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# HAWAII MEDICAL JOURNAL

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## Highlights of the HMA Council Meeting of March 5, 1993

The HMA Council met on 5 March 1993. Members present were: J Chang, A Don, J Spangler, S Wallach, C Kam, R Stodd, L Howard, C Lehman, B Shitamoto, R Lee-Ching, M Cheng, R Goodale, HKW Chinn, P Chinn, HH Chun, W Dang Jr, P Hellreich, M Shirasu, C Wong, C Kadooka, P Kim, J Betwee, H Percy, T Smith, G Goto, J Lumeng, W Chang, N Winn, A Kunimoto, J McDonnell, WWL Dang; F Reppun, Editor, HMJ; Legal Counsel Vernon Woo; Auxiliary representative, Penny Paik Thune; medical student M Rivera and guest Director of the DOH J Lewin; HMA Staff: J Won, L Tong, J Asato, and A Rogness (recording secretary).

President Dr Jeanette Chang and Executive Director Jon Won joined AMA in Washington, DC, during spring break for a "New Partnership" with Congress and President Clinton; physicians are asking government to collaborate on joint efforts to address the health care access and health care reform issues.

Treasurer John Spangler reported the HMA will not experience a deficit for 1992.

The HMA Auxiliary reported on its projected May 23, 1993, Fashion Show at the Sheraton Waikiki with loads of physicians as models as well as their spouses. It pleads for physicians to buy tickets to benefit the Waianae Coast Comprehensive Health Center Scholarship Fund for health care education.

The Council adopted a 5-year dues structure pilot program for young physicians (already defined) with 20% added each year of regular membership until full dues are reached by the 5th year as an incentive for younger physicians to join and remain within organized medicine.

There was much discussion about the proposed Hawaii Health Commission by the legislature, wherein a governmental body will collect data, including specific and individualized data on providers for analysis and dissemination to the public so the public can choose health care services wisely. HMA opposes the current bill but would support data collection and public education on a joint and collaborative public/private-sector approach.

The Council approved financial support for a Forensic Science Fair to be held at the Honolulu Police Department in conjunction with the Department of Education.

It also approved mailing an educational letter to physicians statewide to apprise them of the quality-of-care issue and provide new data received regarding nurse prescriptive authority.

Legislative issues show HMA positions being upheld in a vast majority of cases, including (at time of this writing) these bills that are still alive: 1) blood alcohol level to be changed from 0.1 to 0.08; 2) Involuntary testing for HIV if the patient's blood is already drawn and if exposure to health care workers has occurred; 3) A family practice residency program at Hilo; 4) The County State Hospital to be autonomous; 5) An increased tax on cigarettes. Legislation on prescriptive authority by nurses is dead for this year.

The Council was reminded that Distinguished Medical Reporting Awards will be given at a gala banquet on April 24, 1993; all councilors should sign up for this event.

Fred Holschuh  
HMA Secretary



### Tamoxifen: Pro and Con

The following, submitted to the *Journal* by Steven Moser MD of Maui, was sent to us as a letter-to-the-editor. Under our mandate to have manuscripts peer-reviewed prior to publication, we received mixed responses. It was generally agreed that the subject matter warranted free and open discussion as presented to our readers.

However, since the National Cancer Institute (NCI) has already formulated the program of the National Surgical Adjuvant Breast and Bowel Project (NSABP); and since it has been endorsed for Hawaii by the Cancer Research Center of Hawaii (CRCH), we thought it best to juxtapose this article with a response

from Virginia Pressler MD of Honolulu, who is the local State Project Director for CRCH, in the same issue of the *Journal*. Moser is on the con side, Pressler on the pro side.

Consequently, instead of publishing these points of view as letters-to-the-editor, we have put both under a new heading of "Controversy".

We trust our readers will be interested and will derive benefit from these two presentations in terms of being able to communicate better with their patients as the latter challenge their physicians.

The Editor



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## Long-term care (LTC)

The HMA's Senior Physicians Committee started the year by discussing LTC. At its January 7 meeting, the 20 or so members under its chair, Charlotte Florine, listened to guest speaker Calvin Ichinose, Administrator of Skilled Nursing Facilities at Queen's Medical Center (QMC). On February 4, the guest speaker was Randy Havre, Chair, LTC Financing Board, of the State's Family Hope Program.

Calvin Ichinose gave us some important figures: We have 40 facilities on Oahu, a total of 3,400 beds. The national average is 56 beds per 1,000 population; in Hawaii it is 26 beds, most of them home care. Eighty percent of these beds hold Medicaid clients. SHPDA allowed the establishment of 772 new beds in 1993, of which 712 were supposed to be built/made available in the Honouliuli area. However, the Sierra Club's \$42 million suit against the City to force it to elevate the Honouliuli sewage treatment plant to a secondary level has stymied any further expansion of housing in the area.

QMC — a 500-bed hospital — has applied for a Conditional Lease Permit to build 180 skilled nursing facility beds, but this has been denied so far. QMC has 120 beds tied up by LTC patients as an average at an annual loss in revenue of \$1.2 million.

Ichinose pointed out that the OBRA regulations under the federal law are so demanding, without a thought to the resultant costs of the program, that there is not much incentive for private entrepreneurs to build LTC facilities.

Randy Havre explained why he accepted Governor Waihee's request to serve on the Financing Advisory Board. It was with the provision that Havre would be free to express his opinion as to whether the Family Hope Program was worth the effort or not (the members are all volunteers). Havre had spent a total of 100 hours of work on it so far, together with Harlan Cadinha.

They attacked the challenge by projecting it 75 years ahead, and formatted 11 legislative guidelines rather than 3 or 4 scenarios.

As well as we could catch Havre's rapid-fire expression: (1) Every tax payer in Hawaii (some 600,000) would be taxed according to adjusted gross income—making for a broad base of contributors. (2) Benefits would be vested in a time frame: 50% at once and an added 10% each year times 5, at which full benefits

would ensue. (3) In the long-term, premium payments at 0.025% annually would cease after 40 years. (4) Incoming new residents would be included in the tax-base. (5) Community-based home health care would be promoted, starting at an ADL level of 2. (6) Participation would be on the basis of individual social security numbers, not by couples or families. (7) Maximum co-payment to discourage over-utilization would be limited to a ratio of 80/20 and the cap on such out-of-pocket contributions would not exceed an amount comparable to what one would have to pay in the way of an annual premium for private LTC insurance.

Havre made a good presentation; he also said that John Wilkens, the Program's actuary, was well qualified and was highly rated by *Consumer Reports*. He said the program would be sent out on bid to various private insurers who have the means and expertise to assess the financial aspects of the program.

In answer to the Chamber of Commerce of Hawaii's objection that the program would cost the taxpayers of Hawaii 15% to 30%, instead of 0.025% as envisioned overall, Havre explained that the savings to the State further along in the way of reduction of the costs of LTC for Medicaid clients would result in the tax being kept low (does this actually mean that the people are to pay early on and the State to be reimbursed later? Is that fair ?/Ed).

Our own Walter Quisenberry followed up by citing and reading excerpts from the cover story on LTC in the magazine *Hawaii Investor*. Readers are encouraged to read a copy: the article by Lucy Jokiel is well-written.

To editorialize briefly: It is our view (not necessarily that of the HMA, which has not stated its case so far) that the matter of financing LTC falls far behind the urgent need to provide universal access to medical care, locally as well as nationally. We feel that LTC is very much a personal problem—for individuals to foresee and to fund on their own while they are still young and productive, either by savings and investment or by purchase of insurance while the premium is low. We do not feel it is a societal problem as compared with the access to medical care.

And, the 2 should not be combined in considering legislation to effect universal access.

The Editor

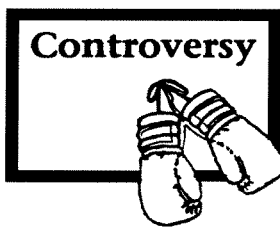
## Lipomas

There is very little in the literature of the past 12 years that has been written on lipomata, as a recent Med-Line search has revealed.

That, together with a suggestion from a former member of the HMA Publications Committee, proposing that we establish a regular column in the *Journal* and name it "Tricks of the Trade",

wherein physician readers might volunteer to announce techniques that work, offbeat items that might save time and effort on the part of the physician and also save costs to the patient or his or her insurer, makes us think that Reinking and Parsa's brief article in this issue of the *Journal* might be of interest to our readers.

The Editor



...a matter for doctor/ patient decision.

## Tamoxifen: A caveat on the con side of the debate

Steven M Moser MD\*

Having reviewed the recent literature on the anti-estrogen drug tamoxifen, I am concerned about the recently initiated National Cancer Institute (NCI) clinical trial to determine the worth of tamoxifen for preventing breast cancer in healthy women, the NSABP (National Surgical Adjuvant Breast and Bowel Project) Protocol P-1. This \$60-million trial will enroll 16,000 women: half placebo controls, and the other half tamoxifen subjects. The latter group includes all women over the age of 60, and women between the ages of 35 to 59 whose minimum 5-year risk is at least that of a woman >60 (calculated by a composite mathematic model weighing family history, age of menarche, number of relatives with breast cancer and other factors).

While there does not appear to be a problem with enrolling women with the highest risk of developing breast cancer in such a trial (those with the diagnosis of lobular carcinoma in situ or those who have both a mother and a sister with breast cancer), the current study design of subjecting all 60-year-olds as well as younger, lower-risk women to prolonged tamoxifen exposure may not be warranted, based on several recent studies that have been released since the protocol was completed. This may be especially true for Hawaiian and oriental populations for reasons that will be explained.

Tamoxifen was chosen for this trial because it has been shown in several large studies<sup>1-4</sup> to reduce the recurrence of contralateral breast cancers in women who have had estrogen receptor-positive (hormone sensitive) primary breast cancer. These studies were all short-term, actuarial trials in nature, looking only at survival rates and disease-free intervals and did not routinely include biopsy or autopsy examinations of study and control groups. This may have led to an underestimation of new, non-metastatic malignancies that were either missed or mistaken for metastatic breast cancer.

This is an important consideration because of the animal and human studies that have demonstrated tamoxifen to be a cancer promoter in uterine, hepatic and estrogen receptor-negative breast cancers. In the Swedish study<sup>3</sup>, there was an excess of nonfatal endometrial cancers in the test group (1.4% tamoxifen group vs 0.2% control group). There are several case reports of uterine cancer in women taking tamoxifen<sup>5-7</sup>. When

combined with the new evidence that tamoxifen is a teratogen in the developing female genital tract, with strong similarities to diethylstilbesterol<sup>8</sup>, these studies predict a danger to both postmenopausal and premenopausal women that is not sufficiently addressed in the current NSABP P-1 Protocol and its informed consent form (1/24/92 version).

Postmenopausal women who have not had hysterectomies are required by the protocol to have pelvic examinations at initiation of the study and every 12 months thereafter. The study protocol states that in the case of menstrual irregularities which persist in the face of normal pelvic exams, the patient should undergo further testing such as hysteroscopy or dilatation and curettage (D&C). These expensive procedures, as are all office exams, lab tests and procedures, are charged to the patient, which might prove to be a deterrent to careful follow up for uninsured or indigent patients. The possibility that endometrial carcinoma may develop in patients without obvious menstrual irregularities until late in the course of their cancer is not addressed. Untreated uterine carcinoma is a major cause of morbidity in women who have it.

Premenopausal women in the study are advised on the one hand not to become pregnant, as tamoxifen is a human teratogen, and on the other hand, they are told not to use birth control pills because estrogens will interfere with the action of tamoxifen. It is well-known that barrier methods of birth control have a high failure rate<sup>9</sup>, as does the rhythm method. The consent form also discourages the use of IUDs because they promote menstrual irregularities. These factors, when coupled with the clomiphene-like propensity of tamoxifen to increase fertility, may increase the likelihood that premenopausal women may indeed find themselves pregnant while taking tamoxifen. At this point, the protocol and the informed consent form also fail to provide funding or moral and legal support for the abortion which would presumably be indicated.

Tamoxifen is a known liver carcinogen in rats. At doses of 35 mg/kg/day, it caused hepatocellular carcinomas at between 31 and 37 weeks of use<sup>10</sup>. Other studies have shown carcinogenicity at lower doses. At an average of 40 kg to 60 kg weight for an average 60-year-old woman in the study, the margin of safety is somewhat less than a factor of 100, which is the accepted standard of protection for humans in the face of a known carcinogen. The half-life of tamoxifen is longer in humans than in rats, which may further compromise this safety factor. The tumors in rats are highly malignant, perhaps explained by the finding of the induction of covalent DNA adducts with tamoxifen, with mutations occurring within a few days of starting the drug<sup>11</sup>.

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(Continued) ►

## TAMOXIFEN: A CAVEAT ON THE CON SIDE OF THE DEBATE

(Continued from page 87)

The Swedish tamoxifen trial<sup>3</sup> found 2 liver carcinomas in its study population, which was several-fold higher than the average incidence of this tumor. As mentioned before, other studies have either not looked for it or may have mistaken it for metastatic breast cancer. Very few healthy women have taken tamoxifen for more than 5 years, and therefore very little adequate human data have been obtained to conclude that tamoxifen is or is not hepatotoxic in humans<sup>12</sup>. The NSABP P-1 protocol does not call for specific liver function testing but mentions only "chemistry tests" to be done every 6 months.

In other work published this year and not referenced by the study protocol is a work by Zimmisky et al in which tamoxifen was found to promote growth of dimethylbenzanthracene-induced, hormone-independent tumors in the rat mammary gland. While growth of hormone-dependent tumors was, as expected, decreased significantly in the tamoxifen group, hormone-independent mammary tumors developed during tamoxifen administration and displayed "...extremely rapid growth"<sup>13</sup>. These tumors grew 3 times faster than similar hormone-independent tumors in control animals, as well as significantly faster than hormone-dependent tumors. In the discussion of this paper, the authors point out that tamoxifen has been shown in other studies merely to delay the onset of hormone-sensitive tumors.

Fentiman, of the Royal Marsden Hospital in London, points out that tumors in younger women are likely to be receptor-negative, and goes on to say, "If, however, the malignant phenotype ie receptor-positive is inhibited for say 2 to 5 years, with subsequent emergence of a more aggressive hormone-independent variant, the prognosis might be worse if no tamoxifen had been given"<sup>14</sup>.

In Hawaii, this consideration of induction of estrogen receptor-negative malignancy carries greater significance because of the greater prevalence of estrogen receptor-negative disease that our Japanese population exhibits<sup>15</sup>.

Other considerations involve the significant incidence of ocular toxicity and thrombophlebitis in women receiving tamoxifen. In a prospective study of 63 women receiving low dose (20 mg/d), long-term tamoxifen, 6.3% of the subjects developed retinopathy and/or keratopathy from between 10 to 35 months of initiation of therapy<sup>16</sup>. Unfortunately, the protocol and the informed consent do not mention the probability of ocular disease development at low doses of tamoxifen to either the investigators or to the prospective study enrollees, and does not recommend or provide for either routine ophthalmological exams or slit-lamps, both of which should be mandated based on this and other information.

In the NSABP B-14 Trial, 3 of 1,414 women in the control group and 18 of the 1,403 women in the tamoxifen group developed deep venous thromboses or embolism. Two deaths occurred from pulmonary embolus<sup>1</sup>. If this incidence is extrapolated to 8,000 healthy women, some of whom have an increased statistical risk of developing breast cancer, we can expect approximately 80 of them to develop deep venous thrombosis or an embolic event, and around 9 or 10 of them to die of massive pulmonary embolus.

In addition, there is ample evidence that tamoxifen causes significant side effects in those who take it over the long term. In

a recent study of 140 patients receiving adjuvant tamoxifen therapy, 17% had moderate to severe vasomotor symptoms and gynecologic symptoms in 4%<sup>17</sup>. In their conclusions, the authors state, "...this study suggests that in a population of postmenopausal women with a history of axillary node negative breast cancer, almost half of the tamoxifen-treated women will report moderate or greater levels of symptoms." Premenopausal women may have an even higher incidence of side effects. How this will affect their compliance with a long-term, preventive tamoxifen trial remains to be seen.

In conclusion, while I do not have a problem with the use of tamoxifen for the prevention of breast cancer in the older, higher-risk patients, there is an obvious ethical problem when we submit healthy women of child-bearing age, who have a nil to slightly increased risk of breast cancer, to a known carcinogen which, in addition to increasing their fertility, is also a demonstrated teratogen. This is especially problematic when they are forbidden the most effective forms of birth control and are not advised to have routine endometrial exams. These risks are compounded by the possibility of an increased incidence of hepatocellular carcinoma and estrogen receptor-negative breast carcinoma, as well as a significant probability of developing ocular toxicity or thrombophlebitis.

Clinicians who are advising patients interested in enrolling in this study would do well to acquaint themselves with the available literature on the toxicity of tamoxifen, some of the most impressive of which has been published since the latest protocol was completed. In this way they may persuade both themselves and their patients that prudence in entering this trial is well-warranted.

### ACKNOWLEDGEMENTS

I would like to express my appreciation to Hazel Cunningham for making me aware of the recent literature regarding tamoxifen, and to Ann Kelminski for supplying me with the NSABP Protocol.

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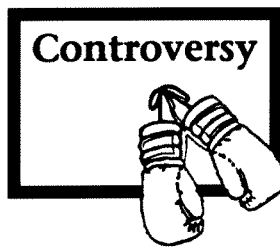
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# Tamoxifen: A caveat on the pro side of the debate

Virginia M Pressler MD\*

Thank you for the opportunity to respond to Dr. Steven Moser's extensive letter-to-the-editor regarding the National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial (NSABP Protocol P-1), also known as BCPT.

Dr. Moser's letter is obviously written out of concern for the safety of participants in this trial and his concerns are deserving of a response. The NSABP P-1 (BCPT) study has been under discussion and development since 1984. All of the concerns mentioned by Dr. Moser have been fully evaluated by the FDA, the National Institutes of Health (NIH), the NSABP and many other groups. At a recent congressional hearing, the Director of the NIH, Dr. Bernadine Healy, described this study as one of the most thoroughly reviewed protocols ever at the National Cancer Institute (NCI)<sup>1</sup>.

Let me address each of Dr. Moser's individual concerns about this trial.

**1. Level of Risk of the Participants:** Contrary to the comment that premenopausal women eligible for this study "have a nil to slightly increased risk of breast cancer," women age 35 to 40 are required to have at least a 9-fold increased risk of breast cancer compared to a population of women without these risk factors before they can be considered for this trial. Most of these women are at an even higher than 9-fold increased risk, and many live in fear of dying from breast cancer. Most of these younger women have had at least 2 first-degree relatives (mother or sisters) diagnosed with breast cancer and some have seriously considered having bilateral prophylactic mastectomies in an attempt to prevent this dread disease. This is not a low-risk population and the fear of developing breast cancer is not a trivial concern in these young women's daily lives.

The NSABP already has randomized more than 5,200 women to tamoxifen or placebo in this trial as of December 1992. Only 4% of the women so far randomized have a risk of developing breast cancer equal to that of a 60-year-old woman. Over 70% of the women of all ages randomized to date have at least a 5-fold increased risk compared to that of a 60-year-old woman and those who are premenopausal on the trial have much higher risks than this.

**2. Level of Reduction in Incidence of Contralateral Breast Cancers:** Contrary to Dr. Moser's claim that this effect may be overestimated, more recent publications than those referenced by Dr. Moser representing 41,000 woman-years of tamoxifen treatment unequivocally demonstrate tamoxifen's

ability to reduce the incidence of recurrent ipsilateral and new contralateral breast cancer<sup>2,3,4</sup>.

Furthermore, Peto's recent meta-analysis of all randomized studies demonstrated a 39% odds reduction in contralateral breast tumors in patients taking tamoxifen<sup>4</sup>.

**3. Uterine Cancer Risk:** It is not surprising that tamoxifen might increase the risk of uterine cancer due to its estrogen-agonist effect. The BCPT consent form states:

"An increased risk of uterine cancer has been reported with the use of tamoxifen. Existing data from several large controlled clinical trials using 20mg tamoxifen shows that 9 out of 3,097 women on tamoxifen developed uterine cancer (0.3%) versus 4 out of 3,091 women not treated with tamoxifen (0.1%)."

Seven randomized trials of tamoxifen all show the same relative rates of uterine cancer. It should be noted that 35% of the more than 5,000 women randomized so far on the BCPT have had hysterectomies. Thirty percent of the women under age 50 who are on the BCPT already have had hysterectomies for benign uterine changes. For those who haven't had hysterectomy, uterine cancer is rare under age 50.

All women on the study are required to have a complete pelvic exam before entry on the trial and at least annually thereafter. The patients and their gynecologists are advised to immediately evaluate any abnormal uterine bleeding and endometrial biopsies are recommended for irregular bleeding.

In the NSABP B-14 study, all of the uterine cancers that developed were diagnosed at Stage 0-1.

**4. Hepatic Cancer Risk:** The 2 liver cancers mentioned by Dr. Moser are the only 2 documented cases of liver cancer in the world in spite of 20 years of tamoxifen use in women with breast cancer. These 2 cases were from a Swedish trial using 40mg a day of tamoxifen (twice the currently used dose). Both of these cases occurred within 15 months of starting tamoxifen therapy. No other cases have been documented in spite of tracking thousands of women by the National Cancer Institute and the FDA.

Although liver cancers have been produced in rats given tamoxifen, this has not been reproducible in any other species. A recent paper by Mani and Kupfer<sup>5</sup> examining activation of tamoxifen to reactive metabolites in microsomes, implied that the human liver is apparently much less active than the livers of rats in activating tamoxifen to reactive intermediates.

A recent publication by Han and Liehr<sup>6</sup> cited by Dr. Moser 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

\* PI, NSABP P-1  
Breast Cancer Prevention Trial  
Submitted for publication February 1993

(Continued on page 92) ►



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rats were sacrificed 4 hours after 1 to 6 daily doses of tamoxifen (intraperitoneal tamoxifen 20mg/kg/day on days 1, 3, and 6). The significance of this phenomenon has been the subject of research by Liehr et al since 1985<sup>7,8</sup>.

In several experimental animal systems, estrogen exposure previously has 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.

Two thousand women in 7 major adjuvant randomized clinical trials using 20mg of tamoxifen have an overall median follow-up of 80 months, extending as long as 135 months for some groups. There have been no reported cases of liver cancer. A small group of 43 patients at the University of Wisconsin continued receiving tamoxifen indefinitely following completion of adjuvant chemotherapy for early stage breast cancer. Follow-up currently exceeds 11 years with no reported cases of primary liver cancer<sup>9</sup>.

Dr. Moser claims the tamoxifen breast cancer prevention trial does not call for specific liver function testing. This is not true. Liver function tests must be drawn on each patient before initiation of the trial and then at 3 months, 6 months, and then every 6 months for the duration of the study.

Dr. Richard Love at the University of Wisconsin has studied adverse effects of tamoxifen for many years and believes that "the much discussed possibility of human primary liver neoplasia consequent to long-term tamoxifen treatment does not deserve listing" as an adverse effect<sup>10</sup>.

The potential risk of hepatic cancer is mentioned in the BCPT consent form and is discussed with every patient.

**5. Risk of Pregnancy:** All women on the trial are advised of the possibility of teratogenic risks of tamoxifen to the fetus. All women are told they must avoid

(Continued on page 94) ►

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## TAMOXIFEN: A CAVEAT ON THE PRO SIDE OF THE DEBATE

(Continued from page 92)

pregnancy. Furthermore, new policies will require that all premenopausal women who could become pregnant must either have a negative pregnancy test at the time of initiating the trial or start the trial during their menstrual period. They are advised that tamoxifen can increase fertility and that adequate barrier contraceptives must be used. Again, it should be noted that 30% of the premenopausal women in this study have already had hysterectomies.

If any woman should become pregnant while on the study, her medication will be immediately stopped and the code broken so that she will know if she was taking tamoxifen.

Premenopausal women have been denied participation in clinical trials for many years because they might become pregnant. If they are denied participation in this trial, we will never know whether or not tamoxifen may benefit this large group of women at risk for breast cancer. The National Cancer Institute agrees that to exclude premenopausal women is discriminatory. Furthermore, it is demeaning to assume they cannot responsibly avoid pregnancy when they have been advised of the risks.

NSABP B-14 data suggests that tamoxifen may actually be more effective in preventing second breast cancers in premenopausal than in postmenopausal women. Furthermore the risks of deep venous thrombosis and endometrial cancer as an adverse effect of tamoxifen are rare in premenopausal patients. It would be wrong to exclude these women from the opportunity to participate.

### 6. Risk of Promoting Hormone-Independent Tumors:

The NSABP is aware of the data in rats showing development of rapidly growing hormone-independent tumors. In humans, we do not know if the breast cancers that are prevented are the hormone-dependent tumors, but we do know that multiple, large, randomized trials have shown benefit in disease-free survival and overall survival in patients with hormone receptor-negative, as well as hormone receptor-positive tumors, treated with tamoxifen. The role of tamoxifen in hormone-independent tumors currently is being evaluated in NSABP Protocol B-23 and other studies.

Dr. Moser also comments that tamoxifen may simply delay the onset of hormone-sensitive tumors. This does not seem to be the case since continued follow-up of disease-free survival and overall survival in patients with breast cancer treated with tamoxifen shows the curves to continue to widen over time, showing prolonged benefit of tamoxifen even many years after it has been discontinued.

**7. Thrombophlebitis and Ocular Toxicity:** Contrary to Dr. Moser's claim that these potential toxicities are not mentioned to patients, they both are included in the consent form.

Thrombophlebitis very clearly is described as an adverse effect of tamoxifen. Women with a prior history of deep venous thrombosis or embolism and women taking coumadin or heparin are not eligible for the study.

In the NSABP B-14 study, 3 of 1,414 women receiving placebo (0.2%) versus 18 of 1,403 women receiving tamoxifen (1.3%) developed deep venous thrombosis or embolism and 2 deaths occurred. This is clearly stated in the consent. Most of the thromboembolic events were in women over age 60 and most of the affected women had a history of thromboembolic problems. These women are excluded from this study. Also it should be noted that these data are from women who all had cancer and are

known to be at increased risk of thrombosis.

Rare ocular side-effects have been reported in patients receiving tamoxifen for breast cancer. These usually consist of retinopathy with fine, white, refractile opacities located superficially in the retina and concentrated especially in the macular region. Cases of optic neuritis also have been reported<sup>11</sup>.

Because of the rarity of the event, the true incidence of retinopathy has not yet been estimated accurately. The NSABP currently is planning a cross-sectional investigation of a subset of patients from protocol B-14 in order to determine the prevalence of retinal and other ocular toxicities associated with long-term, low-dose tamoxifen administration. As of August 1992, women with a history of macular degeneration of the retina are excluded from the BCPT. Tamoxifen is not known to accelerate pre-existing macular degeneration; however, the natural history of the disease is unpredictable.<sup>11</sup>

Participants are questioned on initiation of the study and at 3 months, 6 months, and then at six-month intervals regarding subtle visual changes. More than a simple ophthalmoscopic exam is necessary to identify this rare ocular toxicity and, therefore, would be prohibitive to screen in every participant. Participants who do note any visual changes are referred for ophthalmologic exam. In the meantime, the cross-sectional study of the subset of NSABP B-14 patients will be forthcoming to identify the true risk level.<sup>11</sup>

**8. Benefits of the Study:** What Dr. Moser fails to note in his letter is the potential beneficial impact of this study which far outweighs any potential risks. All medications have some side effects. Cholesterol-reducing drugs and aspirin are other examples of medications that are widely used to treat patients prophylactically to reduce their risk of disease. According to personal communication by Dr. Leslie Ford of NCI, tamoxifen has been considered by the National Cancer Institute to be at least as safe as these drugs and as safe as routine vaccinations.

It is hoped that tamoxifen in this prevention trial will be shown to reduce the incidence of invasive breast cancer by at least 33% and the incidence of myocardial infarction by 20%. Studies also suggest that tamoxifen may delay or prevent bone density loss in postmenopausal women.

I personally know of physicians already prescribing tamoxifen to healthy women at increased risk of breast cancer outside of a clinical trial. This is the real risk, and if this practice becomes more prevalent, we will never know the true relative risks and benefits of tamoxifen. Only through a well-controlled prospective study such as the BCPT can we address the risks Dr. Moser is concerned about. Only through such a trial can we identify those groups of women who have the greatest net benefit from tamoxifen therapy.

The National Coalition for Cancer Research (NCCR) supports the BCPT and states "The NCCR believes" that the bad press about tamoxifen is "sensationalistic...and represents a disservice to the women of this country... There is ample scientific evidence to support the conduct of the study. Women deserve the right to choose whether or not to participate"<sup>12</sup>.

Tamoxifen is a relatively safe medication that potentially could make an enormous impact in saving women's lives. No medication is without side effects but the safest way to determine the relative benefits and risks is through a well-designed, controlled, clinical trial. To exclude women under age 50 from this trial, or to prescribe tamoxifen off protocol, will eliminate the

(Continued on page 98) ►

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# Extraction of Lipomas: A simple technique

Greg F Reinking MD\*  
F Don Parsa MD\*

*Benign lipomas are among the most common subcutaneous fatty tumors. They are often solitary, more common in women and occur frequently during the fourth and fifth decades. They usually involve the posterior neck, back and thighs, and the great majority are less than 2 cm in diameter. Malignant transformation is extremely rare, and they usually do not require treatment. However if removal is desired, surgical excision is curative. In this article we present a simple method of resecting large lipomas measuring 4 cm to 10 cm in diameter.*

## Material and Methods

Twenty three patients were evaluated in this study with lipomas measuring 4 cm to 10 cm with a mean diameter of 5.5 cm. All patients were operated on in an outpatient office under local anesthesia, without any intravenous sedation.

Anesthesia was obtained by infiltration with 0.5% Xylocaine mixed with 1:200,000 Epinephrine. In order to maximize the vasoconstrictive effect of Epinephrine, 15 to 20 minutes were allowed to elapse before making a 1.5 cm to 2 cm skin incision either over the fatty tumor or at its periphery. A Kelly clamp was introduced through the incision and by opening and closing the jaws the fatty tissue was broken down while the tumor was squeezed firmly at its base toward the opening. (See Figure and Drawing 1.) This allows gradual extraction of the lipoma with very minimal bleeding. The wound was closed with interrupted 5-0 or 6-0 nylon sutures and dressed with a compression dressing for 24 hours. No limitation in activities was required and at the end of this period the patient was allowed to remove the dressing. Sutures are removed 5 to 7 days later.

## Results

The 23 patients who were treated by this technique were followed over a period of 6 months. Mild ecchymosis was noted in all patients; there were no hematomas or infections. The incisions healed *per primam* and the scars were acceptable.

Two patients developed mild degrees of hypertrophic incisional scars but these did not require further treatment. Ninety percent of patients experienced none to minimal post-operative pain or discomfort. Only 12% of patients used the Tylenol with Codeine No. 3 prescribed for them.

## Summary

During the past decade liposuction has been described as a desirable technique for removal of lipomas<sup>1-4</sup>. However, this requires special, costly equipment including suction apparatus and cannulae. The method of extraction of lipomas measuring 4 cm to 10 cm as described in our series was found to be simple, fast, and free of morbidity. It can be performed in an office setting. This method avoids cumbersome and costly instrumentations that are required with the liposuction technique.

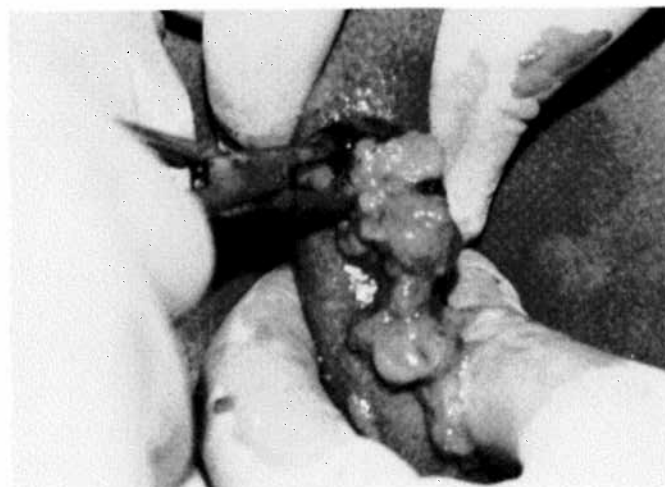


FIGURE 1.  
Photograph and drawing illustrate the squeeze-extraction technique as described in the article.

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From the Department of Surgery (Plastic), University of Hawaii,  
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Reprints should be requested from F Don Parsa MD, Department of  
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Submitted for publication August 17, 1992

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**Action:** Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage, although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalamic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

**Indications:** Yocon® is indicated as a sympatholytic and mydriatic. It may have activity as an aphrodisiac.

**Contraindications:** Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

**Warning:** Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

**Adverse Reactions:** Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.<sup>1,2</sup> Also dizziness, headache, skin flushing reported when used orally.<sup>1,3</sup>

**Dosage and Administration:** Experimental dosage reported in treatment of erectile impotence.<sup>1,3,4</sup> 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to 1/2 tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.<sup>3</sup>

**How Supplied:** Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

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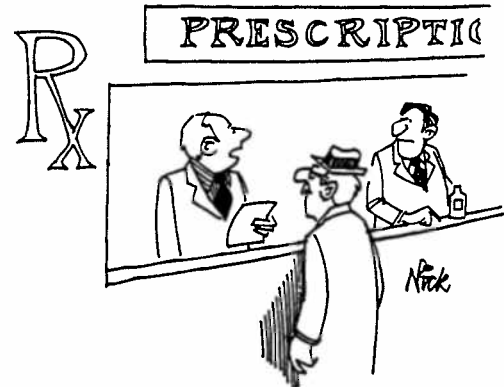
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possibility of ever determining the real relative risks and benefits in this age group. These are the women who may have the most to gain in absolute reduction of incidence of breast cancer. The known risks are well explained in the consent. How can we *not* do this study? If we do not complete this study, women will be treated with tamoxifen empirically and the risks never will be really known. Also, they may not be followed as carefully as they are on the BCPT.

The facts speak for themselves, and it must be concluded that the tamoxifen breast cancer prevention trial is one of the most important, well designed and safest studies ever conducted.

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*Beyond the call*



Henry N Yokoyama MD



Incredible as it may seem, that's Charlie with me at the gateway to Tirilan in Bashkiria at the southern tip of the Ural mountains in Russia on May 22, 1992. We were attending a conference about 100 miles east of Tirilan in Chelyabinsk, Siberia, the locale of the Soviet nuclear weapons complex, on the medical and environmental effects of pollution by radiation similar to what's happened at Hanford, WA in the United States.

We came home on the Trans-Siberian Railway, covering about 4,500 miles in 5 days, to Khabarovsk in Russia's Far-east, then by Aeroflot to San Francisco.

Never in my wildest dreams had I ever thought to return to my birthplace 72 years after Papa, Mama, Eric and I escaped from the Bolsheviks, traveling on the same TSRR, and came to Hawaii thanks to the American Expeditionary Force American Red Cross, the latter under Riley Allen and Arthur Jackson MD!

### Hors de Combat Road Block to Health Care?

Gene Nakamoto MD in a letter to the editor expressed his feeling that the Honolulu Marathon is a roadblock to health care for East-Honolulu residents. "As a physician I am concerned for the health and well-being of East Honolulu residents who perhaps postpone medical treatment on "Non-911" medical situations, which then eventually become 911 emergencies. The medical and legal ramifications are endless...The City & County of Honolulu probably realizes some financial gain from sponsoring the marathon, but I hope we never put a sporting event above human life and well-being". (Ed: Wot rot! Such tirade for one Sunday morning a year? His colleagues certainly do not share his sentiments.)

### Crisis In Mental Health Facilities For Adolescents

In Honolulu, Dennis Mee-Lee, Castle Hospital's psychiatric head, reported that the hospital will close its state-funded residential treatment program for adolescents because of an expected 20% to 25% budget cut in its \$800,000-a-year program.

*Po'ailani*, a private community-based shelter for disturbed adolescents closed because of a 75%

funding cut. *Kahi Mohala*, a private psychiatric hospital, will take over from Castle.

On Maui, psychiatrists are protesting the lack of facilities for children with severe mental health problems. Sally Connolly, staff psychiatrist for "The Children's Place" (a Dept of Health outpatient facility), resigned citing inadequate support and facilities. Royal Randolph, Maui Memorial psychiatric department head, reported that 3 child psychiatrists left the staff to limit their liability for assuming the care of adolescents needing hospitalization.

Gov. Waihee has promised to divert funds from other state programs to address the crisis in mental health services for adolescents.

### Elected, Appointed, & Honored

Psychiatrist and 3rd-year law student, George Bussey of Kailua, won the grand prize worth \$5,000 in a Federation of Insurance and Corporate Counsel Foundation annual essay contest. His paper titled "Mental Stress Claims and the Workers' Compensation System: An Analysis of the Problem and Suggestions for Change" will be published in the Foundation's quarterly. In January, urologist John Edwards replaced pathologist Drake Will as VP of Medical Staff Services at QMC. John has been in private practice since 1974 and served as Chief of Surgery for the past 4 years. Drake will remain as a Queen's consultant.

Quiet, reticent Kailua OB/Gyn Charles Yamashiro was honored at a Castle Medical Center quarterly meeting in January. Charley was retiring after 30 years on the staff and a record 14,602 deliveries.

### National News...

Limits on Malpractice Awards: On Nov 16, the Supreme Court, with one dissenting vote, upheld a Missouri law that limits the amount of money paid to medical malpractice victims (A girl was left blind and brain damaged by an anesthesia error). The justices have left intact similar laws in California and Idaho which limit malpractice awards.

### Oncology Dialogue

Colo-rectal surgeon Ronald Wong presented a 41-year-old woman who had a Stage Ia left ovarian tumor resected in Dec 1991. A year later she developed an anal lesion (cloacogenic Ca) and a second tumor of her sigmoid colon which was adeno Ca on biopsy. The CA 125 was normal. CT scans of the abdomen, pelvis and chest were negative. Moderator Lois Mastrofrancesco initiated the discussion: "We probably have a salvageable adeno Ca..." Ken Sumida intoned, "Negative CT of the abdomen; C 125 normal...And fluid in the cul de sac". Pathologist Larry McCarthy reported, "The second lesion in the colon is probably mets from the ovarian Ca. The anal lesion is different." Radiotherapist Charley Yamashiro offered, "Chemo and implants after surgery." Lois commented, "We have 2 elements to treat; this is a toughie." Pathologist Grant Stemmerman added to the problem: "The lesion in the sigmoid is not necessarily metastatic. She has extensive endometriosis so it may be endometrial Ca." Radiotherapist Thanh Huynh in trying to avoid an A-P resection suggested: "Treat the anal and sigmoid tumors with radiation; then treat the ovarian Ca with chemo."

After much discussion with others joining in the melee, Ken Sumida decided: "We'll go for the home run...Do an A-P resection, debulk the tumor

and hit with chemo." Lois declared sagely: "The quality of life is very important only if you have a life."

### Oncology Dialogue II

Internist Roger Kimura presented a 53-year-old man who had noticed a non-tender testicular mass 2 months earlier. Alpha fetoprotein and HCG levels were normal. The patient did not smoke or drink. CT scans of the chest and abdomen were negative. A LT radical orchiectomy was done and the pathology report confirmed a seminoma. Radiologist Howard Arimoto described the CT scan which showed small periaortic nodes. Pathologist Larry McCarthy described the pathology: "The specimen was twice the normal size and grossly a homogeneous light-tan, lobulated mass. Microscopically, it is homogeneous and cellular...The tumor markers Alph Feto and HCG were negative".

Moderator Ken Sumida turned to oncologist Jonathan Cho: "Can you comment on preop staging." Jonathan: "Staging is helpful. Staging includes CXR, CT scans of the abdomen and pelvis." Radiotherapist Lois Mastrofrancesco interjected, "Lymphangiograms are most helpful". Chemo-therapist Dennis Wachi objected, "Let's ask the radiologist if lymphangiograms are helpful". Howard livened the discussion: "I'm not sure they're helpful". We can see nodes on the CT scan. Besides, it is a logistic problem. Lymphangiograms are a lost art. The younger radiologists are not exposed to lymphangiograms and the older radiologists have a problem with their eyes." Lois pursued her logic: "The reason for lymphangiograms is that the stage has not been determined. It may be a Stage II. It may be my own bias. And lymphangiograms are available in Hawaii. If it is Stage II, a higher dose of radiation is indicated. Fellow radiotherapist Thanh Huynh explained, "Normally we give 2000 to 2500 rads and 500 more rads if it is a higher stage. Lois interjected, "Where I trained, every patient had lymphangiogram." Thanh added: "Stage I with radiation is a 95% survival with no side effects; Stage II survival is 15% to 20%." Ken Sumida tried to soothe feelings with: "If you are to have a malignancy, this is the one to have." Pathologist Grant Stemmerman suggested a more practical approach: "Back to basics. The response to chemotherapy is so good why worry whether it is Stage I or II. Why not wait till there is recurrence". Ken concluded, "It is a judgment call. Get CT of chest and give chemo for recurrence".

### Excerpts From Stitches

(The Journal of Medical Humor November-December 1992)

#### This is True!!

by Ralph Stonim, Miami, Florida  
The receptionist told me my next patient was a gentleman who was concerned about his increasing girth. As I entered the examining room, I remarked, "If I saw that belly on a woman, I'd say she was pregnant."

"That's right, Doc," he answered. "It's been on a woman, and she is pregnant."

"My stomach has gotten so big," he went on, "that I can hardly see my penis. What do you think I should do?"

"Why don't you diet?" I asked.

He thought this over for a moment, then said, "I'll give it a try. What color would you suggest?"

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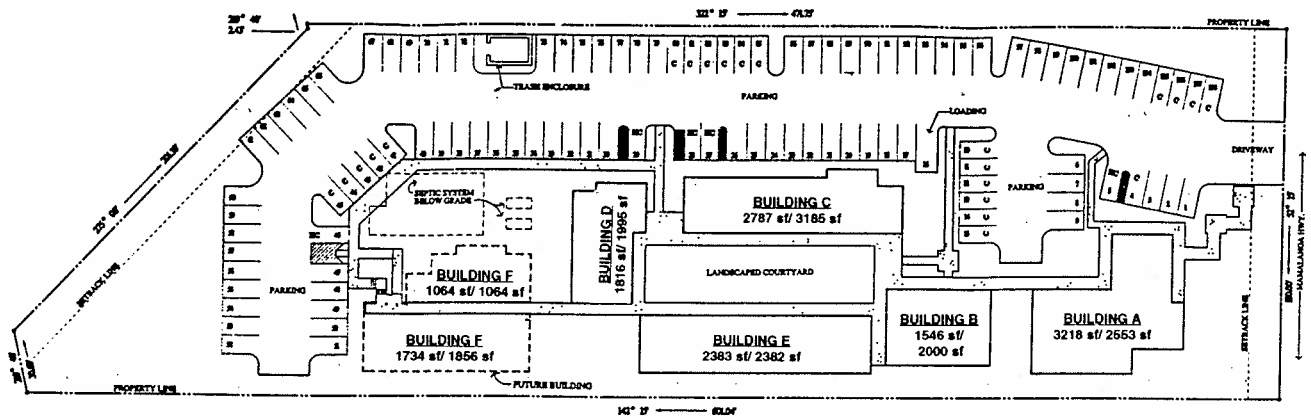
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## TAMOXIFEN: CON SIDE

(Cont'd from page 88)

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**Reference:** 1. Jones PH, et al. Once-daily pravastatin in patients with primary hypercholesterolemia: a dose-response study. *Clin Cardiol*. 1991;14:146-151.

**PRAVACHOL® (Pravastatin Sodium Tablets)**  
**CONTRAINDICATIONS**

Hypersensitivity to any component of this medication.

Active liver disease or unexplained, persistent elevations in liver function tests (see WARNINGS).

**Pregnancy and lactation.** Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. **Pravastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If the patient becomes pregnant while taking this class of drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

**WARNINGS**

**Liver Enzymes:** HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Increases of serum transaminase (ALT, AST) values to more than 3 times the upper limit of normal occurring on 2 or more (not necessarily sequential) occasions have been reported in 1.3% of patients treated with pravastatin in the U.S. over an average period of 18 months. These abnormalities were not associated with cholestasis and did not appear to be related to treatment duration. In those patients in whom these abnormalities were believed to be related to pravastatin and who were discontinued from therapy, the transaminase levels usually fell slowly to pretreatment levels. These biochemical findings are usually asymptomatic although worldwide experience indicates that anorexia, weakness, and/or abdominal pain may also be present in rare patients.

As with other lipid-lowering agents, liver function tests should be performed during therapy with pravastatin. Serum aminotransferases, including ALT (SGPT), should be monitored before treatment begins, every six weeks for the first three months, every eight weeks during the remainder of the first year, and periodically thereafter (e.g., at about six-month intervals). Special attention should be given to patients who develop increased transaminase levels. Liver function tests should be repeated to confirm an elevation and subsequently monitored at more frequent intervals. If increases in AST and ALT equal or exceed three times the upper limit of normal and persist, then therapy should be discontinued. Persistence of significant aminotransferase elevations following discontinuation of therapy may warrant consideration of liver biopsy.

Active liver disease or unexplained transaminase elevations are contraindications to the use of pravastatin (see CONTRAINDICATIONS). Caution should be exercised when pravastatin is administered to patients with a history of liver disease or heavy alcohol ingestion (see CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism). Such patients should be closely monitored, started at the lower end of the recommended dosing range, and titrated to the desired therapeutic effect.

**Skeletal Muscle: Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has been reported with pravastatin and other drugs in this class.** Uncomplicated myalgia has also been reported in pravastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal was reported to be possibly due to pravastatin in only one patient in clinical trials (<0.1%). Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **Pravastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.** **Pravastatin therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.**

The risk of myopathy during treatment with lovastatin is increased if therapy with either cyclosporine, gemfibrozil, erythromycin, or niacin is administered concurrently. There is no experience with the use of pravastatin together with cyclosporine. Myopathy has not been observed in clinical trials involving small numbers of patients who were treated with pravastatin together with niacin. One trial of limited size involving combined therapy with pravastatin and gemfibrozil showed a trend toward more frequent CPK elevations and patient withdrawals due to musculoskeletal symptoms in the group receiving combined treatment as compared with the groups receiving placebo, gemfibrozil, or pravastatin monotherapy. Myopathy was not reported in this trial (see PRECAUTIONS: Drug Interactions). One patient developed myopathy when clofibrate was added to a previously well tolerated regimen of pravastatin; the myopathy resolved when clofibrate therapy was stopped and pravastatin treatment continued. **The use of fibrates alone may occasionally be associated with myopathy. The combined use of pravastatin and fibrates should generally be avoided.**

**PRECAUTIONS**

**General:** Pravastatin may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with pravastatin.

**Homozygous Familial Hypercholesterolemia.** Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. In this group of patients, it has been reported that HMG-CoA reductase inhibitors are less effective because the patients lack functional LDL receptors.

**Renal Insufficiency:** A single 20 mg oral dose of pravastatin was administered to 24 patients with varying degrees of renal impairment (as determined by creatinine clearance). No effect was observed on the pharmacokinetics of pravastatin or its 3 $\alpha$ -hydroxy isomeric metabolite (SQ 31,906). A small increase was seen in mean AUC values and half-life (t<sub>1/2</sub>) for the inactive enzymatic ring hydroxylation metabolite (SQ 31,945). Given this small sample size, the dosage administered, and the degree of individual variability, patients with renal impairment who are receiving pravastatin should be closely monitored.

**Information for Patients:** Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

**Drug Interactions: Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin:** See WARNINGS: Skeletal Muscle.

**Antipyrine:** Clearance by the cytochrome P450 system was unaltered by concomitant administration of pravastatin. Since pravastatin does not appear to induce hepatic drug-metabolizing enzymes, it is not expected that any significant interaction of pravastatin with other drugs (e.g., phenytoin, quinidine) metabolized by the cytochrome P450 system will occur.

**Cholestyramine/Colestipol:** Concomitant administration resulted in an approximately 40 to 50% decrease in the mean AUC of pravastatin. However, when pravastatin was administered 1 hour before or 4 hours after cholestyramine or 1 hour before colestipol and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect. (See DOSAGE AND ADMINISTRATION: Concomitant Therapy.)

**Warfarin:** In a study involving 10 healthy male subjects given pravastatin and warfarin concomitantly for 6 days, bioavailability parameters at steady state for pravastatin (parent compound) were not altered. Pravastatin did not alter the plasma protein-binding of warfarin. Concomitant dosing did increase the AUC and C<sub>max</sub> of warfarin but did not produce any changes in its anticoagulant action (i.e., no increase was seen in mean prothrombin time after 6 days of concomitant therapy). However, bleeding and extreme prolongation of prothrombin time has been reported with another drug in this class. Patients receiving warfarin-type anticoagulants should have their prothrombin times closely monitored when pravastatin is initiated or the dosage of pravastatin is changed.

**Cimetidine:** The AUC<sub>0-12h</sub> for pravastatin when given with cimetidine was not significantly different from the AUC for pravastatin when given alone. A significant difference was observed between the AUC's for pravastatin when given with cimetidine compared to when administered with antacid.

**Digoxin:** In a crossover trial involving 18 healthy male subjects given pravastatin and digoxin concurrently for 9 days, the bioavailability parameters of digoxin were not affected. The AUC of pravastatin tended to increase, but the overall bioavailability of pravastatin plus its metabolites SQ 31,906 and SQ 31,945 was not altered.

**Gemfibrozil:** In a crossover study in 20 healthy male volunteers given concomitant single doses of pravastatin and gemfibrozil, there was a significant decrease in urinary excretion and protein binding of pravastatin. In addition, there was a significant increase in AUC, C<sub>max</sub>, and T<sub>max</sub> for the pravastatin metabolite SQ 31,906. Combination therapy with pravastatin and gemfibrozil is generally not recommended.

In interaction studies with aspirin, antacids [1 hour prior to PRAVACHOL (pravastatin sodium)], cimetidine, nicotinic acid, or probucol, no statistically significant differences in bioavailability were seen when PRAVACHOL was administered.

**Other Drugs:** During clinical trials, no noticeable drug interactions were reported when PRAVACHOL was added to diuretics, antihypertensives, digitalis, converting-enzyme inhibitors, calcium channel blockers, beta-blockers, or nitroglycerin.

**Endocrine Function:** HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal and/or gonadal steroid hormone production. Results of clinical trials with pravastatin in males and post-menopausal females were inconsistent with regard to possible effects of the drug on basal steroid hormone levels. In a study of 21 males, the mean testosterone response to human chorionic gonadotropin was significantly reduced (p<0.004) after 16 weeks of treatment with 40 mg of pravastatin. However, the percentage of patients showing a  $\geq$ 50% rise in plasma testosterone after human chorionic gonadotropin stimulation did not change significantly after therapy in these patients. The effects of HMG-CoA reductase inhibitors on spermatogenesis and fertility have not been studied in adequate numbers of patients. The effects, if any, of pravastatin on the pituitary-gonadal axis in pre-menopausal females are unknown. Patients treated with pravastatin who display clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may diminish the levels or activity of steroid hormones.

**CNS Toxicity:** CNS vascular lesions, characterized by perivascular hemorrhage and edema and mononuclear cell

infiltration of perivascular spaces, were seen in dogs treated with pravastatin at a dose of 25 mg/kg/day, a dose that produced a plasma drug level about 50 times higher than the mean drug level in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs in this class.

A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear (Wallerian-like) degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level similar to that seen with the 60 mg/kg dose.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** In a 2-year study in rats fed pravastatin at doses of 10, 30, or 100 mg/kg body weight, there was an increased incidence of hepatocellular carcinomas in males at the highest dose (p<0.01). Although rats were given up to 125 times the human dose (HD) on a mg/kg body weight basis, their serum drug levels were only 6 to 10 times higher than those measured in humans given 40 mg pravastatin as measured by AUC.

The oral administration of 10, 30, or 100 mg/kg (producing plasma drug levels approximately 0.5 to 5.0 times human drug levels at 40 mg) of pravastatin to mice for 22 months resulted in a statistically significant increase in the incidence of malignant lymphomas in treated females when all treatment groups were pooled and compared to controls (p<0.05). The incidence was not dose-related and male mice were not affected.

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 90 percent in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the eye Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls.

No evidence of mutagenicity was observed *in vitro*, with or without rat-liver metabolic activation, in the following studies: microbial mutagen tests, using mutant strains of *Salmonella typhimurium* or *Escherichia coli*; a forward mutation assay in L5178Y TK +/– mouse lymphoma cells; a chromosomal aberration test in hamster cells; and a gene conversion assay using *Saccharomyces cerevisiae*. In addition, there was no evidence of mutagenicity in either a dominant lethal test in mice or a micronucleus test in mice.

In a study in rats, with daily doses up to 500 mg/kg, pravastatin did not produce any adverse effects on fertility or general reproductive performance. However, in a study with another HMG-CoA reductase inhibitor, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. Although not seen with pravastatin, two similar drugs in this class caused drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation in dogs. The clinical significance of these findings is unclear.

**Pregnancy: Pregnancy Category X:** See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Pravastatin was not teratogenic in rats at doses up to 1000 mg/kg daily or in rabbits at doses of up to 50 mg/kg daily. These doses resulted in 20x (rabbit) or 240x (rat) the human exposure based on surface area (mg/meter<sup>2</sup>). However, in studies with another HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. PRAVACHOL (pravastatin sodium) should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking PRAVACHOL, it should be discontinued and the patient advised again as to the potential hazards to the fetus.

**Nursing Mothers:** A small amount of pravastatin is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants, women taking PRAVACHOL should not nurse (see CONTRAINDICATIONS).

**Pediatric Use:** Safety and effectiveness in individuals less than 18 years old have not been established. Hence, treatment in patients less than 18 years old is not recommended at this time. (See also PRECAUTIONS: General.)

**ADVERSE REACTIONS**

Pravastatin is generally well tolerated; adverse reactions have usually been mild and transient. In 4-month long placebo-controlled trials, 1.7% of pravastatin-treated patients and 1.2% of placebo-treated patients were discontinued from treatment because of adverse experiences attributed to study drug therapy; this difference was not statistically significant. In long-term studies, the most common reasons for discontinuation were asymptomatic serum transaminase increases and mild, non-specific gastrointestinal complaints. During clinical trials the overall incidence of adverse events in the elderly was not different from the incidence observed in younger patients.

**Adverse Clinical Events:** All adverse clinical events (regardless of attribution) reported in more than 2% of pravastatin-treated patients in the placebo-controlled trials are identified in the table below; also shown are the percentages of patients in whom these medical events were believed to be related or possibly related to the drug:

Body System/Event	All Events %		Events Attributed to Study Drug %	
	Pravastatin (N=900)	Placebo (N=411)	Pravastatin (N=900)	Placebo (N=411)
Cardiovascular				
Cardiac Chest Pain	4.0	3.4	0.1	0.0
Dermatologic				
Rash	4.0*	1.1	1.3	0.9
Gastrointestinal				
Nausea/Vomiting	7.3	7.1	2.9	3.4
Diarrhea	6.2	5.6	2.0	1.9
Abdominal Pain	5.4	6.9	2.0	3.9
Constipation	4.0	7.1	2.4	5.1
Flatulence	3.3	3.6	2.7	3.4
Heartburn	2.9	1.9	2.0	0.7
General				
Fatigue	3.8	3.4	1.9	1.0
Chest Pain	3.7	1.9	0.3	0.2
Influenza	2.4*	0.7	0.0	0.0
Musculoskeletal				
Localized Pain	10.0	9.0	1.4	1.5
Myalgia	2.7	1.0	0.6	0.0
Nervous System				
Headache	6.2	3.9	1.7*	0.2
Dizziness	3.3	3.2	1.0	0.5
Renal/Genitourinary				
Urinary Abnormality	2.4	2.9	0.7	1.2
Respiratory				
Common Cold	7.0	6.3	0.0	0.0
Rhinitis	4.0	4.1	0.1	0.0
Cough	2.6	1.7	0.1	0.0

\*Statistically significantly different from placebo.

The following effects have been reported with drugs in this class:

**Skeletal:** myopathy, rhabdomyolysis.

**Neurological:** dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy.

**Hypersensitivity Reactions:** An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

**Gastrointestinal:** pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia, vomiting.

**Reproductive:** gynecomastia, loss of libido, erectile dysfunction.

**Eye:** progression of cataracts (lens opacities), ophthalmoplegia.

**Laboratory Test Abnormalities:** Increases in serum transaminase (ALT, AST) values and CPK have been observed (see WARNINGS).

Transient, asymptomatic eosinophilia has been reported. Eosinophil counts usually returned to normal despite continued therapy. Anemia, thrombocytopenia, and leukopenia have been reported with other HMG-CoA reductase inhibitors.

**Concomitant Therapy:** Pravastatin has been administered concurrently with cholestyramine, colestipol, nicotinic acid, probucol and gemfibrozil. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin or pravastatin is not associated with greater reduction in LDL-cholesterol than that achieved with lovastatin or pravastatin alone. No adverse reactions unique to the combination or in addition to those previously reported for each drug alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended. (See WARNINGS: SKELETAL MUSCLE AND PRECAUTIONS: Drug Interactions.)

**OVERDOSAGE**

There have been no reports of overdoses with pravastatin.

Should an accidental overdose occur, treat symptomatically and institute supportive measures as required.

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PRAVACHOL is indicated as an adjunct to diet for the reduction of elevated total and LDL-cholesterol levels in patients with primary hypercholesterolemia (Types IIa and IIb) when the response to diet alone has not been adequate.

Active liver disease or unexplained transaminase elevations, pregnancy and lactation are contraindications to the use of pravastatin sodium.

Please see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary of prescribing information on the adjacent page.

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