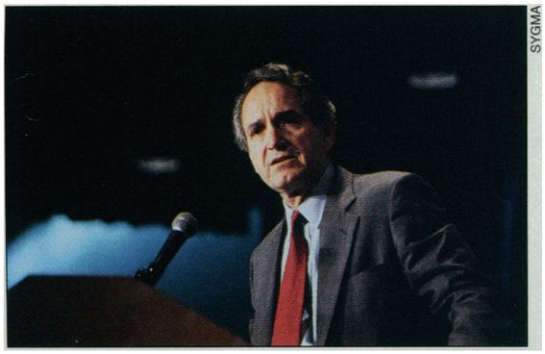
Breast Cancer's Forced March?

By a fluke of politics, the Army has become the lead federal agency in breast cancer research; now there is a tussle over how it should spend a $210 million bonanza

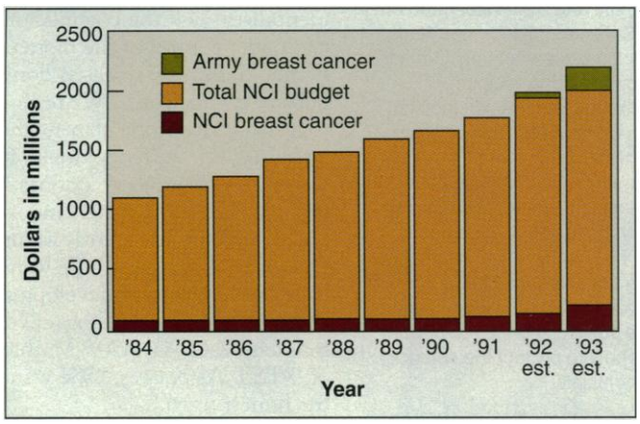
Last week, the U.S. Army's biomedical chiefs huddled with Bernadine Healy, director of the National Institutes of Health (NIH), and Samuel Broder, head of the National Cancer Institute (NCI). The subject of their meeting: How to carve up a 1993 budget windfall. Congress has appropriated $210 million for breast cancer research in addition to the $197 million NCI received for breast cancer this year. A bounty indeed, but the catch is that it was delivered not to NIH but to the desk of Major General Richard Travis, commander of the U.S. Army Medical Research and Development Command (USAMRDC).

What's going on here? Readers of *Science* might be forgiven for thinking that biomedical research funding has moved into a new era in which pork and politics prevail. Only last month, we reported how one company, using master lobbyists, convinced Congress to push through $20 million of Army money in behalf of its AIDS vaccine candidate. Now Congress has marched the Army to the forefront of cancer research.

In the case of the breast cancer funding, women's health groups were the victors in setting the research agenda—except that they never intended the money to go to the military. They meant to steer it to NCI. But in the heat of battle, their champions in Congress took the next best solution, which was to make expedient use of the Army's budget and hope to corral the funds for cancer scientists later. Now, through their connections on Capitol Hill, the same groups are involved in the ongoing negotiations between NIH and the Army over how to spend the money. (Women's groups are also shaping the research agenda in other areas—see story on page 733.)



SYGMA



SOURCE: NCI GRAPH: L. OWENS

Campaign strategist. Senator Harkin *(top)* plotted maneuver to double federal spending on the disease *(left)*.

How to win friends...

It all started when breast cancer groups came to Congress looking for friends. The most effective of these groups was the Breast Cancer Coalition (BCC), a grass-roots organization of former cancer patients with local "captains" in nearly every state. Within a few months of BCC's formation in May 1991, the group hand delivered 600,000 letters to the president and Congress demanding more money for cancer research. Then, last February, BCC summoned researchers to its own hearing on Capitol Hill and put together a detailed request for a $300 million increase in breast cancer studies. Other groups, including the American Cancer Society and the National Coalition for Cancer Research, added their political muscle, and the campaign—aided by an election year in which several senators are running scared on women's issues, and promoted by women in Congress—paid off.

Eventually the crusade joined forces with Senator Tom Harkin (D–IA), who has been committed to this cause for several years, having lost his two sisters to breast cancer. Harkin, who chairs the appropriations subcommittee that handles the budget of the Department of Health and Human Services and is a member of the defense appropriations subcommittee, first tried to add $300 million to NCI as part of a monster "transfer" amendment that would have shifted $4.1 billion out of the Defense Department appropriation into the Department of Health and Human Services.

That tactic lost by a wide margin in early September, largely because Congress was leery of breaching a 1990 budget agreement that expressly forbids transferring funds from military to domestic programs. Undaunted, Senator Alphonse D'Amato (R–NY) then proposed diverting a trickle of funds from the Pentagon to NCI breast cancer studies. That failed too. At this point, says Harkin, "we hit upon an ingenious device," which was to use the defense budget to fund breast cancer research directly.

The House agreed to go along, and conference negotiators worked out words to the effect that the Army will be the "executive agent" of a new $210 million "peer-reviewed" cancer research program. White House budget chief Richard Darman tried to block the funds, arguing that this gimmick breaks the spirit of the budget agreement. But Harkin and his allies responded that Darman had not tried to stop $409 million worth of other "civilian" biomedical funding in the defense bill. Darman didn't change his opinion, but when Harkin and the women's groups accused him of "sexism," he chose not to continue the battle. The bill became law, with little or no comment from the scientific community.

...and influence people

Now the battle has shifted to just what this huge dollop of funds will buy. There's widespread concern that the Army will opt for a quick and easy payout to avoid becoming the sponsor of a domestic health program. Says Marc Lippman, a cancer researcher at Georgetown University, the funds could be invested in a "lot of really worthwhile projects" aimed at understanding and combating the disease. On the other hand, Lippman warns, they could be spent on "standard public health measures—like buying a dozen mammogram machines for every Army base."

Such concerns may be well founded. General Travis referred questions last week to Jean Smith, an assistant who handles procurement, who told *Science* it is "our intent to search for the relatively short-term, high-technology research." According to Smith,

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