Tamoxifen and Informed Consent Dissent

Congress, outside advisers cite reservations about NIH cancer-prevention trial

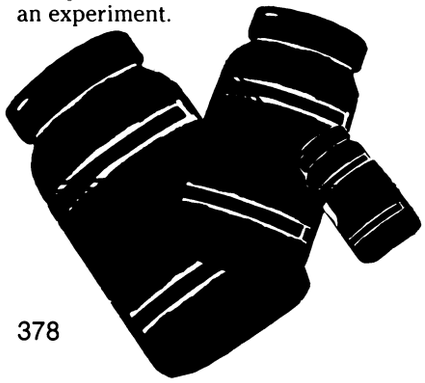
By JANET RALOFF

Medical research relies on human trials to test the safety and efficacy of new treatments. But all drugs — even aspirin — pose some risk. For example, a $68 million National Cancer Institute (NCI) trial now in its early stages will attempt to prevent breast cancer in 8,000 healthy women by giving them daily doses of tamoxifen for five years. Yet this synthetic hormone can itself induce cancer and fatal blood clots in a small percentage of women.

Have the designers of the trial done everything they can to minimize the risks to these 8,000 volunteers? Is it even ethical to expose healthy recruits to a drug with such serious side effects (SN: 4/25/92, p.266)?

These were among the questions raised last month at a hearing before the House Subcommittee on Human Resources and Intergovernmental Relations. And though officials at the National Institutes of Health (NIH) promised some changes, including major revisions in their informed-consent process, subcommittee chairman Rep. Donald M. Payne (D-N.J.) says he was not reassured by what he learned: "I remain very concerned."

Not all medical centers involved in the trial are providing potential recruits with an up-to-date synopsis of the risks that may be associated with tamoxifen, one panel of medical witnesses testified. And an analysis by the subcommittee of 268 different informed-consent forms being used by the medical centers participating in this trial found that most contained one or more potentially serious omissions of risk data. State and federal laws require that volunteers sign such consent forms before taking part in medical experiments. The aim is to establish that each recruit understands — and accepts — the specific known risks associated with an experiment.



The Oct. 22 hearing also turned up evidence that two federally impaneled groups of independent medical experts had unsuccessfully challenged the trial's design before it began. The panels charged that the trial's entry criteria permitted the recruitment of women whose risk of developing breast cancer was unacceptably low.

How NIH responds to charges leveled at the hearing may affect medical research well beyond the tamoxifen trial. This is the first major disease-prevention study to use a drug "that carries such serious risks," asserts Arthur L. Caplan, director of the Center for Biomedical Ethics at the University of Minnesota in Minneapolis. As such, he maintains, this trial "is a watershed, in terms of ethics" and may set a precedent for risk disclosure in future disease-prevention trials.

Moreover, says Seattle attorney Leonard W. Schroeter, "there's more to this than the ethics. There is a human rights issue."

Ever since the Nuremberg trials of Nazis accused of war crimes, Western law has prohibited medical experimentation on humans without the participants' full and informed consent, he notes. So "any person who is harmed as a consequence of these trials, without first having been fully informed of [tamoxifen's] risks, most probably has an appropriate lawsuit against both the dispensing doctor and the government," says Schroeter, the immediate past chairman of the environmental, toxic, and pharmaceutical torts section of the Association of Trial Lawyers of America.

Since disease sufferers may well accept side effects and risks that healthy people will not, "prevention clinical trials are very different from treatment trials," notes Peter Greenwald, director of NCI's Division of Cancer Prevention and Control in Bethesda, Md.

A woman's risk of breast cancer increases with age and several other factors, such as having a mother or sister with the disease. To ensure that only those women most likely to benefit from tamoxifen will face its risks, the new study is restricting entry to women who are at least as likely as a normal 60-year-old woman to develop breast cancer. With no other risk factor besides her age, such a woman has a 1.7 percent chance of developing breast cancer during the five-year trial.

Volunteers who clear this first risk-assessment hurdle then undergo a medical examination. Based on recent reports of serious eye problems in tamoxifen users (SN: 7/4/92, p.12), the study's principal investigators now bar women with macular degeneration, an eye disease that can cause blindness. Because birth defects have occurred in mice on tamoxifen, premenopausal recruits must pledge to prevent pregnancy. The trial also excludes women who have had blood clots.

Finally, Greenwald says, physicians will not dispense tamoxifen until each recruit attends an orientation session on the study's design and signs an informed-consent statement in which risks of participation "are noted in detail."

While most people "neither want nor expect to live in a risk-free world," Caplan observes, "Americans are strongly committed to the view that each person must decide what sorts of risks and hazards they want to face in the service of attaining goals they hold dear."

But one can't weigh risks against benefits without a full disclosure of each. And Caplan testified that "there is evidence that inaccurate, incomplete, or incomprehensible information has been or is now being provided to women recruited to participate in the [tamoxifen] study."

Clinical investigators tend to "overemphasize benefits and underemphasize risk" in descriptions of the study to potential recruits, he says. For instance, he notes that among the potential benefits cited are lower serum cholesterol and increased bone density — factors that could reduce a participant's risk of heart disease and osteoporosis, respectively.

"But women should not enter this study in hopes of getting thicker bones," Caplan said in an interview. "We're not taking in people who are at high risk of falling down. The point of this study is to see if tamoxifen has a preventive effect against breast cancer. Period. You might want to mention potential ancillary benefits in an appendix, but don't raise them as part of the risk-benefit equation for participating in the study. They only distort an assessment [of relevant] trade-offs."

At the hearing, Nancy Evans, a San Francisco-based medical writer, described neurological side effects she suffered while taking tamoxifen last year — problems she says are not well spelled out in the revised model in-

formed-consent statement prepared by NCI.

Evans began taking tamoxifen shortly after recovering from breast-cancer surgery. "Within a month," she recalled, "I experienced a loss of concentration and poor short-term memory. . . . When reading, even for pleasure, my eyes recognized the words, but at the end of the page I had no recollection of what I had read." A friend later described similar problems: "I have lived in the same house for 25 years," the friend told Evans. But after beginning tamoxifen therapy, "I couldn't remember how to get home."

When each woman stopped taking the drug, her symptoms disappeared. "While these side effects were not life-threatening," Evans acknowledges, "they certainly threatened the quality of my life."

Her debilitating disorientation stood out because it was so uncommon in a woman Evans' age, just 53. But in much older women, including many entering the cancer-prevention trial, such confusion might be attributed to aging – allowing treatment to continue indefinitely, Evans says. Moreover, she asserts, older women, particularly those in their 70s, "are much less likely to question what they've been prescribed and [more likely] to just assume that doctor knows best."

Michael W. DeGregorio reviews more insidious side effects in the September JOURNAL OF NIH RESEARCH. A pharmacologist at the University of Texas Health Science Center at San Antonio, he notes that in both human and animal studies – including some of his own – tamoxifen has spontaneously transformed from a helpful Dr. Jekyll into a monstrous Mr. Hyde. While it may initially prevent some budding cancers from growing, such tumors eventually can "become dependent on tamoxifen for growth" – proven by the fact that stopping the drug halts the tumors' growth or even shrinks them.

"This is not new or unique to tamoxifen," notes Susan G. Nayfield, a physician and tamoxifen expert at NCI. "When one treats a breast-cancer patient with tamoxifen or any hormonal agent, we find that the agent works for a while. But eventually the patient's cancer begins to grow again." Regaining control over tumor growth requires switching to another hormonal agent, she says.

DeGregorio interprets these and other data to suggest that long-term tamoxifen therapy may breed a resistance to the drug. If true, he argued at the hearing, and if any study participants ever do develop a tumor, tamoxifen – currently medicine's premier breast-cancer-fighting drug (SN: 2/22/92, p.124) – will provide them little protection. In fact, he noted, several studies with rats have hinted that tamoxifen induces aggressive, hormone-independent breast tumors.

Nayfield is less worried by these data. Pharmacologists suspect that tamoxifen can starve breast tumors of estrogen, a hormone most of these tumors crave for growth. Some data suggest that tamoxifen may not work as effectively at preventing estrogen-independent tumors – cancers inherently more resistant to treatment. "So it's not clear that tamoxifen stimulates [estrogen-independent] tumors," says Nayfield. "It may just not prevent them."

Moreover, she notes, data on Swedish women taking tamoxifen appear to refute animal data on the innate aggressiveness of tumors that develop during tamoxifen therapy. More aggressive tumors should prove more lethal, she says. But in a study reported in the Sept. 18, 1991 JOURNAL OF THE NATIONAL CANCER INSTITUTE, tumors that developed while a woman was taking tamoxifen responded as well to treatment as tumors that developed in women not receiving the drug.

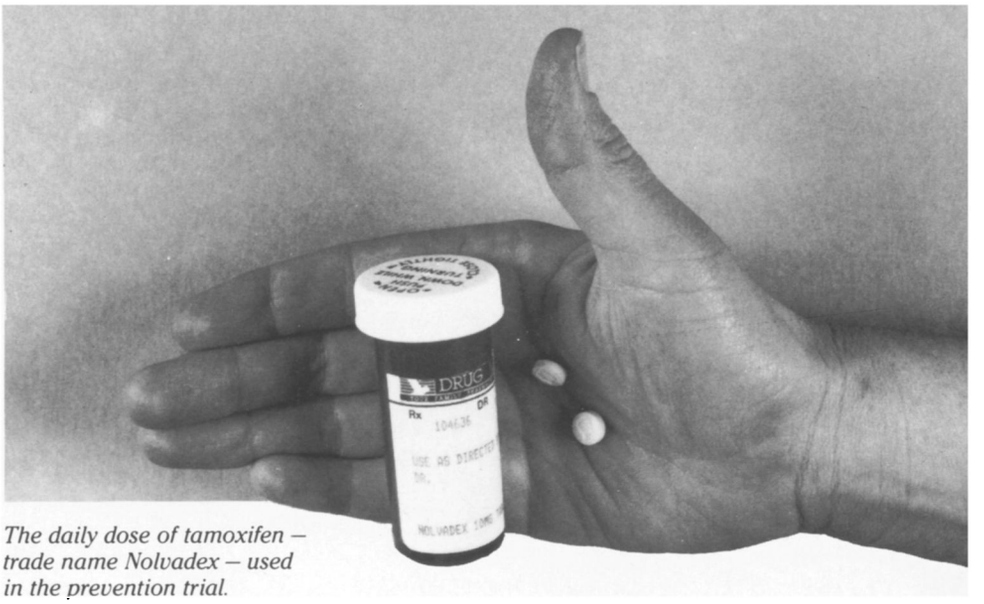
DeGregorio remains skeptical. At a minimum, he would like to see women recruited into the new tamoxifen trial briefed on these data.

Rep. Payne expresses reservations about offering tamoxifen to healthy, premenopausal women. His concern goes beyond the risk that younger women in the new trial might inadvertently become pregnant while taking the drug – exposing their fetuses to a dangerous substance. New data seem to indicate that pre- and postmenopausal women respond differently to the drug, Payne noted, citing a 1992 study in ACTA ONCOLOGICA (vol. 31, p.251) by Michael Baum of the Royal Marsden Hospital in London and his colleagues.

This study, which involves more than 2,000 women who had recovered from breast cancer, focused on their development of new cancers. Overall, Baum's team reported, postmenopausal women who received tamoxifen were less likely to develop a new breast cancer than women who did not. Premenopausal tamoxifen users, however, proved somewhat *more* likely to develop a new cancer.

Payne notes that even NCI's outside advisers, charged with reviewing the proposed design of the tamoxifen study, concluded the new trial should limit participation to postmenopausal women.

"That is correct," acknowledges Leslie G. Ford, the NCI official overseeing the trial. However, she adds, those reviewers had been concerned that such women might not be at high enough risk of developing cancer. The new study's design "is substantially different than the document that the peer reviewers looked at . . . [and the risk required for eligibility has] been substantially increased," she says. "In fact, women 35 years old have to have a lifetime risk of 50 percent –



The daily dose of tamoxifen – trade name Nolvadex – used in the prevention trial.

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minimum — to be eligible."

Payne notes that on July 2, 1991, the U.S. Food and Drug Administration (FDA) oncologic drugs advisory committee recommended that the agency withhold approval for NCI's new tamoxifen study. Most wanted "to restrict [entry] to women at higher risk of breast cancer," explains Steven Piantadosi of Johns Hopkins University in Baltimore, a member of the advisory committee.

But NCI "expressed concern that it would not be possible to accrue enough subjects to achieve the study's objectives if the risk of breast cancer was increased," testified Carl C. Peck, director of FDA's Center for Drug Evaluation and Research.

On Sept. 6, 1991, an FDA official wrote advisory board members telling them that even though NCI had decided not to limit the study to higher-risk women, "we are leaning towards allowing the study to proceed." Most committee members wrote back voicing major reservations.

For instance, I. Craig Henderson of the Harvard Medical School in Boston concluded that "the eligibility criteria are still inappropriate . . . eligibility should be restricted to postmenopausal women."

Kathleen I. Pritchard, head of medical oncology at the Toronto-Bayview Regional Cancer Centre in North York, Ontario, and Waun Ki Hong of the University of Texas' M.D. Anderson Cancer Center in Houston also argued that NCI should restrict entry to higher-risk women. Like oncologist David L. Ahmann of the Mayo Clinic in Rochester, Minn., Hong also voiced concern over problems in the study's design — problems that he charged might "hamper the ability . . . to determine the efficacy of tamoxifen as a chemopreventive agent."

But Ahmann offered the most pointed criticisms: When blood clots "could occur [in] up to 1.5 percent" of the study's participants, and uterine cancer in almost as many, "one really wonders whether or not the therapeutic benefits might be outweighed by therapeutic misadventures."

In the end, FDA did not require NCI to recruit higher-risk women.

One of Payne's primary concerns remains the quality of risk information provided on informed-consent statements. NCI designed a model form on which the participating medical centers were to pattern theirs. Though Payne says the model form "seems overly optimistic about benefits and omits crucial information about risks," his staff found that 182 (68 percent) of the consent forms being used by participating research centers contain even less risk information or less accurate risk data.

For instance, 62 percent (166) provided misleading or no information about blood clots. While NCI's model form says that three deaths from blood clots can be expected among the study's 8,000 participants receiving tamoxifen, 23 forms said only three *cases* of blood clots were predicted. In fact, some 21 cases are expected. Another 52 percent (140 forms), downplayed the risk of liver cancer, Payne says, with 10 failing to mention the risk at all. NCI's model statement notes that two liver cancers have occurred in women taking twice the tamoxifen dose used in this trial.

"We are aware of loopholes," Thomas Puglisi of NIH's Office for Protection from Research Risks (OPRR) acknowledged at the hearing. However, he added, NIH is already at work plugging them.

An outside panel of experts, known as an institutional review board (IRB), approves a medical center's informed-consent statements. For NIH-sponsored human trials involving a single center, NIH reviews the final informed-consent document. "And for a while we did that with these multicenter trials too," explains OPRR's John G. Miller. But "we are just a small office, and it was overwhelming." So NIH abandoned that final oversight, he says.

That wouldn't have posed a problem, he maintains, *if* the IRBs had compared their locally written informed-consent document to the NIH document describing the study and NIH's model consent statement. "It's been our presumption — and a fairly accurate one — that those IRBs see our documents," Miller told SCIENCE NEWS. But an NIH internal review shows that hasn't always happened in the tamoxifen study, he said.

To correct the problem in the future, Puglisi says, locally drafted informed-consent statements for all NIH-funded multicenter studies must contain "all of the information on the model document" — or the center must send NIH the minutes of its institutional review board's deliberations to explain why not. NIH would have to approve such omissions. Miller said letters explaining the policy change should go out soon to investigators of all NIH-sponsored, multicenter clinical trials.

In an initial survey of informed-consent documents used with the tamoxifen trial, NIH found that 6 percent of the centers omitted data serious enough to warrant barring those centers from recruiting more women until the forms are rewritten. Women who signed the old forms must reconsent to participate.

But "NIH has only responded to the most egregious cases," Payne told SCIENCE NEWS. NIH "promised that other centers will be required to review their consent forms again," he says, "but in the meantime, women who are enrolling in the study may be misled about the expected risks and benefits."

That could have costly legal ramifications, some researchers believe. In a Nov. 7 commentary in LANCET, physicians Adriane Fugh-Berman of the Washington, D.C.-based National Women's Health Network and Samuel Epstein of the University of Illinois School of Public Health in Chicago write that "informed consent is protective only when all facts relevant to benefits and risks are affirmatively disclosed." Because all risks are not being routinely disclosed, Epstein says, "any institution and clinician, investigator, or oncologist that participates in this trial is at major risk from future malpractice and punitive-damage claims."

Indeed, argues attorney Schroeter, under these circumstances, "there's not only the potential for litigation, you have the virtual certainty of it."

"We do not conduct trials without believing, based on scientific evidence, that those [involved] will reap more benefits than undergo risk," NIH Director Bernadine P. Healey testified. However, she added, "I strongly endorse some of the comments I heard today [at the hearing], saying that patients must be informed in every way and have every question answered. That is the purpose and that is the spirit of informed consent. And we recognize our obligations."

The subcommittee will continue to investigate changes in the study, as well as research on tamoxifen, and will report its findings sometime next year. □