Animal Tests Take Back Seat to Clinical Data

When researchers put drugs into clinical trials, they usually rely on animal studies to predict how toxic the compounds will be to people. In the case of the tamoxifen breast-cancer prevention trial, however, they have more direct evidence: nearly two decades of testing and using the drug to treat breast cancer. This wealth of clinical data is the primary source of information that will determine whether the prevention trial should resume (see main story). But some toxicologists argue that animal tests are producing worrisome results that are not being fully considered.

Originally developed—and abandoned—as an oral contraceptive in the late 1960s, tamoxifen was developed as a treatment for breast cancer during the mid-1970s. The experiment seemed worth trying because tamoxifen attaches to a cellular receptor for estrogen, blocking the natural hormone's growth-promoting effects. Tamoxifen quickly proved its value in chemotherapy. It extended the lives of patients with breast cancer, showed virtually no side effects, and reduced second cancers in the opposite breast by 40%.

Curiously, though, tamoxifen is not a "pure anti-estrogen." It seems to mimic estrogen by stimulating the endometrium and may inhibit bone loss and lower blood lipid levels. For this reason, clinicians were concerned that the drug could cause endometrial tumors. Against that concern they weighed the knowledge that endometrial cancer is rarely fatal. Finding the risks acceptable, the National Cancer Institute (NCI) launched the Breast Cancer Prevention Trial in 1992, planning to give tamoxifen to 8000 healthy, high-risk women to prevent breast cancer.

Many toxicologists warned from the start that the drug's side effects weren't understood well enough for it to be given to women who, as yet, didn't have breast cancer. Others, like Lewis Smith, chief of the United Kingdom's Medical Research Council's (MRC's) Toxicology Unit at the University of Leicester, say tamoxifen may have been shifted from cancer treatment to preventive therapy "before all the information on the toxicology of tamoxifen was available." Indeed, MRC has declined to join as a sponsor of a British prevention trial for tamoxifen.

Published data from toxicologists who continue to study the effects of tamoxifen on animals have recently raised concerns in the following areas:

■ **Liver cancer.** Joachim Liehr, a toxicologist at the University of Texas Medical Branch in Galveston, found in 1992 that tamoxifen binds to and damages the DNA of rats, suggesting that the drug could initiate tumors in this species. Shortly thereafter, in 1993, toxicologist Gary Williams of the American Health Foundation in Valhalla, New York, showed that high doses of the drug caused liver tumors in rats. And earlier this year, David Kupfer of the Worcester Institute for Experimental Biology in Shrewsbury, Massachusetts, demonstrated that tamoxifen becomes highly reactive in rat liver and that 50% of all liver cancers that he finds in tamoxifen-fed rats have specific mutations in the tumor-suppressor gene *p53*. Biochemist Jeff Bodell of the University of California at San Francisco has shown that tamoxifen produces the same type of DNA damage in rat and human liver microsomes.

Whether any of these rat studies are relevant to human health is still unknown. To date, neither excessive liver cancer nor DNA damage has been reported in the thousands of women taking tamoxifen for breast cancer. But Kupfer says clinicians may not find human liver tumors because they aren't looking for them. "You would just assume that it was a metastasis from the original breast cancer—not that it was directly due to treatment with tamoxifen," says Kupfer.

Speculation of this kind draws a scathing response from Craig Jordan, the pharmacologist at Northwestern University in Evanston, Illinois, who developed tamoxifen as a chemotherapy agent. It's equivalent to saying physicians are "too incompetent to tell the difference" between a metastasis and a primary tumor—which Jordan considers improbable. Yet concerns about liver cancer prompted MRC to ask Smith's group to take a closer look. Smith concludes that rats and humans metabolize tamoxifen in the same way, but at vastly different rates. He finds this reassuring. In addition, Smith's group has reviewed liver biopsies from eight women who have taken tamoxifen and found no unusual DNA damage.

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—Craig Jordan

■ **Endometrial cancer.** Recent reports of a few deaths from endometrial cancers among breast-cancer patients taking tamoxifen have some researchers speculating that the drug may cause a particularly aggressive form of this cancer. University of Texas Health Science Center at San Antonio pharmacologist Michael DeGregorio recently reviewed tamoxifen-associated endometrial cancers reported in the literature and found that in women taking the standard dose of tamoxifen, "a certain subset of tamoxifen-induced endometrial cancers are poor prognosis, whereas typically endometrial cancers are not aggressive."

Pharmacologists Kenneth Nephew and Soahib Kahn of the University of Cincinnati published a paper in December showing that tamoxifen, like synthetic estrogen, appears to turn on oncogenes in the rat uterus, but tamoxifen's effect seems to be more long-lasting. Nephew adds that his data don't show "cause and effect." Nephew will study long-term tamoxifen exposure in the rat uterus, while MRC's Smith and UCSF's Bodell plan to see if the human uterus sustains DNA damage similar to that in the rat liver.

■ **Breast cancer.** University of Kansas pharmacologist Stephen Zimniski found rat breast cancers that appear to be stimulated by tamoxifen. DeGregorio has found these tumors to have a puzzling feature: They can be dependent upon tamoxifen for growth. And some of the tumors are aggressive. DeGregorio thinks this could explain why "some women who develop tamoxifen-resistant tumors see their tumors regress once they stop taking tamoxifen."

Jordan, who says he has seen breast-cancer cells "be trained" into becoming tamoxifen-stimulated in rats, argues that these are "hormone-independent tumors," and are not informative about tamoxifen's effects in humans at all. Jordan says, "The women who ultimately do get breast cancer while they are on tamoxifen were likely going to get hormone-independent breast cancer in the first place."

Jordan agrees that because tamoxifen is risky, its use must be limited to women with a high likelihood of developing breast cancer. But he stresses that "tamoxifen is the only thing we've got now" for preventing breast cancer. Jordan, meanwhile, praises the "courageous" women now in the prevention trial; he thinks they will "tell us everything we need to know" about tamoxifen. The best way to understand the risks and benefits of using tamoxifen as a preventive, he says, is to complete the prevention study, a recommendation that baffles toxicologists like Liehr, who continues to argue that animal testing should precede a large clinical trial.

–Lisa Seachrist