THE CANCER LETTER

Vol. 21 No. 41
Oct. 27, 1995

Price $255 Per Year US
$280 Per Year Elsewhere

P.O. Box 15189 Washington, D.C. 20003 Telephone 202-543-7665

Heart Institute Withdraws Sponsorship Of Breast Cancer Prevention Trial

The National Heart, Lung and Blood Institute has withdrawn its support for the Breast Cancer Prevention Trial, the large study of the potential of the drug tamoxifen to prevent breast cancer, heart disease and osteoporosis.

In a letter earlier this month, NHLBI said it would provide no further funding, stating that the enrollment of women over age 55 was too low to

(Continued to page 2)

In Brief

Pinedo To Receive Josef Steiner Prize; Lurie Cancer Center Gets $2.5M Donation

HERBERT PINEDO, professor of medical oncology, Free Univ. Hospital of Amsterdam, the Netherlands, will receive the Josef Steiner Prize on Nov. 3 at a ceremony in Berne, Switzerland. The prize, awarded by the Josef Steiner Foundation, recognizes Pinedo's work on the development of anti-cancer drugs and the establishment of the New Drug Development Office of the European Organization for the Research and Treatment of Cancer (EORTC), which coordinates drug development within the EORTC. . . . **ROBERT H. LURIE** Cancer Center of Northwestern Univ. received a gift of $2.5 million from the DiMatteo Family Foundation in honor of Dominick DiMatteo Jr., founder of the Dominick's grocery store chain, who died of cancer two years ago. The 17 laboratories adjoining the center's administrative offices will be named the Dominick DiMatteo Cancer Research Laboratories. Most of the gift will establish a permanent endowment, the income of which will be used to support the center's research infrastructure. The remainder will be used to meet the center's immediate needs and to upgrade laboratory equipment and renovate the facility. . . . **RONALD HERBERMAN**, director of the Univ. of Pittsburgh Cancer Institute, has been appointed associate vice chancellor for research, health sciences, at the Univ. of Pittsburgh. In the new position, Herberman will be responsible for coordinating and facilitating biomedical scientific research programs for the university. He will continue to direct the NCI-designated comprehensive cancer center. . . . **SUSAN G. KOMEN** Breast Cancer Foundation has presented the 1995 Brinker International Awards for Breast Cancer Research to two scientists. **Helene Smith**, director, Geraldine Brush Cancer Research Institute, Univ. of California, San Francisco, received the Basic Research Award. **C. Kent Osborne**, chief of medical oncology, Univ. of Texas Health Science Center at San Antonio, received the Clinical Research Award.

California Weighs Listing Tamoxifen As Carcinogen
. . . Page 4

MIT Researcher Ingested P-32; NRC Investigating
. . . Page 4

Letter:
Cancer Centers Need Ingenuity To Continue Clinical Research
. . Page 5

Program Project Guidelines Available
. . . Page 6

RFA Available
. . . Page 6

Too Few Women Over 55 Enrolled In Study, NHLBI Says

(Continued from page 1)

determine in reasonable time whether tamoxifen would reduce the risk of cardiac events, officials informed NCI.

"When this project was conceived and developed, it was expected than over 16,000 women would be recruited by June 1994 and that at least two-thirds of them would be 55 years or older," NHLBI Director Claude Lenfant wrote in a letter to NCI Director Richard Klausner. "As younger women have very few cardiovascular events, reaching the recruitment goal of at least 10,000 women aged 55 or older is critical."

So far, 11,500 women have enrolled, and fewer than 5,000 are over 55, Lenfant wrote in the memo dated Oct. 5. "It has become apparent that the study does not have the power to provide significant data regarding the cardiovascular clinical end points," Lenfant wrote.

A copy of the letter was obtained by **The Cancer Letter.**

Since the start of the trial in 1992, NHLBI has transferred over $3 million to NCI and was expected to transfer another $5 million for its share of the trial.

NCI plans to spend $60 million on the 10-year study.

NCI Will Pick Up Costs

NHLBI's pullout is likely to mean that NCI would have to pay for the EKG and blood lipid studies that NHLBI was to have funded, NCI officials said.

"The Breast Cancer Prevention Trial is alive and well, and it is critically important that we complete randomization as quickly as possible," Leslie Ford, chief of the NCI Community Oncology and Rehabilitation Branch, said to **The Cancer Letter.** "We still consider the cardiovascular benefit [of tamoxifen] to be important to the risk-benefit calculation and we will continue to follow women for cardiovascular end points."

In smaller studies of breast cancer survivors, tamoxifen has been shown to protect women from recurrence as well as to lower the level of lipids in the blood, Ford said.

The randomized, placebo-controlled BCPT was designed to determine whether taking tamoxifen for five years reduced the incidence of breast cancer, heart disease and osteoporosis in healthy women at high risk of breast cancer.

The trial was designed to demonstrate a 35% to 40% reduction in breast cancer and heart disease, a 30% to 33% reduction in osteoporosis, and an overall mortality reduction of 30% to 35% for women taking tamoxifen (**The Cancer Letter**, May 8, 1992).

"There is no question that tamoxifen lowers lipids; the question is whether it reduces the incidence of cardiovascular events," Ford said.

"The older the women entering the trial, the faster you would see the effect. The fact that younger women are entering means it would take longer to reach the cardiovascular endpoint," she said.

In the memo to Klausner, Lenfant said that only 3% of the women enrolled in the study were minorities, and most participants were well-educated. "It was expected that these women would include a significant number of minorities and that they would be representative of all socioeconomic strata," Lenfant wrote.

The NHLBI withdrawal comes one year after the Breast Cancer Prevention Trial resumed enrollment following the controversy over the National Surgical Adjuvant Breast and Bowel Project, the cooperative group conducting the BCPT.

In April 1994, NCI officials halted enrollment in all NSABP studies, including the BCPT. In addition, NCI ordered that informed consent forms for the BCPT be rewritten to reflect new information about the risk of endometrial cancer for women taking tamoxifen. A revised protocol for the trial was finalized in October 1994, and randomization resumed.

Altogether, the controversy created about 6-month hiatus in enrollment, Ford said.

THE CANCER LETTER

Editors: **Kirsten Boyd Goldberg**
Paul Goldberg
Founder & Contributing Editor: **Jerry D. Boyd**
P.O. Box 15189, Washington, D.C. 20003
Tel. (202) 543-7665 Fax: (202) 543-6879
E-Mail: 73322.2044@compuserve.com
Subscription $255 per year US, $280 elsewhere. ISSN 0096-3917. Published 48 times a year by The Cancer Letter Inc., also publisher of The Clinical Cancer Letter.

Lawrence Friedman, director of the NHLBI Div. of Epidemiology and Clinical Applications, said the NSABP controversy was not a factor in the Heart Institute's decision to pull out of the trial.

"This has nothing to do with NCI or the merits of the study for breast cancer," Friedman said to **The Cancer Letter**. "We had hoped that we could work with NCI in the study, but it became clear over the past year that for obvious reasons, they were selecting women at high risk of developing breast cancer, but those women are not necessarily at high risk of developing heart disease."

Women under the age of 55 have very few cardiac events, Friedman said.

"When only 40% of the women are over 55, there are just not going to be enough cases of heart disease over the next six to eight years to see if tamoxifen does any good," Friedman said. "It would mean continuing the study beyond the time the Cancer Institute plans to, and if they got an answer on the breast cancer question, they wouldn't continue the study."

NHLBI has no plans to conduct further clinical trials of tamoxifen, Friedman said.

If that study is ever attempted, NHLBI would have difficulty randomizing the study's participants, he said.

"If tamoxifen is shown to be beneficial for breast cancer, then those women would reap whatever other benefit there might be for heart disease," he said. "If tamoxifen shows no benefit for breast cancer, then there are lots of other drugs for lowering lipids.

"The question was, is there some extra benefit for tamoxifen?" Friedman said. "It is still an interesting question, but not every study turns out the way you intend."

"A Colossal Missed Opportunity"

Victor Vogel, a BCPT investigator at M.D. Anderson Cancer Center, and a member of the study's steering committee, said he did not know about the Heart Institute's decision until contacted by **The Cancer Letter** this week.

"Eliminating the cardiovascular end point takes something away—diminishes the scientific value of the trial," Vogel said. "We aren't going to know if tamoxifen lowers cardiovascular risk. We aren't going to have a chance to prove a modest benefit."

For postmenopausal women who have had hysterectomies, and therefore have no risk of endometrial cancer, tamoxifen might be preferable to estrogen, since estrogen is known to increase the risk of breast cancer, Vogel said.

"This question should remain a priority in postmenopausal women, and it needs to be confirmed in healthy women: whether to give estrogen or tamoxifen," he said. "It would represent a colossal missed opportunity if we did not get an answer to the question."

The BCPT may be able to get an answer to the question of cardiac benefit if the study were to follow women for 10 to 15 years, as opposed to the two year followup originally planned, Vogel said. "We do have those women identified and we can follow them. That's something that shouldn't be lost for lack of funding."

Even if most of the 4,000 women needed to complete enrollment were over 55, the numbers would be inadequate to reach the statistical power specified in the trial, Vogel said.

"There was no way to anticipate this in the beginning," Vogel said. "Many of us thought we would enroll few premenopausal women. In fact, the trial attracted more premenopausal women because they have more anxiety about breast cancer."

Younger women tend to greatly overestimate their risk of breast cancer, while older women tend to vastly underestimate their risk of both breast cancer and heart disease, Vogel said.

Another problem, minority enrollment, has plagued the trial from the start, Vogel said. "Many sites have done everything but stand on their heads to bring minority women in, but we have not identified the proper recruitment strategies, despite national and local efforts to include minority women in recruitment issues and breast cancer prevention and screening issues."

"Healthy Volunteer" Effect?

When the BCPT was begun in 1992, then-NCI Director Samuel Broder said he believed the cardiac benefits of tamoxifen could cause the trial to end early.

"I personally believe that this study could require an early stopping point on cardiovascular disease due to heart attacks [in the placebo group]," he said (**The Cancer Letter**, May 8, 1992).

"That's what we were all hoping for—that's what we saw in studies in breast cancer patients," Vogel said. "Many of us felt that there might be an early stopping because of the cardiovascular event rate."

The BCPT may be suffering from the "healthy volunteer" effect, Vogel said. "Whenever you get volunteers, you get healthy people,and you tend to have a lower event rate," he said. "It may be that the event rate is low."

California Weighs Listing Tamoxifen As "Carcinogen"

The California Environmental Protection Agency earlier this month held a hearing on the incidence of endometrial cancer deaths associated with tamoxifen.

The hearing was requested by NCI in an effort to convince the California authorities to reverse an earlier decision to place tamoxifen on the list of recognized carcinogens.

The state's EPA compiles the lists of carcinogens and developmental toxicants under the Proposition 65 law. Products placed on the lists have to be labeled as carcinogens or developmental toxicants.

Last May, the Cancer Identification Committee, an advisory group to the state Office of Environmental Health Hazard Assessment, recommended placing tamoxifen on the list of carcinogens.

However, in an unusual move, OEHHA deferred placing tamoxifen on the list of carcinogens.

"Just prior to publishing a notice of intent to list tamoxifen, OEHHA received a call from NCI, expressing concern over the interpretation of the significance of the increased incidence of endometrial cancer," state officials said in a statement.

As a result of the call, the OEHHA executive staff decided to defer listing the agent pending another hearing, which was held on Oct. 10.

No date has been set for CIC action on the measure, said George Kostyrko, a spokesman for OEHHA.

Tamoxifen has been on the state's developmental toxicants list since 1991.

MIT Researcher Ingested P-32; Case Similar To NCI Exposures

A postdoctoral fellow at the Massachusetts Institute of Technology last summer ingested a 579-microcurie dose of Phosphorus-32, the institute acknowledged last week.

The incident, which occurred in August, appears to bear striking similarities to the contamination of a group of NCI employees, including one pregnant woman, who ingested the highest dose.

In both cases, the victims ingested P-32. In both cases, the individuals affected were post-doctoral fellows in high-pressure laboratories.

Though MIT officials have not identified the researcher who was contaminated by the agent, press reports confirmed by several sources identify him as a postdoctoral fellow from China. In the NCI incident, too, the highest exposure to radiation was sustained by a Chinese postdoctoral researcher.

Moreover, the cases occurred only six weeks apart. At NCI, the exposure occurred on June 28, at the Div. of Cancer Treatment Laboratory of Molecular Pharmacology (**The Cancer Letter**, Oct. 20). At MIT, the exposure occurred on Aug. 14, and was discovered during a routine check five days later.

Because of the apparent similarity between the cases, the Nuclear Regulatory Commission gave the MIT case a higher priority than it had given to the NCI case earlier, Joe Gilliland, the commission's director of public affairs, said to **The Cancer Letter**. "We don't know if there is any connection, except for the obvious: personal contamination with P-32," Gilliland said.

While the NCI incident was investigated by an "augmented inspection team" sent from the regional office, the MIT incident is being investigated by an "incident investigation team" sent from the NRC headquarters, Gilliland said.

According to Gilliland, the investigators sent to NCI examined the Institute's safety and security measures. By contrast, the team sent to MIT will examine both the compliance by the licensee and the problems of regulatory oversight.

The investigators were expected to complete their work at MIT and announce their preliminary findings later this week, Gilliland said.

In the MIT case, the exposure went undiscovered for five days and was found during a routine Geiger counter check on Aug. 19, the institute said in a statement dated Oct. 16.

"Investigators have thus far been unable to determine whether the radioactive material intake was accidental or deliberate," the statement said.

According to the institute, the assessment of the scientist's exposure began immediately. "The researcher was examined by the Medical Department [on Aug. 19] and then released to go home," the

institute said in a statement. "He subsequently was seen by the Medical Department and by Environmental Medical Services a number of times.

"No physical health effects were noted," the statement said.

Following the incident MIT's Radiation Protection Office temporarily took control of radioactive materials in the laboratory "to take inventory of the materials and account for their use," the statement said.

MIT did not release the name of the postdoctoral fellow and did not identify the laboratory where he was employed.

However, the journal Nature reported in the issue of Oct. 19 that the scientist was working in the laboratory of the Nobel laureate Susumu Tonegawa. Nature identified the scientist as Yuqing Li.

According to Nature, MIT reported the incident to NRC and issued a public statement on the incident after the journal notified the institute of its plans to publish the story on the exposure.

Institutions licensed to handle radioactive materials are obligated to notify NRC about all exposures exceeding 600 microcuries.

The researcher's intake of 579 microcuries falls within "the permissible one-time and annual limit of 600 microcuries of P-32 for a person working with radiation," MIT said in a statement.

An attempt to reach Li was unsuccessful. Tonegawa's laboratory referred press inquiries to the MIT news office. MIT spokesman Kenneth Campbell declined to comment on the Nature story.

"Not Connected To Our Case"

Lynne Barnabei, an attorney for the NCI researchers, said she knows of no connection between the NCI case and the MIT case.

"He is not connected to our case at all," Barnabei said of the MIT researcher.

In the NCI case, the pregnant researcher, Maryann Wenli Ma, said she was exposed to P-32 as a result of ingesting leftover food that was kept in the office refrigerator.

According to NIH officials, Ma received 500 microcuries of P-32. However, an outside expert hired by the researcher disagreed, saying that Ma received about 1,000 microcuries.

Besides Ma, 25 NIH employees were exposed to radiation as a result of drinking from a water cooler that was also contaminated with P-32.

Ma and her husband Bill Wenling Zheng, a postdoctoral researcher at the same laboratory, have petitioned NRC to revoke the NIH license to handle radioactive materials.

Letter to the Editor

Centers Will Need Ingenuity To Continue Clinical Research

To the Editor:

I was deeply troubled by the headline of the Sept. 29, 1995 issue of **The Cancer Letter** ("Survey of Centers Finds Little 'Crisis' In Clinical Research").

Indeed, the crisis is in health care delivery and its effect is chronological and occurs (in about this order) on patient care, physician life and income, hospital solvency, academic medicine, and finally, clinical research. The impact of managed care on the first three areas was recently well covered by the Los Angeles Times. I suggest that anyone seriously interested in the topic should order and read the series of five articles (Part A, Aug. 27, 28, 29, 30 and 31). If you haven't really heard it before, the articles in toto will chill your bones.

A critical feature in examining the impact of changes must be the recognition that the level of managed care penetration various enormously, based largely on geography, and its impact is felt in different ways dependent on the level of penetration: 10%, phase I, no concern; 25%, phase II, patient census falls, real concern a la M. D. Anderson; 50%, phase III, cut rate contracting, census falls, panic; 75%, phase IV, capitated care, primary care physicians drive the system, desperation.

Most academic centers, because they are large, will survive to phase IV. Whether they survive beyond this phase as viable academic medical centers capable of doing clinical research depends on ingenuity and the exercise of creative new ways to do things as well as tremendous personal and financial sacrifices.

Remember, the intent of capitated managed care (phase IV) is to put 30% of all subspecialists out of a job by the year 1999. The oncologist, particularly the medical oncologist, may well be on the way to becoming extinct early in the next century. We are already seeing the physician gatekeeper holding onto cancer patients or referring them for one consultation: "Tell me what chemotherapy to give." Many schools in California are restructuring to give their internal

medicine residents dedicated training in the subspecialties, so that they, in effect, become broadly trained generalists.

But what about clinical cancer research?

What we see are: fewer referrals by HMOs, more self-referrals, more staff and physician time spent with more and more paperwork, incipient inertia developing under this burden, more litigation (involving HMOs), continued tightening of the screws and eventually fewer patients on clinical trial.

Recently our county launched OPTIMA, a managed care system for Medicaid funded patients. The rate of reimbursement—$56 per person per month for all costs. For those of you familiar enough with managed care to know, that number should make you feel queasy indeed.

The effect of the changes in health care delivery have been profound on those academic centers in geographic areas where managed care sufficiently has penetrated. Those centers whose geographic areas have not yet been penetrated should be grateful and should spend the time remaining preparing themselves for the inevitable before the tidal wave hits.

The sea change is inevitable as managed care is now a big business with huge profits being carved out of the hides of patients, health care providers, and medical centers. For-profit managed care businesses have been among the most successful of all companies on the stock exchange in the last two to three years. The only thing that drives most of them is green.

Only two things will slow them down. Well-prepared medical centers working closely with their physicians to form their own managed care network, or demand for quality from those managed care systems they work with. And, patient-initiated litigation seeking improved access and quality will force change as well.

For those of us who have been inundated, we are in phase VI or VIII and swimming very hard. There are stories to tell about what comes next, but many of my colleagues, unpenetrated, would find them not believable or too scary to contemplate seriously.

Frank L. Meyskens Jr.
Director
Clinical Cancer Center
Univ. of California, Irvine

*Has managed care precipitated a crisis in clinical cancer research? **The Cancer Letter** invites your accounts and opinions.*

Program Project Guidelines Available From NCI

NCI announces the availability of updated guidelines for program project (P01) applications that are likely to be assigned to the NCI for review and funding.

Investigators anticipating submission of a P01 should request a copy of the guidelines, which explain NCI policies and procedures relating to the preparation, submission, and review of P01 applications.

Inquiries: Investigators may obtain copies of the guidelines and referrals for information regarding programmatic interests in such applications from: Referral Office, Div. of Extramural Activities, NCI, Executive Plaza North Room 636, 6130 Executive Blvd. MSC 7405, Bethesda, MD 20892-7405, tel: 301/496-3428, fax: 301/402-0275, e-mail: friedbergt@dea.nci.nih.gov

RFA Available

RFA CA-96-001

Title: **Prevention Clinical Trials Utilizing Intermediate Endpoints And Their Modulation By Chemopreventive Agents**

Letter of Intent Receipt Date: Nov. 21

Application Receipt Date: Jan. 18

The NCI Div. of Cancer Prevention and Control invites applications for cooperative agreements (U01) to support clinical trials that are directed toward examining the role of various chemopreventive agents and/or diet in the prevention of cancer. This is a follow-up to earlier RFAs that requested grants, and then later, cooperative agreements in this area. Approximately $1.5 million in total costs for the first year will be committed to specifically fund applications submitted in response to this RFA. It is anticipated that three to five awards will be made. The total project period may not exceed five years. The earliest feasible start date for the initial awards will be Sept. 30, 1996.

Inquiries: The RFA may be obtained electronically through the NIH Grant Line (data line 301-402-2221) and the NIH GOPHER (gopher.nih.gov) and by mail and e-mail from Marjorie Perloff, DCPC, NCI, Executive Plaza North Suite 218, Bethesda, MD 20892, tel: 301/496-4664, fax: 301/402-0553, e-mail: PerloffM@dcpcepn.nci.nih.gov