Estrogen Drugs: Do They Increase the Risk of Cancer?

A recent flurry of reports has sparked concern that estrogen drugs may be associated with an increased risk of cancer for the women taking them. A number of investigators have now found that women who take estrogens for relief of menopausal symptoms are several times more likely to develop cancer of the uterine lining than are comparable women not using the drugs. Additional studies indicate that the incidence of this cancer has risen in the past few years, a period following the rapid expansion of estrogen use that began in the 1960's. Although the investigators point out that statistical associations such as these do not prove that estrogens cause cancer, they at least think that the data provide a hypothesis that should be explored in further research.

Investigators have long thought that estrogens could be potential carcinogens. The normal functions of the hormones include stimulating the division of cells of the uterine lining (endometrium) and of breast tissue. Cancer, of course, involves the unregulated division of cells. Moreover, there have been reports that estrogens induce cancers in laboratory animals. Determining whether the hormones do likewise in humans is not an easy task, however. Most cancers, including those of the uterine endometrium and of the breast, are associated with a variety of environmental, genetic, and physical factors that influence an individual's susceptibility to the disease. These must all be controlled for in studies designed to assess the importance of an additional factor such as use of a drug.

The current studies are retrospective ones in which the estrogen use of patients with endometrial cancer was compared with that of matched controls. The women were all of menopausal age or older and the estrogens were of the type—conjugated estrogens, for the most part—usually taken during and after menopause to relieve symptoms such as "hot flashes" and atrophy of the reproductive tract that may accompany the abrupt cessation of ovarian function.

The results of all of the studies showed that significantly more of the cancer patients than of the controls had been estrogen users. For example, Donald Smith and his colleagues at the University of Washington Medical School found that 152 of 317 patients with endometrial cancer had taken some kind of estrogen for at least 6 months before their cancers were diagnosed. In contrast, only 54 of the 317 controls had done so. The controls were women with other gynecological cancers, including cancers of the cervix, ovary, and vulva. Smith has calculated that estrogen users are 4.5 times as likely as nonusers to develop endometrial cancer.

In another study, Harry Ziel and William Finkle of the Kaiser Permanente Medical Center in Los Angeles compared 94 patients with endometrial cancer with twice that number of controls. The controls were women selected from the membership files of the Southern California Kaiser Foundation Health plan. They all had uteruses and were matched with the patients according to several criteria. The investigators found that 57 percent of the patients had used estrogens whereas only 15 percent of the controls did. According to Ziel and Finkle, the risk of getting the cancer is 7.6 times greater for the users than the nonusers. In a third independent retrospective study, Thomas Mack of the University of Southern California Medical School determined that estrogen use increases a woman's risk of endometrial cancer by a factor of 8.

Frequency of Endometrial Cancer

Since the frequency of endometrial cancer in all postmenopausal women who have uteruses is about 1 per 1000 per year, these studies indicate that the frequency should be 4 to 8 per 1000 per year for estrogen users. Or, as Mack puts it, a woman who has a uterus and uses estrogens has a risk of developing endometrial cancer that is greater than her usual combined risk from cervical, breast, and endometrial cancers.

All of the investigators say that their statistical analyses eliminated the possibility that the increased risks they observed were really due to other factors known to predispose a woman to endometrial cancer. These factors include high blood pressure, obesity, age, and not ever having had a child. In fact, Smith and Mack say that the estrogen-related relative risk appears greatest for women with none of these predisposing conditions.

Dependence of an observed effect on the magnitude and duration of a treatment usually indicates that treatment and effect are in fact causally related. According to Ziel, the relative risk ratio (risk for the users divided by that of nonusers) of endometrial cancer increased from 5.6 for women taking estrogens for 1 to 5 years, to 7.2 for those taking them for 5 to 7 years, and to 13.9 for those on estrogens for more than 7 years. Mack said that the risk also increased as the dosage of the hormone increased. Thus both dose and duration dependencies were observed, although not in the same study.

Most of the women who take estrogens for menopausal symptoms take a type called conjugated estrogens, usually the sodium salt of estrone sulfate. This steroid derivative is the principal constituent of the drug Premarin (thus called because the material is isolated from the urine of pregnant mares), produced by Ayerst Laboratories. About 80 percent of the women taking hormones during and after menopause use Premarin, for which physicians write almost 8 million prescriptions annually. A spokesman for Ayerst said the company would not comment about the reports linking sodium estrone sulfate with cancer except to say that they were working to devise a new package insert and label for Premarin in order to meet Food and Drug Administration (FDA) requirements (see box).

The association between estrogens and endometrial cancer may not be limited to the conjugated variety, however. Some women—probably less than 20 percent of the total but still a significant number—had taken a nonsteroidal estrogen called diethylstilbestrol (DES) This agent has been linked to the development of a rare form of vaginal cancer in the daughters of women who took it during pregnancy. Mack found that women who had taken any estrogen, whether DES or a conjugated or other kind of estrogen, were eight times as likely as the controls to develop cancer whereas those who had taken only a conjugated estrogen were six times as likely to do so. Thus, inclusion in the study of women taking estrogens other than the conjugated kind at least did not appear to decrease the magnitude of the risk increase. Further work is needed to pinpoint the relative contributions of the different estrogens to the increase.

At one time, investigators who thought that estrogens might be involved in the etiology of cancer had to confront two observations that seemed to contradict the hypothesis. One is that the Third National Cancer Survey, conducted between 1969 and 1971 by the National Cancer Institute, showed that the incidence of endometrial cancer had not increased since previous surveys. If estrogens induce endometrial

cancer, then the incidence of that disease should increase as more and more women are exposed to the drug. The second is that the incidences of endometrial cancer and breast cancer increase after menopause at a time when estrogen concentrations should be declining.

One explanation for the failure of the Third National Cancer Survey to detect an increase is that not enough time had elapsed for the cancers to develop to the detectable stage by the end of the survey. Conjugated estrogens were introduced for treatment of menopausal symptoms in the early 1960's and came into widespread use by the end of that decade. Many investigators think that the latent period between exposure to a carcinogen and the development of cancer is ten or more years.

This explanation is supported by more recent data—acquired since 1971. According to Noel Weiss of the University of Washington and Donald Austin of the California Tumor Registry, their studies do indicate a rise in the incidence of endometrial cancer. In general, the increase was most marked in Caucasian women 50 years of age or older who are in the high socioeconomic groups. In other words, it is greatest among the women most likely to

Estrogens and the FDA

The question of the safety of estrogen-containing drugs is a very important one. As many as 15 to 20 million women in the United States take some form of the hormone. And all members of the population may be exposed, at least occasionally, to DES, a synthetic estrogen. This hormone is given to food animals such as beef and sheep to increase the efficiency of the fattening process. According to the U.S. Department of Agriculture, DES residues were found in about 1.5 percent of the beef livers analyzed during the first three quarters of 1975.

The FDA has the responsibility of overseeing the safety and effectiveness of drugs and food additives. The following is a short summary of FDA actions with regard to the various estrogen-containing drugs.

• DES. Federal law permits the use of a carcinogen as a drug for animals only if no residue is found in edible tissues analyzed by approved methods. There is evidence that DES increases the incidence of cancer in female mice and the hormone has been associated with a rare form of vaginal cancer in the daughters of women who took the agent during pregnancy to prevent miscarriages. Since DES residues are being found in beef livers, the FDA has proposed to withdraw approval of the use of the agent as a growth promotant for animals. If this sounds somewhat familiar, it is because the FDA previously attempted to ban the use of DES for this purpose, only to have the ban overturned by the U.S. Court of Appeals of the District of Columbia in 1974 because the agency had not provided DES manufacturers with an adequate opportunity for a hearing. This time, there have been at least four requests for a hearing, which will be held only if the FDA decides that it is justified. Pending the results of the hearing, if it is needed, and appeal processes, the use of DES as a growth promotant can continue.

The FDA has approved DES for human use only for the treatment of cancers of the uterus and prostate. It was not approved either as a means of preventing miscarriages (which it did not do in any event) or as a treatment for menopausal symptoms. The agency did, however, announce in 1975, that it would approve DES as a morning-after contraceptive in "emergencies" such as after rape or incest, provided that certain conditions are met. These include a warning for the consumer that the drug has been associated with cancer, that it has unpleasant side effects such as vomiting, and that the women should consider an abortion because of possible fetal injury should the drug not prevent pregnancy. One company has submitted an application for approval of DES as a morning-after contraceptive; the application is being reviewed.

• Conjugated estrogens for use during and after menopause. The FDA is requiring new labeling that warns of the increased risk of endometrial cancer for women who take the drugs and stresses that physicians should prescribe the lowest effective dose and should periodically stop the therapy in order to determine whether the conjugated estrogens are still needed. This would help to minimize any risk, since epidemiological studies indicate that incidence of the cancer increases with the size of the dosage and length of time administered.

• Oral contraceptives. Much of the concern about the adverse effects of birth control pills centers not on cancer but on blood clotting problems such as stroke, thrombophlebitis, pulmonary embolism, and heart attack. Investigators have also reported increases in blood pressure and in gall bladder disease in women using oral contraceptives. Sequential pills may be associated with a higher level of side effects than combined pills and are somewhat less effective. The pregnancy rate for users of combined pills is about 0.1 per year per 100 women; for users of sequential pills, it is 0.5. Even though the FDA's advisory committee on Gynecology and Obstetrics recommended only a labeling change for sequential oral contraceptives, the FDA is moving to withdraw them from the market. However, the agency is allowing the three firms now marketing sequentials pills an opportunity to show that there is a group of women for whom the benefits of sequential pills outweigh the risks. The original deadline for this was in mid-January but that has been extended.

The process of withdrawing approval for a drug involves publishing in the Federal Register a "notice of opportunity for hearing on proposal to withdraw approval" so that the manufacturers can state their case against the withdrawal if they desire to do so. Although a spokesman for the FDA said that the agency plans to publish the notice concerning sequential pills if new data justifying their use is not submitted, there is now no date set for the publication.

Nor has the agency set a date for requiring new labeling for the combined type of oral contraceptives. The new label was to include a warning that women over 40 years of age should use some form of birth control other than the pill. The label was to cite reports from Royal College of General Practitioners in England that use of oral contraceptives increases the risk of heart attacks for these women and also for younger women, although not to the same degree. This will probably be modified in the light of more recent data from the Royal College that shows that the pill-associated risk of heart attacks for these older women is not as large as originally estimated although it is still greater than the risk for nonusers. Current labels already include information about the other blood clotting disorders mentioned earlier.—J.L.M.

be taking estrogens. The fact that the number of hysterectomies has increased dramatically in the last 10 years complicates the interpretation of these data. Part of the observed increase could be due to the greater number of uteruses available for pathologic examination. On the other hand, since there are fewer women in the population with uteruses, the incidence of the cancer in women actually at risk must be even higher than the measured overall incidence.

Estrogen Production After Menopause

Recent evidence that estrogens, especially estrone, are synthesized in peripheral tissue after menopause may provide an explanation of how cancers that are thought to be estrogen-dependent become more prevalent following cessation of cyclical estrogen production by the ovaries. According to Pentti Siiteri of the University of California Medical School in San Francisco and Paul MacDonald of the University of Texas Southwestern Medical School, estrone is synthesized in body fat from precursors formed in the ovaries and adrenal glands. The amount formed is proportional to total body weight. This observation is consistent with the fact that obesity is one of the factors predisposing to endometrial cancer. Moreover, Siiteri and MacDonald found that women with the cancer produce about twice as much estrone as control women even though both groups produce similar quantities of the precursor.

Thus, the cyclical production of the estrogen estradiol that occurs during the menstrual cycle is replaced at menopause by the sustained production of estrone. In addition, the ovaries no longer produce the hormone progesterone that may counteract the action of estrogens and protect against their cancer-causing potential.

The view emerging from these studies is one in which estrogens, especially when unopposed by progesterone, may play a causal role in the development of endometrial cancer. Consequently, many investigators have expressed caution about continuing the widespread and frequently prolonged use of estrogens during and after menopause. Ziel said that he would hesitate to prescribe the hormones at all except for unusually severe menopausal symptoms. Smith thinks that there is still a role for conjugated estrogens—but it would be much more limited than it is in current practice. The hormones might be prescribed for short-term use during menopause to alleviate the symptoms of abrupt stoppage of secretion of the ovarian hormones. However, Smith emphasizes that certain safeguards are required. These include periodically stopping the drug to see if it is still needed (the symptoms do diminish with time) and using progressively smaller doses. In addition the woman would need periodic careful examinations to make sure that no abnormal changes were occurring. (These guidelines are essentially the same as those specified by FDA.)

Oral contraceptives that are now prescribed for up to 10 million women are another major class of drugs that contain estrogens. At present, no one really knows whether these pills—often collectively called "the pill"—are involved in any way in the etiology of cancer. A few studies have indicated that the pill should at least be viewed with caution; on the other hand, other studies have shown no connection between oral contraceptives and cancer.

There are a number of reasons why it is difficult to study any possible relationship between birth control pills and cancer. One is that cancer is a relatively rare occurrence in women of the age group who would practice birth control. Another is that the pill is really a spectrum of pills with different concentrations and even different formulations of estrogenic and progestogenic hormones. And finally—and perhaps most importantly—it may still be a bit early to tell whether oral contraceptives, which did not come into widespread use until the middle to late 1960's, are associated with cancer in humans.

There are indications, although they are preliminary and gleaned from a limited sample of cases, that one type of oral contraceptive may be associated with endometrial cancer. This is the sequential pill in which an estrogen is taken alone for the first 2 weeks of the menstrual cycle and a progestogen is taken during the third. Stephen Silverberg of the University of Colorado Medical School in Denver identified 26 cases in which women who had used oral contraceptives developed endometrial cancer. He said that nine of these had taken the pill for less than a year before the cancer was discovered or they already had some suspicious condition of the reproductive tract (such as abnormal bleeding) before they began the medication. Of the remaining 17 patients, 15 had been taking the sequential pill whereas only 2 had been taking the combined type, in which every pill contains both an estrogen and a progestogen. Silverberg thinks that this is surprising because combined oral contraceptives account for 90 percent of the market, with sequentials comprising the remaining 10 percent.

There are three brands of sequential pills now on the market—at least for the time being (see box). These are Oracon, produced by Mead-Johnson Laboratories; OrthoNovum SQ, produced by Ortho Pharmaceutical Company, and Norquen, produced by Syntex. Of the 15 endometrial cancer patients taking sequentials, 14 were taking Oracon. Silverberg says that he cannot explain the overrepresentation of this particular product although it might reflect the drug's share of the sequential market. This constitutes from 40 to 70 percent of the sequentials sold; the size of the estimate depends on who is doing the estimating.

Panel Convened

According to a statement prepared by Mead-Johnson, a panel of "eminent medical authorities," convened by the company, reviewed the data concerning the occurrence of endometrial cancer and its relationship to use of sequential oral contraceptives. The panel concluded that "the incidence of cancer in Oracon users would fall within published incidence figures of the general population in the specific age group and type of patients for which sequential oral contraceptives would be prescribed." (Since Oracon was introduced in 1965, more than 55 million cycles of the drug have been distributed in the United States.) A spokesman for Mead-Johnson declined to identify the medical authorities who reached this conclusion.

In any event, Silverberg points out that he accumulated the data by advertising in medical journals 2 years ago and asking physicians to send him pertinent cases. Since he depended on others to refer cases to him, Silverberg does not know the total number of cases of endometrial cancer in women of reproductive age during the time in question or how the number of cases in women taking the pill compares with that in women not taking an oral contraceptive. However, he does note that the excess representation of users of sequentials in his sample is consistent with current thinking that unopposed estrogens may be more hazardous in regard to cancer than estrogen counterbalanced by progestogen.

In a retrospective study, Ralph Paffenbarger of the California State Department of Health in Berkeley detected no effect of contraceptive pills on the overall incidence of breast cancer. But he says that the data do indicate some worrisome, even if preliminary, trends. Use of the pill further increased the risk of breast cancer in two groups of women already known to have somewhat higher than normal chances of developing the disease. These include women with benign breast disease, including cysts, although they had to use the pill for 6 or more years for the increase to be

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significant, and women who did not have their first pregnancy until their late twenties. Finally, women who took the pill for 2 to 4 years appeared to have a somewhat higher incidence of breast cancer than women who took it for less than 2 or more than 4 years. Paffenbarger said that these data may indicate that contraceptive pills accelerate the development of preexisting but undetected cancers, rather than initiating the development of new cancers.

Other studies have not uncovered any relationship between oral contraceptives and breast cancer. One of the largest of these is a prospective study including 23,000 women that has been conducted since 1968 by the Royal College of General Practitioners in England. This study and several others have also shown that there is a decreased incidence of benign breast disease in pill users. Since benign conditions predispose to breast cancer, this means that the pill may actually be protective for some women.

The Walnut Creek Study

In the United States, the Walnut Creek Contraceptive Drug Study carried out under the auspices of the Kaiser-Premanente Health Foundation in Walnut Creek, California, is another large prospective study concerned with the side effects of oral contraceptives. According to Savitri Ramcharan, the study director, it involves a total of 18,000 women who have participated in the program for up to 7 years. Because of the rarity of cancer in women of reproductive age—probably no more than one case per 1000 women per year—Ramcharan says that they are just now accumulating enough cases to give statistically significant results. It will be several months before an analysis of the data is completed.

Because of the importance of questions concerning the effects of oral contraceptives on cancer incidence, Heinz Berendes of the National Institute of Child Health and Human Development (NICHD), the institute with primary responsibility for research related to oral contraception, wrote to all the investigators under contract to NICHD to determine whether they had collected data that might provide answers. Unfortunately, most investigators did not have appropriate data. Conducting epidemiological studies that are large enough to produce statistically significant results in a reasonable period of time is difficult. Thus, it may be a while before there is a definite answer to questions about the pill and cancer.

—JEAN L. MARX

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Mathematicians are also using variational inequalities to solve optimal stopping problems, which are stochastic problems derived from economics. These problems, unexpectedly, turn out to be equivalent to moving boundary problems. An optimal stopping problem considered by Friedman and his colleague Robert Anderson of the University of Pittsburgh involves quality control in a manufacturing plant. Two products are made by a machine: product A, which is a good product, and product B, which is made when the machine goes haywire but which cannot easily be distinguished from product A. The director of the plant loses money each time he checks the machine to determine whether it is making product A or B. On the other hand, he also loses money if he does not check and product B is made but not detected. The question, then, is how often should he check the machine so as to minimize his costs? The question is a stochastic one because there can be only probabilistic estimates of how often the machine will go haywire and make product B. Friedman and Anderson showed that such optimal stopping problems can be transformed into variational inequalities. They are solving these inequalities with analytical techniques.

J. L. Lions and Alain Bensoussan of the Institut de Recherche d'Informatique et d'Automatique in France are also solving optimal problems with variational inequalities. For example, these mathematicians analyzed a problem involving the ordering of stock from a warehouse. A business must pay a service charge each time it places an order for stock, independent of the amount of stock ordered. The business must also pay a penalty if it runs out of stock. The question, then, is how often should stock be ordered so as to minimize costs? The problem is a stochastic one because there can be only probabilistic estimates of how much stock will be purchased by customers at any time.

Perhaps because moving boundary problems are of such practical importance, the pace of research on these problems has been extremely rapid. A great deal of work begun in the past decade has now come to fruition and, consequently, the entire face of the field has changed. Now, many believe, there is reason to be optimistic that practical problems involving moving boundary problems can be solved.

—GINA BARI KOLATA

Additional Reading

1. J. R. Ockendon and W. R. Hodgkins, Eds., *Moving Boundary Problems in Heat Flow and Diffusion* (Clarendon, Oxford, 1975).