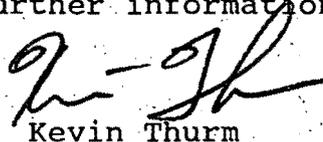


~~SEP 20 1993~~

MEMORANDUM FOR CAROL H. RASCO

Attached is a proposed response to Ms. Hazel Cunningham's letter raising her concerns about the Breast Cancer Prevention Trial, which is sponsored by the National Cancer Institute and is testing the drug tamoxifen in healthy women. Also attached is a fact sheet prepared by NCI providing background information on the trial, and an article from the Journal of the National Cancer Institute published this month. Dr. Broder, the head of the National Cancer Institute, personally supervised the preparation of the draft of this letter and these materials, and I believe that they are responsive to the issues raised by Ms. Cunningham.

I would be happy to provide any further information that you would like.



Kevin Thurm

Enclosures



SEP 16 1993

MEMORANDUM

TO: The Chief of Staff
Through: ES *Crosley 9/16/93*

FROM: Elizabeth Hadley *EHH*
Policy Coordinator

SUBJECT: Response to request from Carol Rasco for draft response to letter discussing Tamoxifen Breast Cancer Prevention Trial in Healthy Women and for briefing memo

Carol Rasco requested a draft response to a letter from Hazel Cunningham raising a number of questions and concerns about the Breast Cancer Prevention Trial sponsored by the National Cancer Institute. Ms. Rasco also requested a briefing memo.

The Cunningham letter raises a number of questions about the rationale for the clinical trial, the assumptions on which it is based, and the data supporting these assumptions. Ms. Cunningham attaches copies of letters that she wrote to the Medical Schools at both Duke and the University of North Carolina at Chapel Hill, which are conducting the trials, as well as a letter addressed to the Clintons when he was Governor of Arkansas. Ms. Cunningham's general concern is that the use of tamoxifen in healthy women may create the risk of damage to their reproductive capacity, similar to the damage caused by DES a generation ago, and that the postulated benefits of the drug are based on questionable data and do not outweigh its risks.

Attached is a draft reply prepared by the National Cancer Institute, as well as an extensive fact sheet and an article from the Journal of the National Cancer Institute published this month. Dr. Broder personally supervised the preparation of the draft letter and these materials, and they appear responsive to the concerns raised by Ms. Cunningham.

Please let me know if you would like further information.

The Breast Cancer Prevention Trial (BCPT) is an especially important investigation in that it may identify a practical method of preventing the development of breast cancer in a large number of women at increased risk of developing the disease. It will measure the preventive effects of tamoxifen on three major diseases in women—breast cancer, heart disease, and osteoporosis—and the potential risks for the development of side effects and other types of cancer. It is hoped that the BCPT will provide essential information for women and their physicians so they can make informed health care choices. The purpose of the BCPT is to increase the number of options available to women at high risk of developing breast cancer, so that they are not limited to the current options of intensive screening or prophylactic mastectomy.

The concept and program-planning activities for the BCPT were initiated and conducted in a deliberate and systematic fashion between 1984 and 1989. During the development process, the BCPT concept was carefully reviewed by and received unanimous endorsement from outside experts on three National Cancer Institute (NCI) scientific advisory bodies. The detailed protocol for this study was developed with input from medical experts and the public. Also, the U.S. Food and Drug Administration (FDA) conducted extensive reviews of the protocol and consent form, including a public hearing, before approving the use of tamoxifen in this research. Just as with estrogen replacement therapy, there is reason to expect that tamoxifen for breast cancer prevention has been introduced into clinical practice without results from a controlled randomized

clinical trial. The BCPT allows the evaluation of tamoxifen for breast cancer prevention before there is a more general adoption of this practice.

Information from the trial is constantly reviewed to ensure that no participant is exposed to unnecessary health risks. When new data become available, action is taken to plan further studies, update the BCPT consent form (all revisions are sent to every enrolled participant so that she may reconsider her continued participation), and/or modify the protocol, as indicated by the results of the review. Scrutiny of new information by the BCPT Steering Committee and independently by the End Results/Safety Monitoring and Advisory Committee (ERSMAC) is also an ongoing process. ERSMAC members review all new information about tamoxifen as well as unblinded data from the trial. Based on this continuous monitoring, recommendations are made regarding protocol and consent form actions and study participation.

You question whether the trial would ever have received approval from FDA without strong data to suggest that postmenopausal women would receive protection from heart attacks as well as breast cancer. You also raise the question that a study by Drs. Trudy Bush and Kathy Helzlsouer of Johns Hopkins University has shown that the number of heart attacks that would be prevented has been inflated.

In this context, encouraging information has recently been provided by the Stockholm Breast Cancer Study Group based on a trial of adjuvant tamoxifen therapy in early stage breast cancer patients. A copy of this report,

published in the September 1, 1993, Journal of the National Cancer Institute, is enclosed.¹ The Swedish investigators observed a statistically significant 32-percent overall reduction in the risk of cardiovascular disease incidence. This benefit was observed after a 2-year period of tamoxifen therapy and was even greater when the tamoxifen treatment period lasted 5 years. The Stockholm results suggest that the observed reduction in incidence of cardiovascular events may eventually lead to a 20-percent reduction in cardiac mortality. The expectation of cardiovascular benefit is likely to be limited to women who are 60 years of age or older and consequently at high risk of cardiovascular disease. Other studies and analyses have previously suggested a decrease in cardiovascular morbidity or mortality associated with the use of adjuvant tamoxifen.^{2,3} With the availability of the newly published results from Stockholm, the evidence in favor of benefit from tamoxifen has been further strengthened.

The North American Breast Cancer Prevention Trial with tamoxifen, which is being conducted by the National Surgical Adjuvant Breast and Bowel Project, is only one of several large trials testing the worth of tamoxifen for preventing

¹Rutqvist, L.E, Mattsson, A. for the Stockholm Breast Cancer Study Group. "Cardiac and Thromboembolic Morbidity Among Postmenopausal Women With Early-Stage Breast Cancer in a Randomized Trial of Adjuvant Tamoxifen," Journal of the National Cancer Institute, 85:1398-1406, 1993.

²McDonald, C.C., and Stewart, H.J. "Fatal Myocardial Infarction in the Scottish Adjuvant Tamoxifen Trial," The Scottish Breast Cancer Committee. British Medical Journal 303:435-437, 1991.

³Early Breast Cancer Trialists' Collaborative Group. "Systemic Treatment of Early Breast Cancer by Hormonal, Cytotoxic, or Immune Therapy, 133 Randomized Trials Involving 31,000 Recurrences and 24,000 Deaths Among 75,000 Women," Lancet, 339:1-15, 71-85, 1992.

breast cancer. In the BCPT, approximately 30 percent of registrants fall into the age category associated with a reduction in cardiovascular morbidity. In the 60 and older age group, the cardiovascular benefit from tamoxifen may be as important as the breast cancer prevention potential of the medication.

The results from the Stockholm Breast Cancer Study Group support the continuing effort to develop tamoxifen therapy for disease prevention.

Tamoxifen prevention trials were first organized to test the main idea that tamoxifen prevents the development of breast cancer. This idea was strongly supported by the combined results from eight randomized, controlled clinical trials of adjuvant tamoxifen therapy, which showed a highly significant 35 percent reduction in new primary breast cancer in the contralateral breast. This is the only pro-active intervention known to prevent the development of new primary cancers in humans. The primary endpoint for the BCPT, and the one used for trial planning and size calculations, has always been decreased incidence of breast cancer. However, with the early evidence of cardiovascular benefits and the accumulating support from newly reported studies, it is as important as ever to follow study subjects carefully for cardiac endpoints as well.

You also express concern that postmenopausal women who are randomized to the placebo group are denied the protection from heart attacks and osteoporosis that hormone replacement therapy with estrogen would provide. Although replacement estrogen has been shown to be effective in reducing the risk of osteoporosis and possibly of cardiovascular disease, like tamoxifen, it also

has been linked to an increase in endometrial cancer. There is some suggestion that it is linked to breast cancer as well. Unfortunately, estrogen replacement therapy (ERT), despite its widespread use, has never been fully evaluated in a clinical study of risks versus benefits. Scientists at the National Institutes of Health (NIH) have long recognized the importance of clarifying the risks and benefits of replacement hormones, and are supporting research to help answer questions about this issue. To that end, NIH has launched the Women's Health Initiative. One of the components of the Initiative is a randomized, placebo-controlled study of the utility of ERT to protect women against cardiovascular and skeletal morbidity.

~~Thank you for your interest in our women's health studies.~~

~~Contact Person: NIH/NCI/OD/SBroder~~

P6(b)(6)

Background Information on the Breast Cancer Prevention Trial

The following is important information about the Breast Cancer Prevention Trial (BCPT) that addresses concerns about the administration of the drug tamoxifen to healthy women.

- The Breast Cancer Prevention Trial is designed to differentiate between the real benefits and side effects of tamoxifen and those occurring by chance. It will provide information to estimate more reliably the true magnitude of benefit and risk in the general population—which includes premenopausal women. It will also provide data useful for identifying those groups of women that would have the greatest net benefit from tamoxifen use.
- The response from women concerned about breast cancer has been overwhelming. As of July 1, 1993 more than 45,000 risk assessments had been performed, identifying approximately 31,000 women eligible to participate in the BCPT based on their risk of developing breast cancer. At this time, over 8,000 women have been entered in the trial and are taking either tamoxifen or placebo. Many of the remaining eligible women are awaiting the additional screening exams and formal randomization to enter the trial. Early participation indicates that this is one of the most active research clinical trials that has ever been launched.
- Women interested in participating in the BCPT receive a full discussion of the protocol as they are evaluated for eligibility and consider whether they want to participate. In general, this multistep process starts with an orientation session that provides introductory information and a brochure describing the BCPT. If interest in participation is sustained, the woman must sign up to receive a risk assessment and then participate in an assessment interview. A followup appointment is used to discuss the risk assessment and to review the protocol in detail. If the woman chooses to continue, informed consent is obtained and medical examinations are completed to confirm eligibility.
- The expectation that tamoxifen therapy is a reasonable intervention for breast cancer prevention is based on years of experience with this drug in controlled clinical trials. Clinical trial experience with tamoxifen in adjuvant therapy for breast cancer was summarized in the January 4, 1992, issue of Lancet. For 30,000 women in 40 trials, a 25-percent reduction in recurrence and a 17-percent reduction in mortality on average were observed. In addition, a 40-percent reduction in new breast cancers in the opposite breast (contralateral breast cancer) was reported. This benefit accrued to premenopausal as well as to postmenopausal patients. In the NSABP B-14 trial, there was an overall 50-percent reduction in new contralateral breast cancers. The data from this trial suggest an even greater benefit in reduction of contralateral breast cancers for premenopausal women than for postmenopausal women. In premenopausal women participating in NSABP B-14, there were no cases of endometrial cancer, and the rare case of thromboembolism responded to therapy. (A recently reported study from Sweden in the September 1, 1993 issue of the Journal of the

National Cancer Institute showed no increase in thromboembolism associated with adjuvant therapy.) Other side effects were comparable in the pre- and postmenopausal groups. Consequently, it is projected that the potential risks of tamoxifen therapy in premenopausal women are fewer than those for postmenopausal women.

Another justification for including premenopausal women in the BCPT is that some are at an unusually high level of risk based on such factors as an extensive family history of breast cancer. Because many years elapse between a breast tumor's inception and its detection, a preventive intervention may be more effective if used earlier in life, especially before a tissue abnormality develops. In cases where risk is unusually high, it is unfair to deny younger women the opportunity to participate in reasonable preventive research, especially when many are at risk of undergoing such extreme procedures as bilateral prophylactic mastectomy.

- Endometrial cancer. Data pertinent to the development of endometrial cancer occurring in the setting of long-term tamoxifen therapy have been provided by numerous studies, including NSABP B-14, using the same dose of tamoxifen as in the BCPT (20 mg per day). As stated in the consent form:

An increased risk of uterine cancer has been reported with the use of tamoxifen. Existing data from several large controlled clinical trials using 20 mg of tamoxifen show that 9 out of 3,097 women on tamoxifen developed uterine cancer (0.3 percent) versus 4 out of 3,091 women not treated with tamoxifen (0.1 percent). No deaths from uterine cancer were reported. The uterine cancers that have occurred have been at an early stage and are thought to be curable. The treatment for early stage uterine cancer usually involves a hysterectomy (surgical removal of the uterus) and may include radiation therapy.

It is important to note that this increased risk is similar to that recently reported in women on conventional hormone replacement therapy. Also noteworthy is the fact that none of the 437 premenopausal women on tamoxifen in NSABP's B-14 trial developed endometrial cancer.

Women in the trial will be required to have an annual pelvic examination. In addition, any reports of abnormal bleeding will be investigated immediately.

- Thrombosis/embolism. Women on tamoxifen have an increased risk for developing phlebitis and blood clots. In the NSABP B-14 study, 3 of 1,414 women receiving placebo (0.2 percent) versus 18 of 1,403 women receiving tamoxifen (1.3 percent) developed deep-vein thrombosis or embolism. Two deaths occurred from complications of deep-vein thrombosis. Because of the information gained in NSABP B-14, women with a history of deep-vein thrombosis or embolism will be excluded from the BCPT.

- Liver (hepatic) cancer. The followup of 4,028 women who received tamoxifen for at least 2 years as participants in seven large randomized trials of adjuvant therapy for early stage breast cancer has been reported. Two patients developed liver cancers; both were participants in the Stockholm trial, which prescribed high doses of tamoxifen (40 mg a day). (These cases were reported by Fornander et al. in Lancet in 1989.) Both cases appear to have occurred early in the course of treatment (within the first 2 years the women were in the study). To date, no liver cancers have been reported in women receiving 20 mg a day.

In the United States, clinical trials of tamoxifen in an adjuvant setting have required evaluation of liver lesions occurring during therapy (for purposes of determining whether they are a new primary liver cancer or a breast cancer that has metastasized to the liver). Liver biopsy for suspected first recurrence has been mandatory. When liver lesions have necessitated evaluation for recurrence, no primary hepatocellular cancer has been found.

- Ocular Toxicity. Pavlidis et al., writing in Cancer, June 15, 1992, reported four cases of ocular toxicity in 63 patients receiving tamoxifen at a dose of 20 mg a day for varying durations. The four patients, who had taken tamoxifen for periods ranging between 10 and 85 months, had complaints of decreased visual acuity and findings of macular edema and dotlike paramacular deposits; in addition, one patient had subepithelial corneal opacities. These changes were reversible with discontinuation of medication, and acuity returned to previous levels, with slight residual visual impairment in one eye in one patient. The findings of Pavlidis et al. were inconsistent with previous reports of ocular toxicity that implied a much lower rate of occurrence. A study is being conducted to evaluate the true ocular effects of tamoxifen.

THE WHITE HOUSE

WASHINGTON

August 24, 1993

Secretary Shalala

I need a draft response
and briefing memo please.

Thanks!

Carol J. Rasco

P6/(b)(6)

AUG 23 REC'D

18 August 1993

Ms. Carol H. Rasco
Assistant to the President
for Domestic Policy
The White House
Washington, D. C.

Re: Tamoxifen Breast Cancer Prevention Trial in Healthy Women

Dear Ms. Rasco:

As you no doubt are aware, the previous administration committed some \$69 million dollars to a controversial five year study of tamoxifen, a powerful hormone modulating agent which is carcinogenic to both animals and, ironically, women.

This experiment on 8,000 healthy women, ages 35-75, hopes to demonstrate the drug will prevent 62 cases of breast cancer and 52 fatal heart attacks over the next five years. The trialists, sponsoring National Cancer Institute, and the FDA, citing these numbers, believe the benefits greatly outweigh the known and potential risk of tamoxifen-caused disease.

A careful review of the rationale for the trial, the assumptions upon which it is based, and the current protocol indicates it is very unlikely the trial in its current form would have received FDA approval without strong data to suggest postmenopausal women in the experiment would receive substantive protection from fatal and nonfatal heart attacks as well as breast cancer.

This is because previous experience with the drug indicates it significantly elevates the risk of both uterine cancer and fatal blood clots. Also, there is a literature suggesting the risk of eye damage also may be elevated. The literature further suggests chronic administration of the drug may increase the long term risk of ovarian cancer, liver cancer and even potentially untreatable breast cancer itself.

Accordingly, it is very alarming to learn, via a study by Drs. Trudy L Bush and Kathy J. Helzlsouer of Johns Hopkins University, that the heart attack benefit numbers are inflated. (In press. Tamoxifen for the Primary Prevention of Breast Cancer: A Review and Critique of the Concept and Trial)

The authors found that 13 rather than 52 heart attacks theoretically may be prevented in the 8000 treated women; that this substantive decrease in heart attack prevention as well as another reasonable set of assumptions indicate more harm than good, in terms of actual adverse 'events,' may occur.

They concluded:

In the face of the uncertainty of the net benefit of the trial, ranges of these risks and benefits should be provided to potential and enrolled participants. The lack of significant benefit to participants seen with the recalculations may raise the question of whether the trial should continue as designed. One option would be to limit trial participation to postmenopausal women only, since in postmenopausal women 1) breast cancer is more common; 2) tamoxifen is more effective; 3) cardiovascular disease is more common; and 4) reductions in cholesterol levels and preservation of bone mass have only been documented in postmenopausal women. Even in this case, however, the fundamental philosophical question of whether large numbers of healthy women should be "treated" with a toxic drug for the primary prevention of a rare event remains.

I ask your independent review of this situation before any additional women are randomized to receive tamoxifen. It is my understanding trial recruitment is about 50% complete with about 4,000 women currently taking the drug on a daily basis and another 4,000 receiving a placebo.

It seems fair to ask if an error of this magnitude were simply the result of sloppy work or something less benign.

I enclose copies of earlier correspondence as well as correspondence with both the committees charged with protecting the rights of human subjects at both the University of North Carolina and Duke, two test sites in this state. These committees constitute the Institutional Review Boards or IRBs for their institutions.

The UNC committee at least has agreed to consider reviewing whether UNC's test subjects should receive periodic endometrial biopsy exams, as is strongly recommended BUT NOT MANDATED by the protocol.

Duke policy apparently precludes discussion of the protocol so my request for a meeting with the chairman of the human subjects protection committee was denied.

It is ironic indeed that NCI-HHS consistently claims that the risk:benefit of the trial was thoroughly reviewed by not only peer reviewers but the FDA's own Oncologic Drugs Advisory Committee, as well as the Institutional Review Boards (IRBs) of the participating institutions, implying my concerns and the concerns of others have been adequately addressed.

In fact, a review of the transcript of the FDA Oncologic Drugs Advisory Committee meeting in July 1991 disclosed this committee of experts voted 5-2 the risks outweighed the benefits. The concept of a trial of this drug was approved, 6-1, by this group if the entry criteria were radically altered to limit the trial to truly high risk women.

A Congressional hearing last October disclosed NCI peer reviewers recommended the trial exclude premenopausal women.

The entry criteria was not changed.

Any healthy woman age 60, with no known risk factor except age, may join the trial, providing she forgo using estrogen replacement therapy (ERT) for the duration of the trial. Older women in the tamoxifen-treated group theoretically will receive some ERT-like benefit as the drug

apparently has both estrogen-like effects as well as anti-estrogen properties.

The trialists and their consent forms are silent on the potential risk to older women in the placebo group: for five years they must forgo alleged the heart attack and osteoporosis protection offered by ERT.

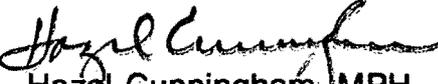
It is, of course, necessary for women in the placebo group to die of heart attacks over the next five years (as well as be diagnosed with breast cancer) in order to show a substantial "prevention" in the tamoxifen-treated group.

Women 35-59 are eligible if their theoretical risk, as computed by an adjusted NCI model based on a national breast cancer monitoring study, is equal to or exceeds the risk of the aforementioned 60 year old.

In sum, the risk:benefit rationale for this trial, shaky at best, is seriously challenged by the reanalysis by the Johns Hopkins' researchers.

I look forward to hearing from you at your earliest convenience.

Sincerely,


Hazel Cunningham, MPH

11 August 1993

To: Drs. Kraybill and Herion, UNC
From: Hazel Cunningham, MPH

Re: Tamoxifen breast cancer trial in healthy women

Thank you for providing copies of the updated tamoxifen trial protocol, Committee minutes, and letters from your outside reviewers.

Frankly, it is disturbing that neither the Committee nor its external consultants, neither of whom apparently is a toxicologist, consulted the current literature relating to the toxicity of tamoxifen.

Please consider the following:

Your consultants gave their unqualified endorsement to a protocol which did not adequately protect against the possibility of a woman beginning therapy while pregnant. In the recently revised protocol, an FDA-mandated change attempts to guard against that possibility.

Your consultants did not ask whether your UNC subjects would receive routine endometrial sampling, as is recommended but not required by the protocol.

Your consultants made no comment regarding the potential risk of ocular toxicity and the need for periodic monitoring by specialists.

I would appreciate receiving copies of the letters sent by the Committee to your consultants to put their responses in context.

Whatever the Committee's request or questions to these epidemiology experts may have been, it is surprising neither apparently studied the protocol closely enough to notice the overall risk:benefit is seriously skewed due to an error related to the incidence of myocardial infarction. This error was noticed by Johns Hopkins researchers whose overview is scheduled for publication next month.

In reviewing the revised protocol, I call your attention to the trialists' disclosure other potential revisions are the subject of discussion with the FDA at present.

Does your Committee have the right to know--and independently evaluate--any changes proposed by the FDA or NCI which may relate to the safety/protection of the health of human subjects in your trial?

For example, would it have made a difference in your initial review and approval of the original protocol if you were aware that at least two expert government advisory and peer review committees had serious reservations about including premenopausal women in the study?

I am attaching notes made this afternoon after reviewing the revised protocol and the Johns Hopkins study.

Additional points for consideration by the UNC IRB re tamoxifen:

The protocol calls for recalculation of the risk:benefit to participants after 25% accrual, e. g. 4,000 participants. As of December 1992, NSABP had randomized more than 5,200 women. It seems likely that by the end of last month perhaps 8,000, or 50% of the target 16,000, may be entered in the trial.

Has the UNC-IRB been informed of the new risk:benefit calculations? If so, can a risk:benefit table now be calculated for UNC participants?

The protocol you approved makes it clear the risk:benefit equation is skewed if prevention of breast cancer is the major outcome, assuming the enrollment generally follows the assumption by the investigators that 2% of the women enrolled will be 35-39 years old, 71 % of participants will be between 40-59 years of age, and 27% will be aged 60 years or older (a 'middle-aged distribution'.)

A recent calculation of the trial's risk:benefit using another set of reasonable assumptions shows a negative to a small positive effect overall. Johns Hopkins researchers found the trialists had erred in their calculations regarding heart attack risk, which had the effect of considerably inflating the potential overall study benefits. If the probability of adverse ocular events were included in the net-benefit equation, they found "more harm than good will result." (Bush & Helzlsouer, "Tamoxifen for the Primary Prevention of Breast Cancer: A Review and Critique of the Concept and Trial," Epi Reviews, in press)

Assuming a 'middle-aged' population distribution and a two-fold increase in a participant's risk of endometrial cancer, the protocol anticipates treating 8,000 women may prevent 62 breast cancers but may result in 32 excess cases of endometrial cancer. Assuming a three-fold increase in the risk of endometrial cancer, to prevent 62 breast cancers tamoxifen may result in 57 cases of uterine cancer, a net total cancer 'benefit' of 5.

(However, the risk of endometrial cancer may be greater than twofold. The B-14 Trial experience regarding uterine cancer, frequently cited as gospel for projected side effect rates when these rates are LOWER than those found in other tamoxifen studies, e. g. liver toxicity and liver cancer, is NOT mentioned in the consent form. If it were, it would show

there were zero endometrial cancers in the placebo vs 6 in the tamoxifen treated group AS OF MAY 1991. Assuming the development of at least one case in the placebo group, this means there could be a fivefold, rather than twofold increase in risk in the treated prevention group.)

A fivefold increase in endometrial cancer means the trial may create more cancer than it will prevent. Assuming all participants have the breast cancer risk of women 70-74 years, as predicted by SEER Breast Cancer Incidence Rates, treating 8,000 women may prevent only 52 cases of breast cancer but subjects the group to 30-100 cases of uterine cancer.

The protocol, as of July 1993, still maintains endometrial cancers detected following the use of either ERT or tamoxifen "can be identified in an early stage and should be readily curable."

The protocol, as of July 1993, fails to update the B-14 data regarding endometrial cancer risk.

Of greater concern, however, is the revised protocol's silence regarding the Yale tumor registry study, cited in my letter to the Committee earlier this month, which found endometrial tumors which did develop in tamoxifen-treated patients were high grade with poor prognosis. (Margriples et al. High-grade endometrial carcinoma in tamoxifen-treated breast cancer patients. J Clin Oncol 1993; 11; 485-90

The protocol recommends but does not require participating centers to perform endometrial sampling at the onset of treatment and at intervals during therapy. It nominates in particular participants with risk factors of "obesity, hypertension, diabetes, nulliparity, and previous or current adenomatous hyperplasia." (BCPT-PI, 2.8)

Does the UNC protocol require endometrial sampling as recommended? If not, is this ethical and/or best medical practice in light of the mounting literature recommending same?

As noted by Bush:

There is an assumption made by the investigators and stated in the informed consent document that tamoxifen-induced endometrial cancers behave

like estrogen-induced cancers, i. e., they are relatively benign and associated with a good prognosis.

However, a recent report of women with breast cancer who had a secondary primary endometrial cancer diagnosed suggests that women receiving tamoxifen are at risk for high-grade endometrial cancers that have a poor prognosis.

Given this situation, the lack of routine endometrial monitoring by the trial personnel, who are administering a drug known to cause this particular tumor, is very troubling. If the first principle of clinical studies is that the safety of those who volunteer is preeminent, then it could be argued that regular endometrial monitoring is mandated in this trial.

For these reasons, the overall risk:benefit of the protocol rests heavily on prevention of heart attacks or strokes. Yet the total number of myocardial infarctions projected to be prevented in the tamoxifen-treated group is considerably lower than the prediction stated in the protocol, according to Bush ' reanalysis and recalculation of the tamoxifen risk:benefit equation, based on the early enrollment of over 2000 participants.

Using protocol assumptions, she calculated tamoxifen treatment may prevent 13 myocardial infarctions; "this number is in marked contrast to the 52 expected to be prevented by the trial investigators.

Assuming tamoxifen may confer a heart attack protection 'benefit' on 13 members of this 'middle-aged' population distribution and prevent 52 breast cancers there would be a total benefit of 65 prevented adverse events. However, the predicted 57 endometrial cancers (at only a twofold increase) knock the net benefit to only 8.

This assumes tamoxifen poses no excess serious pulmonary embolic risks to participants. Assuming only a twofold increase in this risk, the total net benefit is reduced to 5.

However, the NSABP's own trial found a 4.7 % increase in serious embolic events (deep vein thromboxix requiring hospitalization, life-threatening pulmonary emboli, and death) in the tamoxifen group compared with placebo. The Eastern Cooperative Oncology Group has found similar elevations in risk. The protocol, however, only includes death from pulmonary embolism as a detrimental outcome.

As discussed in my recent letter, the model protocol does not call for systematic monitoring of participants for ocular toxicity, despite an account published in July 1992 which, on a prospective basis, found six percent (4/63) of patients treated with 20 mg tamoxifen/day for 25 months developed such toxicity. (decreasedvisual acuity, macular edema, retinal opacities.)

Dr. Bush concludes:

If the association between tamoxifen and retinopathy is real, then it could be argued that this detrimental effect should be included in any net-benefit equation. Given that the reported incidence...is probably an overestimation, we assumed that ocular events would occur in 0.5 percent of patients treated, and recalculated the net-benefit table. When this is done, the net-benefit of the trial is now entirely negative, with estimates ranging from -31 to -57 (adverse events caused). Currently in the trial, monitoring for ocular toxicity is only being done by self-report (via questionnaires). Similar to the situation for endometrial cancer monitoring, regular systematic eye examinations should be mandated for all trial participants.

P6/(b)(6)

July 1, 1992

Dr. John Herion, Chairperson
Committee on Human Rights
Office of Human Research
CB 7000 MacNider Bldg
School of Medicine
University of North Carolina
Chapel Hill, N. C., 27599-7000

Re: Tamoxifen Breast Cancer Prevention Trial in Healthy Women

Dear Dr. Herion:

This to request the Committee on Human Rights reconsider its approval of the NSABP P-I Clinical Trial to Determine the Worth of Tamoxifen for Preventing Breast Cancer.

I further ask the Committee suspend recruitment and implementation of the trial while it takes a second look at the protocol's efficacy, feasibility, including compliance, lack of a prior pilot study, definition of women at high risk of breast cancer, and potential risk of tamoxifen to study participants.

A number of these issues were raised at the Food and Drug Administration hearings prior to federal approval of this NCI-sponsored initiative. I am enclosing a consensus letter submitted to the FDA last November by the National Women's Health Network, joined by two dozen epidemiologists and health scientists across the nation, most of whom are affiliated with leading medical and research institutions, including UNC Chapel Hill.

The scientists concluded the trial was "premature and unethical."

In the intervening months, additional deleterious information has surfaced, including reports suggesting participants, in addition to the

well known risks of a thromboembolism event and endometrial hyperplasia and cancer, may run the risk of liver failure and liver cancer with chronic exposure, a substantive risk of eye damage, and the possible induction or promotion of aggressive, exclusively hormone independent mammary tumors.

I am enclosing copies of letters to Dr. Louis Sullivan, Secretary of the U.S. Department of Health and Human Services, detailing these concerns.

Please note that European tamoxifen trialists have reported but not yet published an indication that long-term treatment elevates the risk of gastrointestinal cancer.

I can't emphasize strongly enough my concerns regarding the potential for unintended pregnancies in treated, premenopausal women, the subject of my letter of May 18, 1992 to FDA Commissioner Kessler., also enclosed for review.

Surely your Committee would not sanction an experiment with the potential of contributing to another DES national tragedy !

In this regard, please note that the NSAP P-I Model Consent Form , approved 1/13/92, specifies the experimental subjects are prohibited from using a hormonal contraception method, e. g. 'the pill.' However, the UNC consent form, revised 2/25/92, reads: "The importance of barrier or hormonal contraceptive methods has been discussed with me."

Is this a typographical error?

I note your approved consent form on the face sheet specifies the prevention of approximately 62 breast cancers and 52 heart attacks over the next five years and the causation of 38 uterine cancers and 3 deaths due to blood clots in the lungs is predicated on the assumption most of the women in the national study will be 40-60 years of age.

I ask that your second look include a risk-benefit study and analysis by the University of North Carolina's well respected epidemiologists, toxicologists, and health scientists from appropriate disciplines, detailing risk/benefit to your North Carolina subjects, whose ages, as a group, may differ.

Your study might also look at the risk to a postmenopausal North Carolina woman, previously taking estrogen to prevent heart attacks and bone thinning, whose fear of breast cancer prompts her to join the trial. In this case she must forgo ERT. If she were previously protected from heart attacks and osteoporosis by ERT, will she lose this protection if assigned to the placebo group? Can or should this eventuality figure in any risk-benefit assumptions? Is she entitled to know the extent to which she may run the risk of losing her ERT protection?

I assume your second look would include an extensive review of the CURRENT literature. I note with some alarm that the operating protocol, dated Jan. 24, 1992, which was the basis for IRB approval for at least one Western cooperating institution and possibly yours as well, has virtually no tamoxifen adverse effects literature cites later than 1989 !

In your initial approval did you exclusively rely on the out of date protocol references?

If you did an independent adverse literature review the first time around, did you consider the 1991 Lancet report signed by Spicer, Pike, and Henderson, raising alarm that including premenopausal women runs the risk of ovarian stimulation that could lead to ovarian cancer?

I would like clarification of your consent form statement regarding the payment for pre-entry workup and monitoring. Is your institution providing these services free of charge or are they to be billed to insurance carriers, as is the plan in the two California institutions with which I am most familiar?

At U.C .Davis, for example, prospective participants were counseled by the the principal investigator to have their physicians bill their insurance carriers. When one participant pointed out her policy would not cover any costs incurred as an experimental subject, she was advised: "Your insurance company doesn't need to know why these tests are being done."

I assume insurance fraud is not counseled at your institution.

I further ask your review of the ethics of the whole process of the 'selling of the tamoxifen trial.' It seems to me NCI and the media, relying on NCI,

are stampeding women frightened of contracting breast cancer to sign up. This puts pressure on personal physicians to cooperate, many of whom are unfamiliar with the tamoxifen literature.

One woman who was considering joining the UNC trial told me last week that in her counseling session with a physician trial risks were trivialized.

In the informational sessions I attended at U.C. Davis and at Sutter Hospital, the second institution participating in Sacramento, potential risks indeed were glossed over. Breast cancer risks, however, were stressed.

There was no attempt to inform potential participants that a sixty year old woman with no other known risk factors had less than a 1.7% chance of being diagnosed with breast cancer in the next five years. That the 'one in nine lifetime chance of being diagnosed with breast cancer' did not mean that she carried ALL of this statistical risk at age 60.

I do not know what kind of publicity your trial has had in your communities. I do know that Channel 11, the ABC TV station serving the Chapel Hill area, on June 29, 1992, carried a health feature promoting the trial and urging viewers to call an 800 number to learn how to join the trial. This program, I was later told by the station, originated out of state and was in fact 'canned,' with a script provided the health reporter. The script said the only side effects expected were minor GYN symptoms -- hot flashes, etc. The physician interviews were not locally generated but were provided by the feature service.

"Are there other side effects?," the station representative asked me.

Finally, I challenge the ethics of approving a study recruiting healthy women in which neither the sponsoring institution receiving the grant nor the federal government makes any provision to cover the medical treatment or other costs if a subject develops a medical complication from such participation.

Is your Committee clear that the women being recruited into this trial are healthy....they are not patients.

Is it ethical to require healthy women to sign a form which states, as yours does:

I understand that in the event of physical injury directly resulting from the research procedures, financial compensation cannot be provided. All forms of medical diagnosis and treatment, whether routine or experimental, involve some risk of injury. In spite of all precautions, I might develop medical complications from participating in this study. If such complications arise, the researchers will assist me in obtaining appropriate medical treatment but the University of North Carolina at Chapel Hill does not provide financial assistance for medical or other costs....

Your form does NOT state that one retrospective study of 70 women on tamoxifen for five months to two years, asymptomatic on regular GYN examination, when checked by biopsy had a high rate of hyperplasia. Does your institution's protocol require an endometrial biopsy prior to entry and periodically during the course of the 'at least' five years of treatment? If not, why not?

In light of case reports and a recent prospective study of patients dosed with tamoxifen (20 mg/day) which found four of 63 (6.3 %) with ocular toxicity, will the women in your institution's study receive free ophthalmological exams prior to entry and at appropriately scheduled intervals throughout their treatment? If not, why not?

If you or any member of your committee would be interested in further information regarding any of these issues, please let me know.

I look forward to hearing from you at your earliest convenience.

Sincerely,

Hazel Cunningham, MPH

encs.

28 August 1992

John C. Herion, M.D., Former Chair
The Committee on the Protection of
the Rights of Human Subjects
The School of Medicine
The University of North Carolina at Chapel Hill
CB #7000 MacNider Building
Chapel Hill, N. C. 27599-7000

Re: Tamoxifen Breast Cancer Trial in Healthy Women

Dear Dr. Herion:

I am enclosing copies of recent correspondence and other materials for review by the Committee on the Protection of the Rights of Human Subjects relating to the Tamoxifen Breast Cancer Trial, including two members of the FDA Oncologic Drugs Committee which in July 1991 reviewed the protocol.

It was very disconcerting to learn that this committee of experts had voted 5-2 that the trial's entry criteria likely meant the known health risks of the trial could well exceed the potential benefits and by a 6-1 vote recommended approval if recruitment were limited to high risk women.

The FDA did not insist the entry criteria be tightened, however, disregarding the advice of its own experts.

It is my understanding that the risk-benefit equation apparently may be further eroded by the fact that younger women nationally are disproportionately volunteering for the trial. (Younger women presumably would receive relatively less benefit in five years from a drug under examination for its potential to protect subjects from heart attacks and bone fractures. Younger, premenopausal subjects, however, would be subject to risks of hyperplasia, cancer of the endometrium and uterus.)

Further, I urge your reconsideration include an analysis of the current tamoxifen side effects literature. In checking Med-Line entries last week I found that 127 articles had been published and entered into the system since the first of the year. These entries do not include publications which appeared in late July and August, including the enclosed Lancet article.

Sincerely,

Hazel Cunningham, MPH

P6/(b)(6)

2 July 1993

John C. Herion, M.D., former chair
The Committee on the Protection of
the Rights of Human Subjects
The School of Medicine
The University of North Carolina at Chapel Hill
CB #7000 MacNider Building
Chapel Hill, N. C. 27599-7000

Re: Tamoxifen Breast Cancer Trial in Healthy Women

Dear Dr. Herion:

You may recall I wrote to you from Sacramento, Calif., last summer regarding my concern that the tamoxifen drug trial protocol approved by the Committee on the Protection of the Rights of Human Subjects may have presented a skewed risk-benefit picture, necessitating a second look at the protocol's efficacy, feasibility, including compliance, lack of a prior pilot study, definition of women at high risk of breast cancer, and potential risk of tamoxifen to study participants.

I am now residing in Chapel Hill and I would appreciate an appointment at your earliest convenience to discuss this matter.

I enclose for your convenience my letters of 1 July and 28 August 1992 as well as recent correspondence with U.S. Rep. Patsy Mink.

Sincerely,

Hazel Cunningham, MPH

P6(b)(6)

28 July 1993

Ernest N. Kraybill, M.D., chair
John C. Herion, M.D., former chair
The Committee on the Protection of
the Rights of Human Subjects
The School of Medicine
The University of North Carolina at Chapel Hill
CB #7000 MacNider Building
Chapel Hill, N. C. 27599-7000

Re: Tamoxifen Breast Cancer Trial in Healthy Women

Dear Sirs:

On 3 July 1993 I wrote to Dr. Herion, requesting an appointment to discuss concerns that the tamoxifen drug trial protocol approved by the Committee on the Protection of the Rights of Human Subjects may have presented a skewed risk-benefit picture.

The concerns included the protocol's efficacy, feasibility, including compliance, lack of a prior pilot study, definition of women at high risk of breast cancer, and potential risk of tamoxifen to study participants. I included my letters of 1 July and 28 August 1992 to you as well as recent correspondence with U.S. Representative Patsy Mink. This correspondence summarized my concerns and was included to facilitate your response.

Dr. Kraybill's response of 16 July 1993, in effect dismissing both my concerns and my request for an appointment to discuss these concerns, was extremely disappointing. Efforts to reach Dr. Herion by telephone were also unsuccessful although he did have someone in the School of Medicine return my call to advise me he was not returning my call as he no longer chaired the committee and did not have access to committee files.

The Medical School staff person, whose name I do not recall, advised me an extensive review had been conducted and modifications made to the

protocol and informed consent form.

This is puzzling as Dr. Kraybill's letter of 16 July 1993 indicated the two internationally recognized epidemiologists who reviewed the protocol and my earlier correspondence to the Committee recommended NO protocol changes.

The staff person advised an appointment would be possible later in the month and asked I delineate specific concerns in writing in advance of our meeting.

I do not have the model protocol with me nor have I seen your revised protocol and consent form. I would appreciate receiving copies of these documents prior to our meeting. I would also like copies of the written reports generated for the committee by the two consultants and all minutes of committee meetings at which the proposed/on-going trial was the subject of discussion.

Given the charge of your committee, I assume neither the meetings nor its documents are secret, particularly since my age and family/medical history likely qualify me as a potential trial subject.

Further, as a former graduate school of public health faculty member and long term member of a state medical association's standing committee on toxic agents, I am not only interested in tamoxifen safety and efficacy issues but am equally interested in the process by which this trial was proposed and approved. My interest was heightened in light of the recent announcement that the University of North Carolina at Chapel Hill shortly will be receiving millions of federal dollars in partnership with NIEHS for human subject research in the area of environmental health.

I am particularly interested in how the Committee on the Protection of the Rights of Human Subjects has resolved the following safety and efficacy issues:

1. Carcinogenic risk to participants receiving tamoxifen :

Liver Cancer

The NCI literature I have seen proposes participants be given TAM on a

chronic basis, e. g., at least 5 years, and very likely for the rest of their lives. If TAM is shown to reduce the incidence of breast cancer in the treated group by 30 % or more it will be recommended they continue to take the drug, possibly for the rest of their lives. If only one case of breast cancer rather than the expected 1.7 cases is detected over the next five years in a group of 100 treated women age 60 whose only risk factor is age, and/or younger women whose family or personal history increase their risk to that of the 60 year old group, the trial will be a success and trial participants, those on placebo as well as those in the treated group, will be instructed to take tamoxifen indefinitely. Physicians also will feel justified to perscribe tamoxifen to any woman over the age of 60, as well as younger, premenopausal women with risk at the time equal to those whose only risk is age. This means to avoid one breast cancer, ALL 100 women will be subject to the risks of taking a powerful carcinogen on a chronic basis, e. g. six months or longer.

It is my understanding that, in the absence of adequate human data, toxicologists prefer there be a 1000 to 5000 margin of safety (MOS) above the lowest dose which has been found to be carcinogenic to animals when human subjects will be receiving a dose on a chronic basis. Regulators usually require a MOS of 100 for a non-carcinogenic health effect.

Since there is very little data on the effects of low level tamoxifen treatment of healthy women and incomplete data on women with breast cancer who have been treated on a long-term basis to compute side effect rates with statistical power, surely a 1000-5000 MOS is mandated in any ethical trial of disease-free, healthy women.

As I advised you last year, unpublished data by the tamoxifen manufacturer, ICI, found two types of liver cancer--hepatic adenoma and carcinoma--developed in rats given doses 'equivalent' to the human dose of 20 milligrams. At these doses 3.8 percent developed hepatic adenomas the 11.5 percent developed hepatic carcinomas, in contrast to less than 1 percent of control animals. Therefore, TAM at 20/mg/day, has little if any margin of safety for liver cancer.

In recent months, two published studies have shown that TAM is highly carcinogenic to the female rat liver at high doses.

Hirsimaki et al found liver tumors in four of five female Sprague-Dawley rats studied in a 52 week toxicity study which included a 13-week recovery period. "After the 13-week recovery period all surviving rats in the highest tamoxifen dose group had large liver tumors (diameter up to 2 cm) which appeared to be hepatocellular carcinomas in five out of six rats". (Arch Toxicol (1993) 67; 49-54)

Gary M. Williams et al dosed female Sprague-Dawley rats by gavage daily at 2.8, 11.3 or 45.2 mg/kg/day for up to one year with two recovery segments. TAM induced dose-and time-dependent neoplastic changes in rat liver. The high dose, a level approximately 57 times the maximally used human daily therapeutic dose (HDD), by 12 months caused carcinomas in 75% of the rats, a strong carcinogenic effect. At 12 months, the mid-dose group had evidence of hepatocarcinogenicity (10 % carcinomas) which progressed during the 3 month treatment-free period to 45 %. The authors pointed out carcinogenicity at this dose reduces the margin of safety from 57 to 14 times the HDD.

Although the low dose did not induce tumors after 12 months exposure, the time course of effects at the two higher doses suggest it could prove carcinogenic with an additional 6 months exposure, rather than a dose below a threshold, according to Williams who concluded TAM cannot be regarded as safe for long term human use in the absence of proof that the effects in rats are not relevant to human hazard. "It has been suggested that the carcinogenic effects of TAM will not occur in humans, but no controlled clinical data or research exists to establish that important point. To the contrary, the structural relationship of TAM to the human carcinogen diethylstilbestrol and recent information that it is biotransformed to a reactive product and that it induces alteration in rat liver DNA further compel thorough study of this drug to assess its safety as a cancer prophylactic medication." (Carcinogenesis vol 14 no 2 ppp 315-317)

Unpublished ICI data reported TAM carcinogenic to rats at 5 MG/KG/Day, according to a recent review by Powles in Lancet, dropping the human MOS to less than 6, rather than the preferred 1,000-5,000. (Lancet Vol 340 Nov 7, 1992)

INH White et al by abstract recently reported that in the rat, tamoxifen acts as a genotoxic carcinogen with at least three factors contributing to

its mechanism of action: the rate and nature of metabolism; the degree of damage to DNA; the rate of cell proliferation.

(Cancer Detection and Prevention vol 17 Issue 1 1993 Abstract # 409-44)

While some researchers have argued that estrogen receptors in rats are more avid for estrogen than are human liver receptors, the drug's manufacturer has testified to the U.S. Food and Drug Administration that the half-life of tamoxifen in human beings is 5 days vs 5 hours in rats.

(Testimony of Dr. John Toopham before the Oncologic Drugs Advisory Committee of the Food and Drug Administration, June 29, 1990.)

Further, there is experimental evidence that the drug is retained in normal tissues for more than 1 year after treatment withdrawal. (Cancer Research 51, 4837-4844 September 15, 1991)

A large Swedish tamoxifen trial of women treated for breast cancer found 2 liver carcinomas in its study population, which was several-fold higher than the average incidence of this tumor in the population of that country. Both women received 40 mg/kg/day and the tumors were detected within 15 months of beginning TAM treatment. (Lancet 1989 I; 117-120)

Although other tamoxifen trials have not reported liver cancers, this disease is extremely rare in women and relatively few women have taken the drug for five years or longer. It is possible that liver tumors which have developed in women on the drug were assumed to be metastatic breast cancer. In the absence of routine biopsy or necropsy data there is no way of determining whether a liver tumor is a metastasis or a tamoxifen-induced second primary carcinoma.

Endometrial Carcinoma

The risk of endometrial cancer at a dose of 20 mg daily is increased about five fold, according to the National Cancer Institute. (J National Cancer Inst 1991; 83; 1450-59). The Swedish trial cited above found a 6.5 fold higher occurrence in women with breast cancer receiving tamoxifen than in those with breast cancer not receiving this agent. (Lancet 1989 I; 117-120)

Whether the drug itself is carcinogenic to the endometrium or acts by affecting an endometrium inherently programmed for neoplastic transformation is unknown.

Although the trialists attempt to dismiss this risk by stating this risk is similar to that for estrogen replacement therapy, this argument is specious as high-dose estrogen replacement was discontinued in the seventies precisely because of the increased risk of endometrial cancer. Current low-dose hormone therapies incorporate a progestagen to negate this risk. (Lancet 340; Nov 7 1992, 1144)

In recent months a study of the Yale-New Haven Hospital Tumor Registry concluded "women receiving tamoxifen as treatment for breast cancer who subsequently develop uterine cancer are at risk for high-grade endometrial cancers that have a poor prognosis. These findings also indicate that tamoxifen-associated uterine cancers may have a different basis from those associated with steroidal estrogen treatment."

The authors recommend endometrial sampling of women who are to undergo protracted tamoxifen treatment.(J. Clin Oncol 11; 485-490) "Routine endometrial sampling in asymptomatic women taking tamoxifen may lead to early detection of endometrial cancer and its precursors, allowing for prompt therapeutic intervention," also was the conclusion of Mt. Sinai researchers who reported 11 postmenopausal women with breast cancer who developed endometrial cancer while undergoing tamoxifen therapy. Six of the 11 cases had moderately to poorly differentiated adenocarcinomas, "a larger proportion of undifferentiated lesions than one would expect from cancer that results from unopposed estrogen stimulation." (The Mount Sinai Journal of Medicine Vol. 59 No. 5 October 1992)

Are the women participating in the University of North Carolina sponsored trial receiving routine endometrial sampling ? Does the UNC tamoxifen informed consent form caution that they may develop high grade uterine cancer with a poor prognosis? Or do your protocol and informed consent form continue to speculate that the risk of endometrial cancer is acceptable in the mistaken belief the endometrial cancer associated with tamoxifen is low-stage and low-grade, easily treated with surgical or other means, and does not pose a life-threatening risk to women?

Even if the findings cited earlier are ignored, surely a committee charged with protecting human subjects must consider endometrial tumors requiring surgery a serious complication.

2. Aggressive, hormone independent breast cancer:

Animal laboratory experiments indicate that tamoxifen when co-administered with a known rat mammary tumor agent (DMBA) initially suppresses hormone dependent tumors. However, the tumors which do develop in these animals are aggressive, exclusively hormone-independent tumors. (Cancer Research 52, 235-237, January 1, 1992)

Further research using this model found upon cessation of TAM administration, almost one-third of the tumors regressed and more tumors appeared. Resumption of TAM administration resulted in regrowth of some tumors and regression of the new tumors. The authors concluded these studies demonstrate that some of the TAM-associated tumors are actually dependent upon TAM for growth, while the appearance of new tumors suggests that TAM does not totally prevent tumor formation but may only delay it. They noted that the effects they observed in the rat occur over a matter of weeks; "since breast tumor formation in humans may take 8-10 years before the tumor reaches the level of detection, effects similar to what we have observed may take years to develop in women. Both the development of TAM-dependent tumors and the incomplete preventive action for this drug should be considered in the ongoing prophylactic clinical trials with this agent." (Cancer Research 53, 2937-2939, July 1, 1993)

Is it ethical to subject healthy, disease-free women to an agent which 8-10 years later may lead to untreatable breast cancer? Is this possibility discussed in your informed consent form?

Would it not be in the best interests of your trial subjects to suspend the trial and ask researchers in the UNC School of Medicine to attempt to resolve this issue by characterizing the human cancers--breast as well as second primaries-- presently occurring in North Carolina women in whom long term tamoxifen treatment for breast cancer has failed?

3. Liver toxicity:

Shortly before the NCI launched its trial, the Committee on Safety of Medicines in the United Kingdom reported 5 cases of hepatic failure with 4 deaths and 5 cases of hepatitis with 1 death; 11 other cases of hepatobiliary complications were also noted. (Lancet 1992; 339;940)

Is the Committee aware FDA report files contain similar evidence which has only recently been disclosed? (FDA Adverse Reaction Reports, 1987-1990) Do your protocol and consent forms adequately discuss the potential risks of frank liver toxicity, including hepatic failure and life-threatening hepatitis?

4. Thromboembolic disease:

Thromboembolic disease has been observed up to seven times more frequently in tamoxifen-treated patients than in controls. In NSABP-14 two deaths occurred in the TAM group and none in the controls. Projected incidence of life-threatening thromboembolitic toxicities attributable to tamoxifen in the NSABP protocol discloses approximately 24 of the 8,000 women receiving TAM will be at risk--and 8 of these women may die from complications. Overall, the B-14 trial predicts 1.3 % or 83 of the 8,000 treated women are at risk to thromboembolic events.(NSABP P-1 protocol; Journal of NIH Research, Sept 1992 Vol 4)

Does your informed consent form adequately disclose this risk? The model consent form specifies three deaths from blood clots may occur but is silent on the overall expected number of thromboembolic side effects, an oversight which must be corrected if consent is to be truly informed.

Excluding women with a history of this disease does not necessarily lessen risk: one retrospective study found 7 of 220 women with metastatic breast cancer under treatment with tamoxifen developed thrombosis or pulmonary embolism within six months of starting treatment. None had a previous history of similar events. The authors of this report noted a review of ICI's data from past and ongoing clinical trials, as well as their market drug experience, revealed eight cases of phlebitis, three of thrombophlebitis and four of thrombosis.

"Together, these data bases contain 1975 patient cases, an incidence of slightly less than one case per 1090 treated patients...." (Cancer

Treatment Reports Vol 68, no 6 June 1984)

5. Ocular toxicity:

A prospective study of 63 patients receiving 20 mg/day, long-term tamoxifen found 6.3 % developed retinopathy and/or keratopathy from between 10 to 35 months of initiation of therapy. (Cancer 1992; 69 2961-2964)

Are the women participating in the University of North Carolina-sponsored trial receiving routine ophthalmological exams prior to entry and periodically thereafter?

6. Adverse reproductive outcomes:

It is my understanding your protocol permits tamoxifen, an estrogen-like compound with a structure similar to DES, be given to women of childbearing age with intact uteruses who are counseled against using estrogenic or IUD methods of birth control. Paradoxically, NCI documents state the substance may enhance fertility.

While the protocol specifies pregnancy will not be allowed, family planning experience over the past 30 years makes it probable that unintended pregnancies will occur in both the treated women as well as controls. (Family Planning Perspectives, 1992, 24: 12-16)

The animal literature is clear adverse reproductive outcomes may occur if an unintended pregnancy occurs in a tamoxifen-treated woman. A 1987 publication reported tamoxifen, like DES, elicits changes in the developing female genital tract and concluded the drug is a potent estrogen and has "the distinct potential for eliciting teratogenic change." (Human Pathology, 18: 1132-1143, 1987) Earlier, a researcher reported treated immature female mice developed lesions that "may be analogous to the adenosis that has been observed in diethylstilbestrol-exposed animals and humans." (Am J Obstet Gynecol 1 March 1985)

Immediate cessation of TAM treatment upon diagnosis of pregnancy will not necessarily lessen risk of a birth defect if a decision is made to carry the fetus to term due to the long half-life of TAM in normal human tissues. (Cancer Research 51, 4837-4844, Sept 15, 1991)

Does the UNC protocol/informed consent form now provide funding or moral support if abortion is counseled?

7. Depression:

Does the UNC consent form mention the possibility of depression as a side effect from tamoxifen treatment? Baylor researchers reported in May 1993 that 15% of 155 evaluable node negative breast cancer patients treated with TAM reported depression compared to 3% of 102 evaluable patients who received no TAM or chemotherapy. They concluded "depression as a side effect of tamoxifen therapy is more common than previously believed and should be thoroughly evaluated and treated in patients receiving long term tamoxifen." (Abstract # 112, Proceedings of ASCO Vol. 12 March 1993)

8. Asthma:

Does the UNC consent form mention tamoxifen may provoke bronchospasm in susceptible patients?

...We report a woman with analgesic-induced asthma in whom tamoxifen produced symptomatic and objective airways obstruction ...In December, 1990, carcinoma of the breast was diagnosed and, after surgery, she was started on tamoxifen. This therapy was associated with deterioration in asthma control, especially for a few hours after ingesting tamoxifen. Therefore we arranged to study the effect of tamoxifen upon her pulmonary function tests.... We concluded that tamoxifen provoked bronchospasm in our patient. ICI Pharmaceuticals keep extensive records of adverse events associated with tamoxifen and have received a few reports of bronchoconstriction, although a casual relation was never established....(P)rescribers should be aware of this potentially serious adverse effect of the drug. (Lancet, Vol. 341, March 20, 1993)

9. Risk:benefit equation:

If the UNC tamoxifen cohort has disproportionately enrolled premenopausal women, it is very likely there will be little or no

measurable benefit in this group with regard to protection from fractures and heart attacks. Does the UNC informed consent form make this clear?

Further, does the informed consent form discuss the potential risks to postmenopausal members in the placebo group who must forgo low level estrogen replacement therapy for at least five years?

While there may be some breast cancer protection of extremely high risk, premenopausal women in your cohort, the effect may be suppression rather than prevention. Fentimen of the Royal Marsden Hospital of London has noted that tumors in younger women are likely to be receptor-negative. He warns that if the malignant phenotype is inhibited for two to five years "with subsequent emergence of a more aggressive hormone-independent variant, the prognosis might be worse than if no tamoxifen had been given." (Eur J Cancer, Vol 26 No 6 655-656, 1990)

Lars Rutqvist et al, reporting the findings of the large Swedish tamoxifen trial which identified elevated risks of liver and endometrial cancer, noted: "There has been some controversy over the fact that an increase of endometrial and liver cancers has not been reported from other adjuvant tamoxifen therapy trials. Few such studies, however, have included a prospective collection of data on second primary tumors other than contralateral breast cancers. Nor have such data been available from population-based cancer registries. Therefore, there is probably a considerable under-reporting of second primary tumors and a corresponding lack of statistical power to detect a difference between the treated and control groups in many of the currently available trials of more long-term adjuvant tamoxifen therapy other than contralateral breast cancers" (JNCI Vol 83 No 18 Sept 18 1991)

Under-reporting would seriously weaken the risk-benefit equation upon which the present national study rests. Over-representation of premenopausal women further dilutes the equation, in terms of avoided heart attacks and broken bones, and likely increases overall group risk of endometrial cancer in the short run and liver cancer and/or aggressive hormone independent cancer in the long run as the younger the participant the longer the potential exposure to tamoxifen.

Further, many of the younger, premenopausal women were admitted to the trial based on an elevated statistical risk due to their mothers and/or

sisters being diagnosed with breast cancer. In recent weeks, data from the prospective national Nurse's Health Study revised, downward, much of that excess risk. The authors concluded: "For the vast majority of women with a family history of breast cancer, particularly those whose mother was diagnosed at a later age, the excess risk is not large." (JAMA, July 21, 1993 Vol 270, No. 3 338-343)

Since younger women were recruited based on theoretical risk as computed by NCI's Gail et al 's reworking of data from the retrospective Breast Cancer Prevention Study, should the Committee not consider taking another look at those assumptions in light of the Nurses Health Study results?

Finally, I am most interested in whether your protocol changes include provisions to cover medical treatment or other costs if their previously healthy subject develops a medical complication from such participation.

I look forward to receiving the requested documents and discussing these issues with you at your earliest convenience.

Sincerely,

Hazel Cunningham, MPH

P6/(b)(6)

17 September 1992

Governor Bill Clinton
Mrs. Bill Clinton
Little Rock, Arkansas

Re: Tamoxifen Breast Cancer Prevention Trial

Dear Governor and Mrs. Clinton:

I ask your review of the Administration's current drug initiative to prevent breast cancer in healthy women.

As the enclosed documents indicate, HHS-FDA-NCI refuses to review the safety and efficacy of the \$68 million Breast Cancer Prevention Trial in which 16,000 American and Canadian women are to be given a powerful hormone modulator or a placebo for at least the next five years.

Many reputable health professionals are on record that the tamoxifen trial is premature, unethical and has a high risk of serious side effects for some participants. Adverse tamoxifen published literature grows weekly.

Side effects have been trivialized to the press and to volunteers. The model informed consent form fails its duty to adequately inform of health as well as financial risks if insurance carriers dispute coverage for trial-related tests and, more importantly, trial-related illnesses. Only the drug/placebo is free of charge.

Trial opponents include the current president of the American Public Health Association, Dr. Joyce Lashoff, and at least two former APHA presidents: Dr. Bailus Walker and Dr. John Romani. Although I have not corresponded with her directly, I am told the president-elect of APHA, Dr. Helen Rodriques-Trias, also is opposed. Dr. Rodriques-Trias is a board member of the National Women's Health Network which has opposed the trial for well over a year.

I am hopeful APHA will focus attention on trial risks at its annual meeting in Washington, D.C. in early November.

An organization of which I am a board member, the National Network to Prevent Birth Defects, fears DES-like outcomes in children conceived while their mothers' are taking tamoxifen, a probability as the trial is enrolling sexually active women as young as 35 and denies them use of either an estrogen-based birth control pill or an IUD. It seems possible some women may elect to carry these unintended pregnancies to term.

Congresswoman Patsy Mink of Hawaii, herself a DES victim, shares these concerns.

Federal agencies are playing fast and loose with the facts regarding the endorsement of the trial by the FDA's Oncologic Drugs Advisory Committee. In fact, that committee in July 1991, voted 5-2 the risks of the trial outweighed the potential benefits. It endorsed the trial, 6-1, if the entry criteria were narrowed and limited to extremely high risk women. The disputed entry criteria was unchanged when NCI launched its extraordinarily successful 'selling' of the tamoxifen trial in late April.

The House Subcommittee on Human Resources and Intergovernmental Relations, of which Congresswoman Mink is a member, has been investigating the adequacy of the informed consent forms given participants. I do not know the status of the committee investigation and/or plans to conduct a hearing later this month in light of Chairman Ted Weiss' sudden death earlier this week.

Tamoxifen trial concerns are non-partisan. On Sept.10,1992 California Congressman Richard Dornan asked White House Chief of Staff James Baker's help to suspend the trial pending resolution of toxicity questions.

If you would like additional information, I can be reached in Sacramento until Sept. 30. I will be in Hawaii at (808) 242-7267 Oct. 1- Nov. 5, 1992.

Sincerely,

Hazel Cunningham, MPH

P6/(b)(6)

July 1, 1992

Dr. Jerome Harris, Chair
Human Subjects Experimentation
Grants and Contracts
Duke University Medical School
Box 3001
Duke University
Durham, N. C. 200101

Dear Dr. Harris:

This is to request the Human Subjects Experimentation Committee suspend the NSABP P-I clinical trial to determine the worth of tamoxifen for preventing breast cancer, pending review of new information suggesting the trial as presently constituted compromises public health.

I ask the Committee, drawing on interdisciplinary and ethics experts within and without Duke University, take a second look at the protocol's efficacy, feasibility, including compliance, lack of a prior pilot study, definition of women at high risk of breast cancer, and potential risk of tamoxifen to study participants.

A number of these issues were raised at the Food and Drug Administration hearings prior to federal approval of this NCI-sponsored initiative. I am enclosing a consensus letter submitted to the FDA last November by the National Women's Health Network, joined by two dozen epidemiologists and health scientists across the nation, including the current president of the American Public Health Association, Dr. Joyce Lashoff.

These physicians and scientists concluded the trial was "premature and unethical."

In the intervening months, additional deleterious information has surfaced, including reports suggesting participants, in addition to the well known risks of a thromboembolism event and endometrial hyperplasia

and cancer, may run the risk of liver failure and even liver cancer with chronic exposure.

In recent weeks evidence has been presented chronic exposure may induce or promote aggressive, exclusively hormone independent mammary tumors. Also, unpublished data from three European trials suggests long term administration of tamoxifen to breast cancer patients increases their risk for gastrointestinal cancer.

On June 15, 1992 CANCER published a prospective study of patients treated with 20 mg/day tamoxifen which documented ocular toxicity in 4 of 63 persons (6.3%) in only 5-35 months of administration. One case did not resolve following cessation of treatment.

I am enclosing copies of recent letters to HHS Secretary Louis Sullivan and FDA Commissioner Kessler for your review.

I can't emphasize strongly enough my concerns regarding the potential for unintended pregnancies in treated, premenopausal women. If any of these pregnancies are carried to term, the literature suggests DES-like outcomes are a strong possibility.

I have not seen your informed consent document. If it follows the Model Consent Form, approved Jan. 13, 1992, it inadequately characterizes known risks of the trial.

I assume a second look by your committee would include an extensive review of the CURRENT literature. I note with some alarm that the operating protocol, dated Jan. 24, 1992, which was the basis for IRB approval for at least one Western U.S. cooperating institution and possibly yours as well, has virtually no tamoxifen adverse effects cites later than 1989. In your initial approval did the committee exclusively rely on the protocol references?

The approved consent form specifies the trial may prevent approximately 62 breast cancers and 52 heart attacks over the next five years. It predicts 38 uterine cancers and 3 deaths due to blood clots in the lungs. It does not, however, state the assumptions for these predictions.

Perhaps your second look could include risk/benefit assumptions specific

to the characteristics of the women Duke has enrolled to date.

Your study might also look at the risk to a postmenopausal North Carolina woman, previously taking estrogen to prevent heart attacks and bone thinning, whose fear of breast cancer prompts her to join the trial. To qualify, she must forgo ERT. If she were previously protected from heart attacks and osteoporosis by ERT, will she lose this protection if assigned to the placebo group? Can or should this eventuality figure in any risk/benefit assumptions? Is she entitled to know she may be enhancing her risk of a coronary and/or broken bones if she is on the 'sugar pill'?

If you did an independent adverse literature review the first time around, did you consider the 1991 Lancet report signed by Spicer, Pike, and Henderson, raising alarm that including premenopausal women runs the risk of ovarian stimulation that could lead to ovarian cancer? Would it not be appropriate to include this potential risk in the consent form?

I would like clarification of your consent form statements regarding the payment for pre-entry workup and monitoring. Is your institution providing these services free of charge or are they to be billed to insurance carriers, as is the plan in the two California institutions with which I am most familiar?

At U.C. Davis, for example, prospective participants were counseled by the principal investigator to have their physicians bill their insurance carriers. When one participant pointed out her policy would not cover any costs incurred as an experimental subject, she was advised: "Your insurance company doesn't need to know why these tests are being done."

I assume insurance fraud is not counseled at your institution.

I further ask your review of the ethics of the whole process of the 'selling of the tamoxifen trial.' It seems to me NCI and the media, relying on NCI, are stampeding women frightened of contracting breast cancer to sign up. This puts pressure on personal physicians to cooperate, many of whom are unfamiliar with the tamoxifen literature.

One woman who was considering joining the UNC at Chapel Hill trial told me last week that in her counseling session with a physician trial risks were trivialized.

In the informational sessions I attended at U.C. Davis and at Sutter Hospital, the second institution participating in Sacramento, potential risks indeed were glossed over. Breast cancer risks, however, were stressed.

There was no attempt to inform potential participants that a sixty year old woman with no other known risk factors had less than a 1.7% chance of being diagnosed with breast cancer in the next five years. That the 'one in nine lifetime chance of being diagnosed with breast cancer' did not mean that she carried ALL of this statistical risk at age 60.

I do not know what kind of publicity your trial has had in your communities. I do know that Channel 11, the ABC TV station serving the Chapel Hill/Raleigh/Durham area, on June 29, 1992, carried a health feature promoting the trial and urging viewers to call an 800 number to learn how to sign up. This program, I was later told by the station, originated out of state and was in fact 'canned,' with a script provided the health reporter. The script said the only side effects expected were minor GYN symptoms -- hot flashes, etc. The physician interviews were not locally generated but were provided by the feature service.

"Are there other side effects?," the station representative asked me.

Finally, I challenge the ethics of approving a study recruiting healthy women in which neither the sponsoring institution receiving the grant nor the federal government makes any provision to cover the medical treatment or other costs if a subject develops a medical complication from such participation.

Is your Committee clear that the women being recruited into this trial are healthy? That they are not patients?

Is it ethical to require healthy women to sign a form which states, as does the consent form used by the UNC-Chapel Hill trialists:

I understand that in the event of physical injury directly resulting from the research procedures, financial compensation cannot be provided. All forms of medical diagnosis and treatment, whether

routine or experimental, involve some risk of injury. In spite of all precautions, I might develop medical complications from participating in this study. If such complications arise, the researchers will assist me in obtaining appropriate medical treatment but the University of North Carolina at Chapel Hill does not provide financial assistance for medical or other costs....

This form does NOT state that one retrospective study of 70 women on tamoxifen for five months to two years, asymptomatic on regular GYN examination, when checked by biopsy had a high rate of hyperplasia. Does Duke's?

Does Duke's tamoxifen protocol require an endometrial biopsy prior to entry and periodically during the course of the 'at least' five years of treatment? If not, why not?

In light of the recent prospective study of patients which found low doses of tamoxifen resulted in ocular toxicity, will the women in your institution's study receive free ophthalmological exams prior to entry and at appropriately scheduled intervals throughout their treatment? If not, why not?

If you or any member of your committee would be interested in further information regarding any of these issues, please let me know.

I look forward to hearing from you at your earliest convenience.

Sincerely,

Hazel Cunningham, MPH

encs.

P6/(b)(6)

September 8, 1992

Jerome S. Harris, MD
Chairman
Institutional Review Board
for Clinical Investigation
Duke University Medical Center
Box 3001
Durham, N. C. 27710

Re: Tamoxifen Prevention Trial in Healthy Women

Dear Dr. Harris:

It was disconcerting to learn in your letter of 28 July 1992 that the IRB you chair has limited its reassessment of the safety and potential benefits of the tamoxifen breast cancer prevention trial in healthy women to a request the principal investigator at Duke examine the concerns enumerated in my letter of July 1, 1992 "with the coordinating organization (NSABP) so our Institutional Review Board may be reassured as to the safety and potential benefits of this study."

With due respect, my letter of July asked your committee independently review the protocol's efficacy, feasibility, including compliance, lack of a prior pilot study, definition of women at high risk of breast cancer, and potential risk of tamoxifen to study participants.

To facilitate your independent review, I enclose copies of recent correspondence regarding the risk:benefit of the trial.

It is particularly distressing to learn, via the meeting transcript and subsequently confirmed by Dr. Ahmann's letter, that the FDA's Oncologic Drugs Advisory Committee, after considering the proposed protocol in July 1991, voted 5-2 that the risks likely outweighed the potential benefits of the trial. The committee supported a prevention trial, 6-1, providing the trialists and their sponsors (FDA-NCI) restricted volunteers to women of

truly high risk. Ways and means of making sure the benefits outweighed the risks were left to the discretion of the proposers.

To my knowledge, the entry criteria was not altered, as was recommended by the advisory committee.

It is very disappointing to have NCI-FDA-HHS dismiss safety and efficacy concerns, in part, by declaring the issues were considered by this prestigious expert committee -- with the implication members wouldn't have approved it if these questions were not answered to their satisfaction-- and remaining silent regarding the committee's formal actions.

Another major NCI-FDA-HHS defense is the protocol review by institutional review board committees, such as the one you chair. If the IRB reviewers do not do an independent literature search and analysis they are relying on the protocol's woefully out of date --and inadequately characterized -- toxicity profile for this powerful hormone modulating drug. Informatively, one to two dozen new articles in which tamoxifen is the subject are surfacing in Medline weekly.

Finally, I spoke recently with Nancy Bruning, writer-author, who attended ASCO April meeting in San Diego and subsequently reported aspects of that gathering in a Breast Cancer Action newsletter, a copy of which is enclosed. She has good notes identifying speakers at the conference, including the gentleman whom she says went on at length regarding the need to 'sell' the tamoxifen trial to the press--and others. I assume the 'others' included IRBs.

I regret Duke policy requires confidentiality with regards to the specific details of any protocol. Since I know for a fact the model protocol and consent form inadequately characterize risks, keeping Duke's protocol secret leaves me no alternative but to explore other ways of communicating these concerns to the general public and North Carolina's health advocates in order to reach women interested in or already randomized into your study.

I hope the enclosed information is helpful to you and would appreciate being kept informed of your progress in reevaluating the safety and efficacy of the trial at your institution.

On a personal note, our mutual friend, Dr. Ron Chuang at U.C.Davis, sends his regards.

Sincerely,

Hazel Cunningham, MPH

encs.

P6/(b)(6)

July 28, 1993

Jerome S. Harris, MD
Chairman
Institutional Review Board
for Clinical Investigation
Duke University Medical Center
Box 3001
Durham, N. C. 27710

Re: Tamoxifen Prevention Trial in Healthy Women

Dear Dr. Harris:

I would appreciate an appointment at your earliest convenience to discuss concerns regarding the Tamoxifen Breast Cancer Prevention Trial underway at Duke.

Sincerely,

Hazel Cunningham, MPH

P6/(b)(6)

29 September 1992

David A. Kessler, MD
Commissioner
Food and Drug Administration
Room #14-71
Rockville, Maryland 20857

Re: Citizen Petition to Suspend the
Tamoxifen Breast Cancer Prevention Trial

Dear Dr. Kessler:

Your failure to respond to date to my letter of May 18, 1992 regarding the FDA-approved Tamoxifen Breast Cancer Prevention Trial is very disappointing.

I am enclosing a copy in the event your staff routed it elsewhere.

I am also enclosing copies of correspondence with a member of the FDA's Oncologic Drugs Advisory Committee which confirmed that your agency failed to follow its advice regarding limiting the tamoxifen trial to very high risk women.

This is particularly disconcerting as FDA Associate Commissioner for Legislative Affairs Marc J. Scheineson stated in an Aug. 6 letter to U.S. Representative Patsy T. Mink her concerns "have been carefully considered by the staff of the Food and Drug Administration (FDA) and by the FDA's Oncologic Drugs Advisory Committee in an open meeting in July 1991."

He then proceeded to advise her the FDA "would not permit a clinical trial to proceed unless we concluded that its risks were acceptable.... We believe that research that is well designed and considered valid and ethical by responsible scientists should be blocked only when the risks of the research clearly outweigh potential benefits."

The implication in these statements to Congresswoman Mink is that the FDA Oncologic Drugs Advisory Committee has determined the benefits of the research clearly outweigh potential risks. This is patently false. The committee determined, by a 5-2 vote, exactly the opposite.

When I wrote you on May 15, 1992 I was unaware of your advisory committee's deliberations. The concerns I expressed to you and to Secretary Sullivan, copies of which were provided you, were based on an independent review of the current published literature as well as the arguments put forth by the two dozen epidemiologists and health specialists who endorsed the National Women's Health Network letter and alarming new findings detailed in Science News.

Since then a prospective study of 63 patients taking 20 mg tamoxifen daily identified ocular toxicity in several patients in less than three years (Cancer, June 15, 1992). Your trial mandates at least five years of administration and does not require examination prior to entry nor periodically during the course of treatment.

Your approved protocol does not require endometrial biopsy before or periodically during treatment although the literature is clear this would be a responsible course of action. A recent Lancet report (Aug. 1, 1992) from Israel found 11 of 41 (28 %) symptom-free, postmenopausal breast cancer patients by endometrial biopsy had proliferative endometrium, 1 with endometrial polyp and 1 with endometrial cancer. Please note these women were symptom-free. A 1991 retrospective study by Gal et al found 18 percent with hyperplasia.

In recent weeks cell and tissue experiments by Hawaii researcher Robert Cooney found tamoxifen in optimum doses stimulates protein kinase C (PKC) activity. Does the FDA really believe it appropriate to give healthy women an agent a chronic dose of a substance which enhances PKC activity?

Your failure to respond to these concerns leaves me no ethical choice but to frame this letter as a "citizen petition," to the FDA, as specified by federal regulations.

I ask that you suspend the recruitment and implementation of the trial until and unless toxicity experts of the National Toxicology Program conduct a risk:benefit study which

1. clearly suggests the proposed protocol's potential benefits outweigh risks to individual participants.
2. permits construction of a valid "informed consent" document.

I further ask that once the risk:benefit study and consent forms are complete they be made widely available and public hearings be conducted so that the agency may benefit from review by multi-discipline experts, including ethicists and others.

In support of this PETITION I submit copies of earlier petitions to HHS.

Please advise me of the Docket number for this petition as soon as possible.

Sincerely,

Hazel Cunningham, MPH

P6/(b)(6)

22 September 1992

Dr. Peter Greenwald, M.D.
Director
Division of Cancer Prevention
and Control
National Cancer Institute
Bethesda, MD 20892

Dear Dr. Greenwald:

Thank you for your letter of September 17, 1992 further regarding the National Cancer Institute's justification of its Breast Cancer Prevention Trial in healthy women.

I am not reassured by recitations that the BCPT has been reviewed by multiple panels of unnamed experts. I looked into one such review: the July 1991 FDA Oncologic Drugs Advisory Committee tamoxifen trial review. As you know, this committee of experts voted 5-2 the trial risks outweighed its potential benefits. It did support a tamoxifen prevention trial, by a 6-1 vote, providing the entry criteria were substantially changed. The FDA-NCI ignored this advice.

Nor are the reviews by participating institutional review boards comforting. As you well know, these reviewers in the main rely on the cited references in the protocols under discussion. Further, they rely on the integrity of the trialists-- and their sponsors, in this case, FDA-NCI-- to bring current literature to their attention.

The protocol (and references) provided the IRBs were woefully out of date and both understate and stand silent on tamoxifen health risks as portrayed in the world literature.

Are you routinely summarizing-- and evaluating--the growing published tamoxifen literature and forwarding same to the IRBs?

Have the cooperating IRBs, who are responsible for the safety of human subjects research, been advised of the recently published work of Dr. Robert B. Cooney who found tamoxifen in low doses ENHANCES protein kinase C (PKC) activity? (Carcinogenesis vol 13 no 7 pp 1107-1112 1992)

Do you, as an expert in cancer prevention, personally believe it to be a good idea to give healthy women on a chronic, possibly lifetime basis, an agent which at optimum levels enhances rather than inhibits PKC?

Have the IRBs' attention been directed to recent tamoxifen reviews by tamoxifen researchers Michael W. DeGregorio and Richard Love?

Dr. DeGregorio, writing in the Journal of NIH Research, September 1992 Vol 4, notes:

...the benefits of tamoxifen in preventing breast cancer in healthy women deemed to be at high risk may prove to be minimized when innate and acquired resistance are considered and when weighed against the toxicity of this drug....

...virtually all women who develop breast cancer in the chemoprevention group will be resistant to tamoxifen. Therefore, the net benefit of tamoxifen chemoprevention is reduced because of acquired tamoxifen resistance.

An equally important consideration is the fact that 8,000 women will be subjected to the potential risk of side effects of tamoxifen in the NSABP trial. The side effects of tamoxifen are not limited to reversible hormonal effects, as initially thought, but include induction of secondary cancers. Indeed, the risks to healthy women receiving tamoxifen may be substantial.

Raloff recently summarized the relationship between tamoxifen and secondary tumors, including endometrial liver, and hormone-independent breast cancers. Although little is known about the mechanism by which tamoxifen induces secondary tumors, recent evidence suggests

that the drug produces DNA adducts, which is commonly observed with certain agents associated with known carcinogenic potential. Other data suggest that, in addition to carcinogenic risk, tamoxifen **MAY ACTUALLY STIMULATE THE GROWTH OF ENDOMETRIAL CELLS AND RESISTANT BREAST CANCER CELLS**(estrogen-receptor-positive and negative).... (emphasis added)

Healthy women who develop breast cancer while on tamoxifen chemoprevention would be expected, then, to have tamoxifen-resistant tumors. These women would no longer benefit from antiestrogen therapy, either in the adjuvant setting or if metastatic disease develops. Whether the women will respond to chemotherapy or not remains to be determined.

NSABP has projected that, over the five years of tamoxifen chemoprevention therapy (cumulative dose greater than 36 g), between 31 and 53 patients--depending on age--will be at risk for tamoxifen-induced endometrial tumors. Arguments have been made that this risk is acceptable because the endometrial cancer induced by tamoxifen is low-stage and low-grade, is easily treated with surgical or other means, and does not pose a life-threatening risk to women. Although this contention is perhaps true if tamoxifen is being used to prevent the recurrence of breast cancer, for healthy women in whom tamoxifen is being used solely for chemoprevention, secondary endometrial tumors requiring surgery must be considered a serious complication.

...Evaluation of the projected incidence of life-threatening thromboembolic toxicities attributable to tamoxifen in the NSABP protocol reveals that approximately 24 of the 8,000 women receiving tamoxifen will be at risk--and eight of these women may die from complications. In addition, ocular toxicity has been associated

with tamoxifen therapy. In a recent study, ocular toxicity occurred in four of 63 patients 10 to 35 months after initiation of standard tamoxifen doses (20 mg/d). Compared with the projected number of patients who may actually benefit from tamoxifen chemoprevention, is this associated risk acceptable to otherwise healthy women?

Because many tamoxifen-related side effects are associated with chronic dosing (for more than six months), it is reasonable to assume that women receiving tamoxifen for the duration of the NSABP protocol (five years) will be at significant risk of experiencing tamoxifen-induced toxicities.

... Finally, if tamoxifen chemoprevention leads to unacceptable toxicity, development of tamoxifen-resistant breast tumors, or the induction of a long-term, yet unknown toxicity (e. g., liver tumors), the NSABP trial could impede future cooperation for groupwide trials of chemopreventive agents that are truly effective and nontoxic.

Has NCI forwarded to the cooperating IRBs copies of Dr. Richard Love's review, recently published in *Oncology*, which questions risk:benefit for the thousands of premenopausal women flocking to the trial as volunteers?

Among other alarming information, Dr. Love notes the long-term CRC tamoxifen breast cancer study headed by Dr. Michael Baum has found 10 years of tamoxifen treatment at 20 mg daily resulted in an INCREASED number of contralateral breast cancers in premenopausal women treated for breast cancer compared with controls. (*Acta Oncologica* Vol. 31, no 2 pp 251-257, 1992)

While it may be convenient to dismiss this finding as an anomaly, the rate of suppression of contralateral breast cancers in postmenopausal women

in the study was in general agreement with results in other tamoxifen studies of postmenopausal women.

Why would the CRC study results be valid for postmenopausal women and invalid for women who ovulate?

Are you not concerned long-term administration of tamoxifen to premenopausal women may not only be of no benefit in suppressing breast cancer but may actually increase their risk of developing tamoxifen-resistant breast cancer?

Dr. Love also pointed out:

While the pharmacology of tamoxifen is well known in postmenopausal women, it is incompletely described in premenopausal women, in some of whom major increases in blood estrogens are found. Teratogenic effects in premenopausal women are possible. The duration and timing of tamoxifen chemosuppression of preclinical disease are particularly challenging in premenopausal women.

The impact of tamoxifen therapy in women with histologic evidence of 'pre malignancy' (e. g., atypical epithelial hyperplasia) has not been evaluated because of significant logistical barriers.

In summary, while many biological and symptomatic effects of tamoxifen in postmenopausal women are well described, details are lacking for many others. For premenopausal women limited data are 1) in conflict regarding benefit on rates of second primary breast cancers; 2) inadequate to make projections about heart and bone disease effects; 3) incomplete but worrisome with respect to hormonal effects and thus liver, uterus, and ovarian carcinogenic effects and thrombophlebitis; 4) inadequate to address potential effects on pregnancy, cholelithiasis, and the eye; and 5) inadequate in describing side effects on vasomotor and gynecologic and central

nervous systems. Finally, as Kiang has pointed out, the theoretical basis for this intervention in premenopausal women is poorly developed.

Accordingly, have the IRBs required that women enrolling in the trial in their respective institutions be given revised 'informed consent' forms reflecting the analyses of Kiang, Love and DeGregorio? If not, why not?

Thank you for the update regarding the recent revision of the model consent form to reflect liver toxicity.

As you know, the liver damage report was published in Lancet on 11 April 1992, which predated the trial announcement by two weeks. By the time the first ERSMAC meeting took place on 7 August, at least 1,000 women had been randomized and were on trial, months after publication of that Lancet report. I know for a fact Erik Jansson of the National Network to Prevent Birth Defects forwarded copies to NCI/HHS in early May. If you reviewed the documents which accompanied my June 28 letter to HHS you know I appended a listing of FDA liver toxicity reports as well.

I would appreciate receiving a copy of the recently modified consent form as well as copies of protocol changes during the course of the trial.

Regarding the similarities of tamoxifen and DES, I would appreciate receiving all NCI-initiated or in-house risk analyses done which led NCI to conclude my concerns are unfounded should barrier contraception fail in a tamoxifen-treated premenopausal participant.

It is my understanding tamoxifen and DES are structurally similar. Animal studies not only by Dr. Cuhna but others lead me to believe a tamoxifen-exposed fetus is at risk to DES-like outcomes. My reading of published tamoxifen pharmacokinetics reports is that tamoxifen and its metabolites have long half lives ;the tissues of a woman treated with 20 mg tamoxifen daily accumulate the drug and in two weeks to a month, depending on which metabolite is being measured, steady state is reached .Even if the drug is withdrawn, say after a menstrual period or two is missed, the fetus would continue to be exposed for weeks. Is this incorrect?

Both the manufacturer, ICI, and standard drug reference books relate instances of fetal problems, including birth defects, in cancer patients treated with tamoxifen who become pregnant.(Copies enclosed)

Has NCI determined the birth defect and other adverse fetal reports ICI has in its files are invalid? Is it reasonable for ICI to list these problems in its advertisements for tamoxifen or in package inserts if they believe them to be wrong?

While it is well and good to state that "most women who are eligible for the BCPT are past child-bearing age . . ." -- I am concerned about every premenopausal woman you have enrolled to date, even if there is only one such person in the trial.

If only 10 percent of the enrollees are premenopausal, this means 800 treated and 800 untreated women are at risk to unintended pregnancy. I don't know how many conceptions may occur in this group -- some family planning studies suggest barrier failure rates as high as 30-40 percent.

If the trial is attracting a disproportionate number of younger women, the potential for unintended pregnancy grows while the overall potential trial benefits (decreased stroke, heart attacks, and broken bones) in premenopausal women decrease, further skewing the risk:benefit ratio in that group.

Will treated women be counseled to abort if pregnancy is confirmed?

Thank you for clarifying the NSABP B-14 results published in the NEJM in 1989. I might add, however, that my interpretation of the B-14 results would have been greatly aided by the opportunity to read a 1992 update.

Why was the prevention trial, which relies in the main on the B-14 results to estimate side effects, launched prior to publication of these data? At least one respected reviewer has raised questions about B-14 disease-free interval results, suggesting they may have been spurious. (Surgery, October 1991)

Why didn't NCI hold back funding a trial in healthy women until Dr. Fisher's longer-term data was published and available for review?

I certainly agree that "informed people may disagree...." I doubt, however, that "the large majority of the scientific community accepts . . . the design of the BCPT."

The large majority of the scientific community, like the large majority of the persons comprising the IRBs, is not likely to be up to speed on the published tamoxifen literature. Medline searches show anywhere from 10 to 18 new titles from English-language journals incorporated into the NIH data base WEEKLY.

That so few publically have expressed concern to date may speak more to the chilling effect NCI's sponsorship of a large trial may have on the exercise of free speech in institutions largely dependent on NCI-NIH research funds rather than endorsement of the trial design. Others may prefer to keep their arguments 'in-house,' e. g., in journals, or at scientific meetings, virtually guaranteeing most women frightened into volunteering for the trial remain ignorant of unanswered tamoxifen efficacy and safety issues.

Sincerely,

Hazel Cunningham, MPH

cc: HHS, FDA

Other interested parties

P6/(b)(6)

June 29, 1992

Louis Sullivan, MD
Secretary
Department of Health
and Human Services
200 Independence Ave., SW
Washington, D.C. 20201

Dear Secretary Sullivan:

Re: Petition to Suspend Tamoxifen Trials in Healthy Women

On May 15, 1992 I petitioned you to suspend the NCI-sponsored tamoxifen drug trial in healthy women pending review of toxicity data by the National Toxicology Program and independent experts, noting Great Britain's Medical Research Council (MRC) had cancelled its planned trial because of liver toxicity concerns.

I asked experts review evidence chronic administration of tamoxifen may induce or promote the development of aggressive, hormone independent tumors; increase the risk of life-threatening liver cancer; increase the risk of endometrial cancer, necessitating hysterectomy as 'cure'; increase the relative risk of developing contralateral breast cancer in premenopausal women; and act as a teratogen on the developing human genital tract.

In the intervening weeks I have become aware of additional adverse information, underscoring the need to stop the trials in the interest of public health.

In addition to the serious issues raised in my first letter, a copy of which is appended for your convenience, an expert panel should be convened to examine reports that:

+Three European trials (two in Sweden, one in Denmark) have detected excess cases of aggressive gastro-intestinal cancer in women treated with tamoxifen for breast cancer. These data were verbally presented at U.S. oncology meetings last month.

+Tamoxifen-treated women in England and the United States have suffered life-threatening and fatal liver damage and suppression of bone marrow. I am enclosing a copy of the Lancet report documenting the U.K. reports and a listing of similar reports received by the U.S. FDA.

+A recently published PROSPECTIVE study found 6.3 % of 63 patients treated with 20 mg tamoxifen daily developed ocular toxicity after 10 to 35 months of treatment. One of four cases did not resolve upon cessation of treatment. A copy of this study, "Clear Evidence That Long-Term, Low-Dose Tamoxifen Treatment Can Induce Ocular Toxicity," CANCER, June 15, 1992, is enclosed.

Since writing to you on May 15, 1992, I have also learned that two dozen epidemiologists and health scientists affiliated with leading institutions across the nation late last year objected to the trial, citing, among other things, its potential risk to study participants.

These health scientists, who included Dr. Joyce Lashoff, president of the American Public Health Association and former dean of the University of California School of Public Health, Berkeley, termed the trial "premature and unethical." A copy of their endorsement of the National Women's Health Network's Nov. 27, 1991 letter to the FDA is enclosed for your review in the event the original letter was not brought to your attention.

I have also enclosed a copy of a June 7, 1992 letter sent FDA Commissioner David H. Kessler by Congresswoman Patsy T. Mink.

Writes Mrs. Mink:

It is further said that tamoxifen has chemical properties similar to DES.
NCI handouts to patients state that tamoxifen may make you more fertile.

What happens if premenopausal women in this trial become pregnant and carry their child to term? Will the child be another "DES" baby whose reproductive tract is afflicted with a chemically induced precancerous adenosis? I know whereof I speak, because I am one of those misfortunate DES mothers.

I am deeply concerned that we are about to embark mindlessly on another experiment which will result in foreseeable harm.

These tests without fully researching the possible health risks on otherwise healthy women must not be allowed to proceed.

Copies of a letter of concern the American Public Health Association addressed to the National Cancer Institute late last year and my letter of May 18, 1992 to FDA Commissioner Robert Kessler also are enclosed, as is a copy of a June 8, 1991 letter published in Lancet suggestion long-term tamoxifen treatment of premenopausal women may cause ovarian cancer.

In addition, it is shocking, indeed, to learn that participating women (or their insurance companies) must bear the expense of both the pre-trial workup and extensive monitoring during the course of the five-year trial. These expenses were estimated to be from \$550-\$650 per year in Sacramento, California.

Few, if any, insurance companies in California (and perhaps nationwide) will knowingly cover these charges as their policies prohibit payment of costs incurred by an experimental subject.

On at least one occasion Sacramento women were advised not to tell their insurance company why the tests were being performed.

Participants who cover the costs personally or mislead (defraud?) their insurance companies run the risk of losing coverage should they require care for side effects, including conditions requiring expensive hospitalization and convalescence.

Participants who knowingly assume the risks of participation (as evidenced by their endorsement of the informed consent form) may even run the risk of having their health insurance cancelled.

Arguments that courts in the past have affirmed an insured person the right to continued coverage if medical harm results from taking an experimental drug do not necessarily hold in this trial in that healthy, cancer-free women are volunteering to take a drug which may do them harm. Why should all policyholders assume these financial risks?

I have additional concerns:

+The written and verbal information given me by the NCI information specialists (1-800-4-CANCER) understate health risks and flat-out misrepresent facts regarding the risk of liver cancer. Please note that the enclosed NCI information handout states:

II. Does tamoxifen cause liver cancer?

There has also been some concern that tamoxifen may cause liver cancer. In one adjuvant trial, liver tumors were reported in 2 of 931 breast cancer patients receiving a high dose (40 mg/day) of tamoxifen. In these cases, it is not known whether the liver tumors were caused by the drug or were the result of breast cancer that had spread to the liver. In six other trials using 20 mg of tamoxifen daily ad adjuvant therapy, no liver cancers have been reported.

In fact, it has been determined that the two cases of liver cancer in the adjuvant trial in question were primary to the liver.

The protocol on page 46 inaccurately states an "increased rate of liver cancer has been noted in animal studies at doses greater than that used in humans." On page 11 the protocol further inaccurately states "(e)xperimental studies show an increase in liver tumors in rats who receive high doses of tamoxifen (20-100 times the dose used in

humans.)...Whereas the incidence of hepatic carcinomas was markedly increased with high doses of tamoxifen, the use of doses equivalent to those given in humans resulted in less evidence of an increase in hepatic adenomas of hepatic carcinomas."

In fact, the manufacturers' representative, in testimony before the FDA on June 19, 1990, stated that excess liver tumors were detected in 11 percent of the treated rats at a dose he confirmed was EQUIVALENT to the 20 mg/day dose to be given healthy women in this trial.

Dr. John Topham of ICI reported an incidence of 16-32% for liver tumors in rats receiving a low dose (5mg/kg) of tamoxifen, compared with a 1% incidence of liver tumors in the control group. (Because of way tamoxifen metabolizes in the human, the human dose of .4kg/mg results in mean serum levels comparable to rats given 5 mg/kg.)

Dr. Topham advised the FDA :

There were a number of unscheduled deaths during the course of the study. . . What is interesting is that in all these animals, there was absolutely no liver pathology. . .the first liver tumor was seen in the high-dose group at week 31. After that, they appeared really, rather regularly. Perhaps their most striking characteristic was the speed at which they grew. . . (in the low dose group) the earliest tumor was palpated at week 72; i. e., after about 18 months administration. The first death in this group with a liver tumor occurred at week 86.

In my letter of May 15, 1992, I cited the work of Gary M. Williams, medical director of the American Health Foundation, who found tamoxifen to be "a riproaring liver carcinogen." At the higher doses studied, within one year it produced cancers in 100 percent of the treated animals, which he termed "an astonishing effect." In a lower-dose experiment in which animals received just 10 times the tamoxifen dose typically administered to women, precancerous liver changes --hyperplastic nodules--occured in one year.

Williams told Science News, April 25, 1992," (t)hese are massive liver

tumors....This is the strongest liver cancer effect that I have seen with a chemical carcinogen."

Arguments that differences in metabolism between humans and rats negate these animal findings are not comforting. As pointed out by the National Women's Health Network in testimony to the FDA on July 2, 1991, the half-life of tamoxifen is five hours in the rat and five to seven days in the human, guaranteeing a steady, round the clock dose to the latter. Some liver toxins have been found to be more damaging when the liver is exposed to a steady rather than a sporadic dose.

+The approved protocol inappropriately characterizes other risks and, by design or accident, its references are out of date, raising questions whether the trialists -- and NCI--are keeping up with the published adverse effects literature -- and/or are making these studies known, in timely fashion, to the institutional review boards of the 100+ participating institutions in the U.S. and Canada.

For example, the protocol, approved January 24, 1992, fails to reference the work of Stephen J. Zimniski, Ph.D., who found tamoxifen may promote or induce exclusively hormone independent, very aggressive breast tumors in treated animals.

These hormone-independent tumors grew three times faster in the tamoxifen-treated animals--doubling in size daily. This work was published Jan. 1, 1992, in Cancer Research but the data was made known to chief trialist Dr. Bernard Fisher and the NCI weeks earlier.

Likewise, the protocol fails to reference the work of G.R. Cunha, Ph.D., who in 1987 found tamoxifen to be a potent estrogen in the human fetal genital tract with "the distinct potential for eliciting teratogenic change."("Teratogenic Effects of Clomiphene, Tamoxifen, and Diethylstilbestrol on the Developing Human Female Genital Tract," Human Pathology, 1987)

+The model consent form, following the Jan. 24, 1992 protocol, incompletely and inappropriately characterizes potential risks to participants. Although the consent form relies in the main on the B-14 tamoxifen trial experience to estimate potential side effects, it does not discuss the limitations of this trial to make such estimates.

For example, the B-14 Trial, as published in the New England Journal of Medicine, 1989, disclosed that there was significant attrition in the treatment arm in only four years. Of the 1318 treated at the beginning of the trial, only 188 were still in the study by the end of the fourth year, thus making it impossible to determine the overall four-year rate of side effects based on 1318 subjects.

This trial, as published, did disclose an apparent time-related increased risk of a thrombo-embolism 'event.' After four years of treatment, the article reported a rate of 0.9 of events, including one death, in the treatment arm, compared with 0.2 in the placebo group.

By the end of approximately five years of treatment, the rate had increased to 1.5 % in the treated group, with two deaths, with no increase in the untreated arm, according to the protocol. No data has been published or otherwise presented regarding the risk after 7-10 years of treatment in the B-14.

It seems fair to ask how many of the original 1318 women remained to be 're-randomized' in the second five year trial continuation? If women dropped out of the treatment arm was their complete medical history available to and analyzed by the trialists?

The model consent form also fails to quantify the expected rate of endometrial effects, other than cancer. One non-referenced or discussed 1991 retrospective study indicates precancerous hyperplasia in the treatment arm could run as high as 18 percent.(Gal et al "Oncogenic potential of tamoxifen on endometria of postmenopausal women with breast cancer--preliminary report," Gynecologic Oncology 42, 120-123 (1991))

This means well over 1,000 cases of hyperplasia may result among the 8,000 treated women in this trial.

Although the Jan. 24,1992 protocol recommends endometrial sampling (biopsy) before and periodically during treatment, these procedures are not required of cooperating investigators. Non-uniform monitoring will skew results.

The January 1992 protocol- model consent form inadequately describe

potential reproductive effects if unintended pregnancy occurs, such as vaginal bleeding, early fetal loss, birth defects, and possible DES-like outcomes.

Please note that the enclosed drug toxicity reference spells out risks of the former and the work of Dr. Cunha and others with animals warns of the DES-like outcomes. This should come as no surprise to the trialists in that tamoxifen has been characterized as a "non-steroidal anti-estrogen derived from diethylstilbestrol."

The protocol-model consent form inadequately describe the potential for eye damage among treated participants . The protocol does not require ophthalmologic exams prior to and periodically during treatment, as is recommended as good medical practice in the published literature.

Virtually no tamoxifen toxicity studies published in the refereed literature since 1989 are discussed or referenced in the Jan. 24, 1992 approved protocol. This has the potential of misleading cooperating trialists and/or the human subjects experimentation committees (IRBs) approving participation in the trial nationwide.

I am enclosing abstracts from a recent literature search , and, for comparison purposes, the references listed in the January 24, 1992 approved protocol.

I am enclosing a listing of tamoxifen side effects, animal and human, of which I am aware, and a listing of the potential rate of known side effects, based on the published literature, if known.

Finally, I am enclosing exerpts from published papers (and personal communication) from a number of health scientists in contrast to the materials provided prospective trial members by NCI and the model consent form.

I look forward to hearing from you at your earliest convenience.

Sincerely,

Hazel Cunningham, MPH

P6/(b)(6)

May 18, 1992

David A. Kessler, MD
Commissioner
Food and Drug Administration
Room #14-71
Rockville, MD 20857

Dear Dr. Kessler:

I ask your personal consideration of the adequacy of the FDA-approved tamoxifen breast cancer prevention trial protocol (P-1) with regard to adverse reproductive outcomes.

As it now stands, tamoxifen, an estrogen-like compound with a structure similar to DES, will be given to women of childbearing age who are prohibited from using estrogenic methods of birth control. Paradoxically, the substance may enhance fertility, according to NCI documents, copies of which are appended.

At least one researcher, Dr. Gerald Cuhna, has found tamoxifen, like DES, elicits changes in the developing human female genital tract. In a paper published in 1987 he reported tamoxifen-related changes in the human fetal vagina were comparable to those of DES.

He concluded tamoxifen is a potent estrogen in the human fetal genital tract and has "the distinct potential for eliciting teratogenic change." (Human Pathology, 18:1132-1143, 1987)

Dr. Osamu Taguchi in 1985 reported treated immature female mice experienced developed lesions that "may be analogous to the adenosis that has been observed in diethystillbestrol-exposed animals and humans."

He cautioned:

We have no information about the ultimate fate of adenosis in the tamoxifen-treated mice and have

also little information about that in the diethylstilbestrol-treated mice, but signs of malignancy within the adenosis regions in some older mice after neonatal diethylstilbestrol exposure suggest that some relationship may exist between the adenosis and malignancy.

This is also a significant finding, because a similar abnormality has been reported in diethylstilbestrol-exposed mice and women... Although the daily dose of tamoxifen in this study was about 10 times that for humans, the administration period was only 3 days....

The therapeutic use of tamoxifen in anovulatory women must be applied especially carefully because of the possible fetal exposure.
(March 1, 1985, Am J Obstet Gynecol)

To the best of my knowledge, while the protocol specifies pregnancy will not be allowed in the double blind study of 16,000 women, family planning experience over the past 30 years makes it probable that unintended pregnancies will occur in both the 8,000 treated women as well as controls.

The animal literature is clear many other adverse reproductive outcomes may be expected in premenopausal treated women with unintended pregnancies.

There are numerous additional serious concerns about this human experiment in women of childbearing age, not the least of which are increased risks of liver and endometrial cancer and fatal blood clots.

The risk of life-threatening blood clots in tamoxifen treated women has not been clearly defined.

The protocol specifies exclusion of women with a prior history of deep vein thrombosis or embolism. However, no data has been published regarding the characteristics of the 18 of 1400 tamoxifen-treated

women who experienced thromboembolic events after five years of treatment in Dr. Bernard Fisher's so-called B-14 tamoxifen trial. Two of the "events" were death.

Dr. Fisher's NSABP Protocol P-1 specifies there were six pulmonary embolisms(versus one in the control group)and two deaths (versus zero in the control group) While some of these events were minor, the majority required hospitalization.

If one death per 700 treated women holds for the 8,000 subjects in this healthy women prevention trial, eleven deaths from blood clots can be expected. Overall, the B-14 trial predicts 1.3%, or 83, of the 8,000 treated women may experience thromboembolic events.

The trial consent form specifies three deaths from blood clots may occur but is silent on the overall expected number of thromboembolic side effects, an oversight which must be corrected if consent is to be truly informed.

Eliminating women with a history of these conditions from the trial may not eliminate the risk.

An article published in 1984 reported that in a three year period, seven of 220 women with metastatic breast cancer under treatment with tamoxifen developed thrombosis or pulmonary embolism within six months of starting treatment. None had a previous history of similar events.

The authors reported a review of the manufacturer's data from their past and ongoing clinical trials, as well as their marketed drug experience revealed eight cases of phlebitis, three of thrombophlebitis and four of thrombosis. "Together, these data bases contain 1975 patient cases, an incidence of slightly less than one case per 100 treated patients .. (3.2 %)" (Lipton et al, Cancer Treatment Reports Vol 68, no 6 June 1984)

For brevity, I will not repeat substantive concerns regarding liver and endometrial cancer risks here as they as they have been addressed by the National Women's Health Network in testimony before the FDA. last summer.

However, very alarming research findings published or otherwise reported since the FDA hearings are summarized in a citizen petition submitted to Secretary Louis Sullivan, a copy of which is appended for your review.

I would, however, like to bring to your personal attention the concerns of over two dozen epidemiologists, clinicians and other health scientists, as expressed in a letter in late November to your agency.

These experts concluded "a large trial that includes numerous healthy women is premature and unethical."

I am writing to you directly as it is my understanding the FDA now requires extraordinary care in the prescribing of the birth defect generating drug, Accutane. In addition to counseling regarding pregnancy risks, accutane-treated patients of childbearing age must have a negative pregnancy test and forgo commencing treatment until day three of their menstrual period.

No such requirement has been imposed in this drug trial which will expose fertile women to a drug for at least five years that not only may cause birth defects but has the potential of creating 'tamoxifen daughters.'

The argument that some clinicians already are permitting non-menopausal healthy women to take this drug in off-label fashion, justifying a trial to prove its efficacy and safety, is not only unethical but signals immediate, aggressive FDA action is necessary to protect the health of the public from this practice as well as this trial as presently designed.

I look forward to hearing from you at your earliest convenience.

Sincerely,

Hazel Cunningham, MPH
National Network to Prevent Birth Defects

Encs.

May 15, 1992

Louis Sullivan, MD
Secretary
Department of Health
and Human Services
200 Independence Ave., SW
Washington, D.C. 20201

Re: Petition to Suspend Tamoxifen Trials in Healthy Women

Dear Secretary Sullivan:

Your urgent attention is directed to the National Cancer Institute's recently announced drug trials of tamoxifen in 8,000 healthy women.

I ask these trials be suspended in light of scientific evidence of unacceptable risk in the absence of disease.

Similar trials are on hold in Great Britain because of toxicity concerns.

I further request an interdisciplinary panel of experts be convened to review both new evidence and the adequacy of the risk/benefit assumptions driving federal sponsorship of a drug trial in healthy women including those of childbearing age.

I ask that the full resources of the National Toxicology Program be mobilized to review evidence chronic administration of tamoxifen may:

- +induce or promote the development of aggressive hormone independent tumors
- +increase the risk of life-threatening liver cancer
- +increase the risk of endometrial cancer, necessitating hysterectomy as "cure"
- +increase the relative risk of developing contralateral breast cancer in premenopausal women
- +act as a teratogen on the developing human genital tract

By funding this \$60 million trial through NCI's Clinical Oncology Programs, the need for approval from advisory bodies was generally circumvented and the opportunity for consumer input diminished, according to Dr. Adrienne Fugh-Berman of the National Women's Health Network. A copy of a summary of her concerns regarding this trial is appended for your review.

Absent the convening of an expert panel, I request authorization of an independent review of the adequacy of the informed consent document to be given potential participants and proposed measures of effectiveness in guaranteeing the adequacy and appropriateness of side effects information to be presented verbally by project employees. This review also should include written material supplied by the NCI to inquiring women.

Louis Sullivan, MD
May 15, 1992
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I further request independent evaluation by bioethics panels of the many issues involved in conducting this human experiment.

The concerns of Dr. C. Barber Mueller, Professor Emeritus of Surgery, McMaster University, Hamilton, Ontario, Canada, published in the June 1990 Journal of the Medical Association of Canada, are particularly telling in that he raised ethical questions regarding adjuvant tamoxifen therapy in the absence of benefits "so overwhelmingly superior that it no longer requires statistical analysis." He concluded the "current rush to adjuvant chemotherapy has neither a scientific, clinical, or ethical rationale. After 20 years, the evidence seems to say No." He further noted that "chemical treatment of women who are otherwise well raises profound ethical issues."

I ask your personal consideration of the following:

NCI and the FDA have authorized the administration of an undisputed animal and human carcinogen with a chemical structure similar to DES to 8,000 women with no sign of breast cancer or other disease.

It is extremely likely unintended pregnancies will occur in the tamoxifen-treated group as well as in the 8,000 non-treated 'controls.'

NCI consumer information handouts warn tamoxifen "has been shown to increase fertility in premenopausal women." The trial protocol then limits the sexually active, premenopausal women it recruits to non-estrogenic methods of birth control. Barring abstinence or partner sterilization, contraceptive failure rates are high.

What is the tamoxifen risk/benefit to the developing fetus? If spontaneous abortion does not occur and a participant elects to carry her baby to term, what birth defects can be expected?

What weight in NCI's harm/benefit analyses has been given to the probability of DES-like outcomes, including creation of "Tamoxifen Daughters?"

Dr. G. R. Cunha has found tamoxifen elicits changes in the human fetal vagina comparable to those of DES. In a 1987 paper published in Human Pathology, he concluded tamoxifen is a potent estrogen in the human fetal genital tract and has "the distinct potential for eliciting teratogenic change."

Participants who incur tamoxifen-induced endometrial cancer are assured by NCI it is curable with early treatment. The 'cure' is hysterectomy, chemotherapy and/or painful, multiple biopsies. Paradoxically, the protocol does not call for biopsies as part of the routine medical monitoring for a participant although this is recommended when tamoxifen is administered to a woman with an intact uterus.

As recently summarized by Science News, which publication antedated the trials announcement by NCI, there is increasing evidence participants will run the risk of liver cancer. A copy of this report, "Tamoxifen Quandary - Promising cancer drug may hide a troubling dark side," Science News, Vol 141, p. 266, April 25, 1992, is appended for your review.

Louis Sullivan, MD
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It is extremely alarming to learn Britian's Medical Research Council withdrew its support of trials in healthy relatively young women as the proposed dose is equivalent to the dose which induced liver tumors in rats due to the manner in which tamoxifen accumulates in the body. MRC Secretary Dal A. Rees' noted "there is no dose or safety margin" and was quoted to the effect that MRC cannot justify administering the drug until potentially life-threatening side effects can be ruled out.

As reported by Science News, Dr. Gary Williams in recently completed but unpublished work found animals dosed with just 10 times the tamoxifen dose typically administered to women in one year produced precancerous lesions. Higher dose experiments produced cancers in 100 percent of the treated animals which Dr. Williams characterized as "the strongest liver cancer effect I have seen with a chemical carcinogen."

Work by Dr. David Kupfer and others published Nov. 15, 1991 in Cancer Research indicates that in the livers of rodents tamoxifen produces metabolites that react very strongly with proteins, suggesting "tamoxifen is handled in the liver like a chemical carcinogen, not like a hormone," according to Dr. Williams.

In the March 1, 1992 issue of Cancer Research Dr. Joachim G. Liehr reported finding novel DNA adducts in the livers of tamoxifen-treated rats and hamsters. Although he expected to find DNA damage, he found with repeated doses there was little repair. Liehr also was unable to prevent the formation of DNA adducts in the liver by administering either vitamin C or another drug. In previous trials with tamoxifen's close 'relative,' DES, both treatments quashed adduct formation. He concluded these findings "may make this drug a poor choice for the chronic preventive treatment of breast cancer."

Equally alarming are the findings of Dr. Stephen Zimmiski and his co-author published in Jan. 1, 1992 Cancer Research. They concluded that although tamoxifen is effective in reducing the appearance and growth of hormone-dependent tumors, "the tumors that do appear in TAM-treated animals are exclusively hormone independent. Furthermore, they grow not only more rapidly than dependent tumors in control rats but also significantly faster than untreated independent tumors, suggesting TAM may play an active role in the induction or growth of these tumors."

Dr. Zimmiski cited the work of Dr. M. Baum suggesting "the relative risk of developing contralateral breast cancer for patients taking TAM, while reduced for post menopausal women is actually increased for premenopausal women." Dr. Baum in 1991 reported data on women from his group's experience in a trial after 10 years.

Science News also reported provocative preliminary observations by Dr. Lars E. Rutqvist of Stockholm suggesting "women with hormone independent tumors do worse when they receive tamoxifen than when they don't."

Dr. Rutqvist's group has conducted one of the longest tamoxifen trials with initial enrollment beginning in 1976. As reported by Science News, the finding in a very small subgroup -- about 350 of the roughly 1,800 postmenopausal women he is following -- may be due to chance. Additional years of observation will be required to evaluate this possible effect. Overall, Dr. Rutqvist's group has found a small increased risk of developing new, primary cancers of all kinds in women receiving tamoxifen.

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What weight, if any, was given the findings of these scientists in the risk/benefit deliberations to date? What weight, if any, has been given these findings in the informed consent process?

In sum, immediate intervention is required to protect the public health.

Sincerely,

Hazel Cunningham, MPH
National Network to Prevent Birth Defects

Encs.

cc: White House

Inspector General, HHS

FDA

NCI

Congressional Oversight Committees

Congressional Women's Caucus

ICI Americas

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."

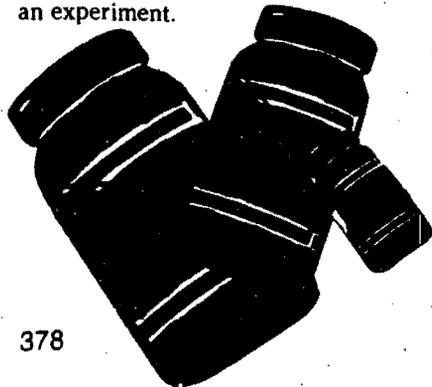
While most people "neither want nor expect to live in a risk-free world," Caplan observes, "Americans are strongly committed to the view that each person must decide what sorts of risks and hazards they want to face in the service of attaining goals they hold dear."

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 "over-emphasize 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."

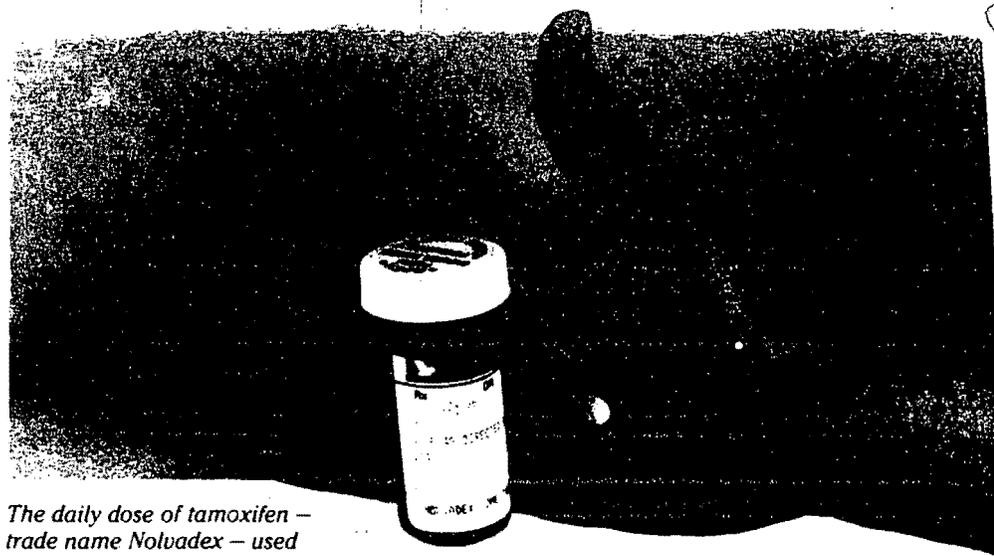
When each woman stopped taking the drug, her symptoms disappeared. "While these side effects were not life-threatening," Evans acknowledges, "they certainly threatened the quality of my life."

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 they've been prescribed and [more . . .] 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-independ-



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

"[A]ny person who is harmed . . . [by] 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."

— Leonard Schroeter

ent 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 —

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 re-consent to participate.

But “NIH has only responded to the most egregious cases,” Payne told SCIENCE NEWS. NIH “promised that Kaplan centers will be required to re-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. □

Aha...



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NIH Funds Off Critics of Tamoxifen Study

NIH officials are under fire for how to spend money on a study (see page 734), the study is being conducted in the wake of allegations that the drug tamoxifen, used in an aggressive study aimed at preventing breast cancer, might be causing liver damage. At a congressional hearing, medical scientists contended that tamoxifen could be dangerous to some patients. But NIH officials defended the study and rejected recommendations that the government stop enrolling healthy women in the clinical trials.

The study is known as the Breast Cancer Prevention Trial, and is being run under way in the United States. It is a large-scale study that aims to recruit 16,000 healthy women and follow them over 10 years to evaluate whether tamoxifen is preventing breast cancer. BCPT researchers at the University of Pittsburgh oncology center are enrolling women with a higher than average chance of getting breast cancer. They select patients based on a combination of risk, which includes the number of first relatives diagnosed with breast cancer, whether a woman has given birth to her first child, and her record of previous benign breast tumors. So far, 3,000 women have enrolled in the trials; another 12,000 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 breasts of women who had already had one breast surgically treated for cancer. BCPT researchers project a similar benefit to 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



THE UNIVERSITY OF NORTH CAROLINA
AT
CHAPEL HILL

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The School of Medicine
The University of North Carolina at Chapel Hill
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Chapel Hill, NC 27599-7000

July 16, 1993

Hazel Cunningham, MPH

P6/(b)(6)

RE: NSABP P-1: A Clinical Trial to Determine the Worth of
Tamoxifen for Preventing Breast Cancer

Dear Ms. Cunningham:

I write in response to your letter of 2 July 1993 to Dr. John Herion. I have succeeded Dr. Herion as Chairman of The Committee on the Protection of the Rights of Human Subjects.

Following receipt last year of your questions about the Tamoxifen trial, the IRB undertook an extensive internal re-review of this study. In addition, the protocol and your 1992 correspondence to Dr. Herion were sent to three outside experts for evaluation. All three are internationally recognized epidemiologists. Two are experts in breast cancer, as well. One of these declined to review it because that individual is on the National Safety and Monitoring Board for the trial. The other two endorsed the trial, and recommended no changes.

You have raised no additional concerns in your letter, and I have no further information to report. Therefore, I do not believe an appointment is needed. If, however, you do have new questions, I would be pleased to consider them.

Sincerely yours,

Ernest N. Kraybill, M.D., Chair
The Committee on the Protection
of the Rights of Human Subjects



DUKE UNIVERSITY MEDICAL CENTER

*Institutional Review Board
for Clinical Investigations*

August 9, 1993

Ms. Hazel Cunningham

P6/(b)(6)

Dear Ms. Cunningham:

I have received your letter of July 28, 1993. Duke University Medical Center policy and confidentiality principles preclude the discussion or release of information regarding clinical research protocols to parties not directly involved in the research. Accordingly, I respectfully must decline your request for a meeting.

Sincerely,

Jerome S. Harris
Jerome S. Harris, MD
Chairman - IRB



THE UNIVERSITY OF NORTH CAROLINA
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August 26, 1992

Suzanne W. Fletcher, M.D.
Editor, Annals of Internal Medicine
Independence Mall West
6th Street at Race
Philadelphia, PA 19106-1572

Dear Dr. Fletcher:

I am writing to ask you to serve as a special consultant to the Committee on the Protection of the Rights of Human Subjects of the UNC School of Medicine, to review an approved, active study that has become the subject of concern to individuals outside this university. I am asking two other individuals to serve in a similar capacity.

The research in question is the Multi-center Clinical Trial to Determine the Worth of Tamoxifen for Preventing Breast Cancer. This NCI-sponsored research got underway at UNC-CH in March, 1992. In July Dr. John Herion, former Chairman of the Committee, received a letter from Hazel Cunningham, asking that the Committee reconsider the project and that subject enrollment be suspended until that had taken place. Dr. Herion chose not to suspend enrollment but asked the Principal Investigator to address the questions raised by Ms. Cunningham and he has done so. We now are requesting special reviews before taking the project back to the full committee for reconsideration.

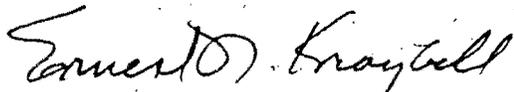
The question about which the Committee would like your opinion is this: **In light of the published literature, do the potential benefits of the research justify the risks to the subjects?** For your use in this review I am enclosing copies of the following documents:

1. The Research Protocol
2. The approved Consent Form
3. Hazel Cunningham's letter

I do not have a rigid schedule for your completion of this review but, obviously, I would like to complete the entire matter as expeditiously as possible. If, for any reason, you choose not to perform this review I would appreciate a call to that effect as soon as possible.

On behalf of the committee I wish to express our deepest thanks for your help in this matter.

Sincerely,

A handwritten signature in cursive script that reads "Ernest N. Kraybill". The signature is written in dark ink and is positioned above the typed name.

Ernest N. Kraybill, M.D.
Chairman of the Committee

cc: Dr. Herion



University of Pittsburgh

GRADUATE SCHOOL OF PUBLIC HEALTH
Department of Biostatistics

September 15, 1992

Carl M. Shy, M.D., Dr.P.H.
Department of Epidemiology
School of Public Health
University of North Carolina at Chapel Hill
CB#7400, McGavran-Greenberg Hall
Chapel Hill, North Carolina 27599-7400

Dear Carl:

Enclosed is the information concerning tamoxifen and liver tumors or other effects on the liver. Sorry for the delay in getting this to you, but it has been quite hectic the past week.

I enjoyed your presentation and the opportunity to meet with you during your visit.

Sincerely,

A handwritten signature in cursive script that reads "Carol".

Carol K. Redmond, Sc.D.
Professor & Chairperson

CKR/sg

Enclosure

Q. What is the "unpublished" data on liver tumors in rats? What about other species?

A. Data on liver cancer in rats is from studies by ICI Pharmaceutical Corporation which were presented at the FDA hearings in June 1990. They reported studies in which rats were given 5 mg/kg/day (Group II), 20 mg/kg/day (Group III), and 35 mg/kg/day (Group IV). Tamoxifen peak blood levels in these animals averaged 166 pg/ml (Group II), 664 pg/ml (Group III), and 636 pg/ml (Group IV), compared to steady-state blood levels of 159 pg/ml in women receiving 20 mg/day. Liver adenomas were observed in 1/104 control rats, 2/52 Group II rats, 6/52 Group III rats, and 9/52 Group IV rats. Cholangiocarcinomas were observed in no control or Group II rats, but in 4/52 Group III rats and in 5/52 Group IV rats. Hepatic carcinomas developed in no control rats, in 6/52 Group II rats, in 37/52 Group III rats, and in 37/52 Group IV rats.

ICI also reported on mice given 50 mg/kg/day for 15 months; while mild hepatic changes were noted in these animals, there was no evidence of hepatic neoplasia in this study. Usual doses of tamoxifen are 20 mg/day, or 0.4 mg/kg/day for a 50 kg patient.

Inter-species differences in the metabolism and toxicology of tamoxifen are marked. For hepatic tumors, this may be due to differences in concentrations of estrogen receptors in liver tissue. Eisenfeld and Aten (J Steroid Biochem, 1987) have demonstrated that the level of estrogen binding in human liver is much lower than that in liver tissue of rat, mouse, rabbit, and green monkeys.

A recent paper by Mani and Kupfer (Cancer Res. 51, 6052-6059) examining activation of tamoxifen to reactive metabolites in microsomes, implied that human liver is apparently much less active than the livers of rats in activating tamoxifen to reactive intermediates. The distinct species dependence of the effect of tamoxifen as either an agonist or antagonist makes it difficult to determine its mechanism of tumorigenesis. This makes cross species extrapolation even more difficult.

At the Biennial International Breast Cancer Research Conference (Miami, FL, March 1-5, 1987), Rattel, et al. presented two chronic toxicity studies in rats and marmosets given tamoxifen 0.6-60 mg/kg orally. They reported "TAM 60 mg/kg over 6 months induced in all tested animals severe signs of hepatic hyperplastic, preneoplastic and malignant neoplastic nodules." However, when Dr. Sieber of NCI contacted the investigators, they informed her of an error in that abstract -- namely, that the high incidence of hepatocellular neoplasia occurred in rats, not marmosets!! The authors could not reproduce their results and withdrew their manuscript from publication.

pathologic review confirmed that these were hepatocellular carcinomas. Both appear to have occurred early in the course of treatment (within the first two years on study); one was diagnosed at autopsy.

With respect to length of treatment, of the seven major adjuvant randomized clinical trials using 20 mg of tamoxifen, two have extended treatment for five years (the Scottish trial, including 661 women on tamoxifen, and NSABP-14, with 1376 on tamoxifen), totaling approximately 2000 women. The NSABP B-14 began re-randomization for up to 10 years of therapy in 1987; to date, approximately 500 women have been re-randomized with average time on study extension of 21 months. Overall the median follow-up for all seven trials thus far is 80 months, extending as long as 135 months for some groups. However, experience with "long-term" tamoxifen therapy is not limited to these two groups. As early as 1977, a smaller group of patients at the University of Wisconsin continued receiving tamoxifen indefinitely following completion of adjuvant chemotherapy for early stage breast cancer. Follow-up of this group of 43 patients currently exceeds 11 years with no reported cases of primary liver cancer (Tormey, Ann Int Med, 1987).

In the United States, clinical trials of tamoxifen in an adjuvant setting have required evaluation of liver lesions occurring on therapy. Biopsy for first recurrence has been mandatory. When a non-liver recurrence is documented, tamoxifen is stopped. When liver lesions have necessitated evaluation for recurrence, no hepatocellular carcinoma has been found. Biopsy of all liver lesions in the face of documented breast cancer recurrence at another site is not feasible.

Q. What about the recent report of DNA adducts and DNA damage?

A. A recent publication by Han and Liehr in *Cancer Research* (Vol. 52, pp. 1360-1363, March 1, 1992) describes the formation of covalent DNA adducts in Sprague-Dawley rat livers after high doses of tamoxifen. These adducts do not necessarily equate with DNA damage, which was not the subject of the investigation and no mutations were reported since rats were sacrificed four hours after one to six daily doses of tamoxifen (interperitoneal tamoxifen 20 mg/kg/day on days 1,3,6). The significance of this phenomenon has been the subject of research by Liehr, et al. since 1985 (*Carcinogenesis*, 1985; *Proc Natl Acad Sci*, 1986).

In several experimental animal systems, estrogen exposure has previously been observed to result in the formation of DNA adducts. A wide range of estrogens can participate in the process, including natural endogenous estrogens. Adduct formation occurs between DNA and an unknown estrogen induced DNA reactive compound. The experimental process is observed in liver and kidney. The details and significance of the reaction process remain a research issue. It is thought that these adducts can be stripped from DNA by normal repair processes.

The basis for Liehr's statement that with repeated administration there is "fairly little repair" is not published.

Q. What about liver cancers in humans? Has follow-up been adequate to detect these tumors?

A. ICI also reported on follow-up of 4,028 women who received tamoxifen for at least two years as participants in seven large randomized trials of adjuvant therapy for early stage breast cancer. Two patients developed liver cancers; both were participants in the Stockholm trial which prescribed high doses of tamoxifen (40 mg/day) and were the cases reported by Fornander, Rutqvist, et al. (Lancet, 1989). Independent pathologic review confirmed that these were hepatocellular carcinomas. Both appear to have occurred early in the course of treatment (within the first two years on study); one was diagnosed at autopsy.

With respect to length of treatment, of the seven major adjuvant randomized clinical trials using 20 mg of tamoxifen, two have extended treatment for five years (the Scottish trial, including 661 women on tamoxifen, and NSABP-14, with 1376 on tamoxifen), totaling approximately 2000 women. The NSABP B-14 began re-randomization for up to 10 years of therapy in 1987; to date, approximately 500 women have been re-randomized with average time on study extension of 21 months. Overall the median follow-up for all seven trials thus far is 80 months, extending as long as 135 months for some groups. However, experience with "long-term" tamoxifen therapy is not limited to these two groups. As early as 1977, a smaller group of patients at the University of Wisconsin continued receiving tamoxifen indefinitely following completion of adjuvant chemotherapy for early stage breast cancer. Follow-up of this group of 43 patients currently exceeds 11 years with no reported cases of primary liver cancer (Tormey, Ann Int Med, 1987).

In the United States, clinical trials of tamoxifen in an adjuvant setting have required evaluation of liver lesions occurring on therapy. Biopsy for first recurrence has been mandatory. When a non-liver recurrence is documented, tamoxifen is stopped. When liver lesions have necessitated evaluation for recurrence, no hepatocellular carcinoma has been found. Biopsy of all liver lesions in the face of documented breast cancer recurrence at another site is not feasible.

October 7, 1992

Ernest N. Kraybill, MD
Chairman
Committee on the Protection
of the Rights of Human Subjects
The School of Medicine
The University of North Carolina at Chapel Hill
CB #7000, MacNider Building
Chapel Hill, NC 27599-7000

Dear Dr. Kraybill:

I am responding to your request to serve as a special consultant to the Committee on the Protection of the Rights of Human Subjects of the UNC School of Medicine, to review an approved, active study that has become the subject of concern to individuals outside UNC. The study in question is the clinical trial of tamoxifen for primary prevention of breast cancer. I read the material that you sent. During the past month, I was also at the Annual Meeting of the American College of Epidemiology, where this trial was discussed, and many of concerns expressed to your committee were aired. Finally, I want you to know that prior to receiving your letter I was asked by Dr. Carol Redmond to participate on the NSABP Endpoint Review, Safety Monitoring and Advisory Committee. I had to decline because of time commitments. At that time I had not read about the trial in any detail.

The letter by Hazel Cunningham, which you sent in the background material, states many different concerns. The most important is the possibility that tamoxifen has severe side effects that make the conduct of the trial unethical. At the meeting of the American College of Epidemiology, a critique of the study included the fact that there has been no prior pilot study. However, tamoxifen has been studied in patients with very early stage breast cancer. From my vantage point, I would count such randomized trials as being equivalent to pilot studies. If



October 7, 1992

severe side effects are common, they should have been uncovered in these trials. Some argue that women with breast cancer are sick and results in such patients should not be generalized to healthy women. However, I think the women in these studies are probably closer to women who have never had breast cancer than to very sick women. This is especially true when considering that their disease-free survival rates are above 90%.

Like all well conducted trials, participants in this particular trial will be monitored for known or unexpected toxicities associated with tamoxifen. The protocol lays out a rigorous system to achieve the monitoring and an advisory committee will oversee this aspect of the trial. From my perspective, careful monitoring is at least as important as pilot studies.

The challenge to the conduct of this primary prevention trial seems to be to go beyond the particular trial in question. An underlying theme to the arguments against the trial is that some otherwise healthy women are likely to suffer adverse effects by participating in the trial and taking tamoxifen. Is it unethical to ask healthy people to participate in studies of primary prevention involving pharmaceutical products? The same generic situation existed in the Physicians' Heart Study. In that study there was a slight increase in hemorrhagic cerebral vascular accidents among physicians taking aspirin, although overall, the incidence of coronary artery disease was decreased by aspirin. Almost any pharmaceutical product has adverse effects and a main reason to undertake randomized clinical trials is to insure the benefits outweigh the adverse effects. As long as participants are told as clearly as possible what these risks and benefits might be, and as long as investigators expect the benefits to outweigh risks, and monitor carefully for adverse effects, from my perspective the study is ethical. The careful protocol and very long consent form in the tamoxifen study meet these standards.

In any study of this size and import it is important to review the track record of the investigators. Certainly, the past work of Dr. Bernard Fisher and the National Surgical Adjuvant Breast and Bowel Project had been outstanding. The protocol for the present study is of very high quality.

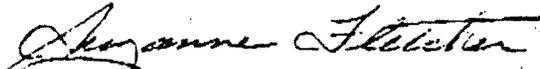
Ernest N. Kraybill, MD

Page 3

October 7, 1992

In sum, I support this study. Not only does it address a very important medical problem, but the investigators and the protocol they have produced strongly suggest it will protect the rights of human subjects involved in the study. I hope these comments are helpful.

Sincere regards,



Suzanne W. Fletcher, MD

SWF/gjl



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lll

August 18, 1993

. Hazel Cunningham

P6(b)(6)

Dear Ms. Cunningham:

Ms. Bauer, Dr. Herion and I appreciated the opportunity to discuss with you your concerns about the clinical trial of moxifen for prevention of breast cancer.

We and others on the Committee are giving careful consideration to the suggestions you gave. While we are unable to evaluate the Bush and Helzlsouer report which evidently is not yet published, we are reviewing other articles that you cited.

I enclose copies of the 1992 letters to the outside reviewers, you requested.

Thank you for your interest in this project.

Sincerely yours,

Ernest N. Kraybill, M.D., Chair
The Committee on the Protection
of the Rights of Human Subjects

Ms. Bauer
Dr. Herion