dissected, say the proof is there. Two papers, one in this issue of *Science* (p. 1165) and another that appeared last week in the *Annals of Internal Medicine* (15 May, p. 798) present a full accounting of the evidence that leads to the ineluctable conclusion that Acer infected Bergalis and the other four patients.

CDC researchers conducted a rigorous epidemiological study of the apparent transmission of the virus in Acer's dental practice and they employed the latest techniques of molecular analysis to nail down the proof. Along the way, the evidence was challenged in a law suit and became the focus of a bitter scientific dispute. And even now, some researchers are not entirely convinced that CDC has a watertight case. "We're not trying to say in any way that these guys' answer isn't correct," says physicist-turned-molecular biologist Temple Smith of Boston University, who along with mathematician Michael Waterman of the University of Southern California in Los Angeles has written a Perspective on the CDC paper in this issue of *Science* (see page 1155). "But probably correct is not the kind of statement that should end up in a courtroom."

Moreover, even as CDC closes the book on one aspect of the Acer case, another remains unresolved: How did Acer infect his

patients? That mystery may never be solved. Yet, frightening as that may seem, the Acer case has, ironically, brought some reassurance about the risks of doctor-to-patient transmission of HIV. Since the case first broke, CDC has been conducting a major study of patients known to have been treated by HIV-infected health care workers. The results, published just last week in CDC's *Morbidity and Mortality Weekly Report* (MMWR), show that of 15,795 patients in 32 practices, only 84 patients were HIV positive, and there was not a single confirmed case of health care worker to patient transmission.

CDC began investigating the dental practice of David Acer in 1990, when Florida health officials reported to CDC the case of Kimberly Berg-

galis, a young woman in her 20s with AIDS who had no identified risk factors for the disease. Based on epidemiological evidence and sketchy molecular analysis, CDC published an article in MMWR on 27 July 1990 raising the possibility that Acer had infected Bergalis. It was a shocking suggestion, for doctor-to-patient transmission of HIV had never been seen before. CDC, bowing to public panic, an-

nounced it would try to compile a list of procedures health care workers should not perform. (No such list has appeared, although revised guidelines about what precautions infected health care workers should take when treating patients are pending.) And there was worse to come: Seven of Acer's other patients were subsequently found to be HIV positive. Although CDC epidemiologists determined that three of them had engaged in behaviors that would put them at risk for contracting AIDS from sources other than Acer, the dentist seemed the most likely source of the virus that infected the other four. All had visited Acer on more than one occasion after the dentist had been diagnosed with AIDS, and all had had invasive procedures.

A clear case of poor hygiene in the dentist's office? Apparently not: CDC could identify no specific lapse in the dentist's procedures that would suggest how he had infected his

**"The evidence strongly suggests that Acer was the proximal source for each of the [five patients'] infections."**

—Gerald Myers

