NIH Fends Off Critics of Tamoxifen Study

Even as it seeks to give the Army some advice on how to spend $210 million on breast cancer research (see main story), the National Institutes of Health (NIH) is fending off allegations that it is misguided in spending $70 million on a massive study aimed at preventing the disease. At issue are clinical trials that aim to find out whether healthy women at risk for breast cancer might benefit from the anticancer drug tamoxifen. At a congressional hearing last week, a panel of medical scientists contended that the drug may do more harm than good to some patients. But NIH officials called the charges inaccurate and rejected recommendations from the critics that the government stop enrolling healthy, premenopausal women in the clinical trials.

The tamoxifen study, officially known as the Breast Cancer Prevention Trial (BCPT), recently got under way in the United States and Canada. Researchers plan to recruit 16,000 healthy women age 35 or older and monitor them over 10 years to evaluate the effectiveness of tamoxifen in preventing breast cancer. BCPT researchers, headed by University of Pittsburgh oncology researcher Bernard Fisher, have begun enrolling women with a higher-than-average chance of getting breast cancer. They select patients according to a computerized calculation of risk, which takes into account the number of close relatives diagnosed with breast cancer, the number of children a woman has given birth to, her age at first delivery, and her record of previous benign breast tumors. So far, 3300 women have enrolled in the trials; another 12,700 are expected to enroll in the next 18 months.

NIH's enthusiasm for tamoxifen arises from several studies that showed that the drug reduced by as much as 50% the incidence of cancer in the "healthy" breast of women who had already had one breast surgically treated for cancer. BCPT researchers project a similar benefit in the healthy women in their study. They predict that 124 women given tamoxifen are likely to get breast cancer, compared to 186 women among the controls.

It's those 124 women that worry Michael W. DeGregorio, an oncology researcher at the University of Texas Health Science Center in San Antonio. In testimony before a subcommittee of the House Committee on Government Operations chaired by Representative Donald M. Payne (D–NJ), DeGregorio charged that treatment with tamoxifen stimulates the growth of a class of aggressive breast cancer tumors that lack estrogen receptors, and he argued that tamoxifen induces the proliferation of tamoxifen-resistant tumors.

NIH Director Bernadine Healy defended the study. "We do not enter these trials lightly," she testified. "I believe this trial is well-grounded in science." Susan Nayfield, a program director in the NCI's division of cancer prevention and control specifically disputes DeGregorio's claims. Tamoxifen seems to prevent tumors that contain estrogen receptors, she notes, but it is unlikely to prevent those that lack such receptors. These tamoxifen-resistant tumors are likely to arise with or without use of the drug, she says.

Tamoxifen's side effects also worry the critics. Adriane Fugh-Berman, a physician with the National Women's Health Network, pointed to published studies that associated tamoxifen with side effects that range from relatively minor symptoms—such as hot flashes and vaginal discharges—to liver damage and an increased incidence of cancer of the endometrium. But even more worrisome, says one congressional staffer, is the defensiveness of NIH officials, whom she described as "circling the wagons" on tamoxifen.

Meanwhile, NIH officials feel that the evidence is strong enough to move ahead with the trials. Moreover, there's another compelling reason for determining whether tamoxifen can prevent breast cancer: More and more physicians are prescribing tamoxifen in women at high risk for getting breast cancer, even though the Food and Drug Administration hasn't approved it for that use. At present, tamoxifen is licensed as therapy only for women who already have breast cancer.

–Richard Stone

the Army would like to avoid duplicating the sort of work funded by NIH—basic research at the cellular level. And she notes that the military services by tradition focus on applied research. One possibility would be to invest in an emerging technology, Smith says, possibly speeding it along with a "large infusion" of federal funds. For example, the Army is interested in improving the quality of mammography through digital imaging and data analysis.

But Army officials say they won't spend the entire amount on such high-tech projects. According to Smith, USAMRDC will support some fundamental research in collaboration with the NIH and NCI. The details of the joint effort haven't been worked out, and it's clear that the two agencies differ sharply in style. While NIH favors small, individual researcher proposals, the Army likes big projects with well-defined objectives. Smith notes that the average NCI grant is for $200,000, but "we anticipate mostly larger projects with specific end points." She foresees organizations—perhaps universities and small businesses—collaborating on proposals. And Smith says that the Army will rely on a contract outfit to do peer review. The most likely candidate is the American Institute of Biological Sciences, which already handles most of the Army's biomedical reviewing.

The Army's approach is not what groups like the BCC had in mind. "We cannot afford to have that money wasted," says BCC president Frances Visco, a Philadelphia attorney. "We do not need more research into how to build a better mammography machine; we need to find out how to stop this epidemic. We want a say in what gets funded, in who is responsible for the peer review." The group also wants a "study section at NIH dedicated to breast cancer," an "expedited review of proposals," and "consumer advocacy representation on the National Cancer Advisory Board."

The group is working primarily through Harkin's office. In a recent interview with *Science*, Harkin said, "I'm going to monitor this on a weekly basis" as it moves through the bureaucracy after the election. "I don't want any foot dragging," he says, "and I don't want [the Army] buying a lot of fancy machines and high-tech equipment." Instead, as Harkin sees it, "the Army will write the checks, but they will have to peer review it...and they will work closely with NIH, the universities."

The outcome of all this—an Army research program modeled on NIH—may look like an oddity produced by election year politics and weird budget rules. But Harkin doesn't see it that way; he likes it. "There's going to be more" of this kind of funding, he claims. He would like to shift R&D money "out of exotic new weapons systems and germ warfare" and into biomedical research. Says Harkin: "I see a whole new field of research in disability—the cure and prevention of disabilities—that the military might get into."

Perhaps this is a generous vision. But, says Paul Calabresi of Brown University, chairman of the NCI's Cancer Advisory Board, it may be generous in the wrong direction. "Asking the Army to do cancer research," he says, "is analogous to asking NIH to build tanks or helicopters." Instead of giving a peace dividend to NIH, he warns, "it seems to me we're giving a new mission to the Army."

–Eliot Marshall