Estrogens: Hormones' Link to Cancer Disputed

During the past 3 years a series of epidemiological studies has suggested that the estrogen drugs taken by many women to relieve the symptoms of menopause cause cancer of the uterine lining (*Science*, 27 February 1976, p. 838). Recently, the validity of these studies has been challenged on the grounds that their design was flawed by bias favoring the detection of the cancer in estrogen users but not in nonusers. Needless to say, the investigators who performed the challenged studies disagree with this contention.

Most of the epidemiological evidence linking estrogen use to cancer of the uterine lining (endometrial cancer) comes from comparisons of the characteristics of women who have the cancer with those of control women who do not. The idea is to identify a difference between the two groups that might explain what caused the cancer. All the studies under question have shown that significantly more of the cancer patients than of the controls were estrogen users. Consequently, the investigators calculated that estrogen use increases a woman's risk of endometrial cancer by about seven- or eightfold.

Ralph Horwitz and Alvan Feinstein of Yale University School of Medicine are now saying that this apparent difference in estrogen use between the case and control groups is an accident of the sampling procedure by which the two groups were selected for the study and does not indicate that estrogen use is a significant risk factor for endometrial cancer.

They point out that estrogens are known to provoke uterine bleeding in some of the women who take the drugs. Because such bleeding is a symptom of endometrial cancer, its appearance usually means that the woman will have to undergo the diagnostic test for the cancer. Diagnosis of endometrial cancer requires a surgical procedure called dilatation and curettage, more commonly known as a D & C, to obtain a sample of material from the uterine lining. (Endometrial cancer is not detectable by the Pap test, which is routinely done to detect cancer of the uterine cervix.)

Horwitz and Feinstein propose that the high proportion of estrogen users among women with endometrial cancer reflects the fact that the users experience more bleeding than nonusers. Because the users will thus be more frequently referred for D & C's than members of the general population of women, Horowitz and Feinstein contend that estrogen use leads not to a true increase in the occurrence of the cancer but only to its increased detection.

The Yale investigators say it is necessary to choose the controls for the epidemiological studies in such a way as to compensate for this overrepresentation of estrogen users among the cancer cases. They suggest that the way to do this is to select both the controls and the cancer patients from among women subject to the same kind of medical surveillance. Thus, they conducted a study in which the controls and the cases were chosen from among the women referred to the Yale–New Haven Medical Center for the D & C procedure because of suspected uterine disease. In contrast, the controls for the studies questioned by Horwitz and Feinstein were selected from among women in the community or from among patients with gynecological cancers not characterized by uterine bleeding.

The results of the Yale study indicate that estrogen use is much less of a risk factor for endometrial cancer than suggested by the questioned studies. Horwitz and Feinstein calculate that estrogens increase the risk of the cancer only by a factor of 2 or less.

Estrogen Risk Underestimated?

The investigators who performed the studies supporting the hypothesis that estrogens cause endometrial cancer maintain that the high proportion of estrogen users among the cancer patients in their studies was not the result of a selection bias. Moreover, they think that the cancer group of Horwitz and Feinstein was also not biased in favor of estrogen users. Thus, there is no reason to introduce such a bias into the selection of the control groups. By doing so, they argue Horwitz and Feinstein greatly underestimate the influence of estrogen drugs on the risk of endometrial cancer.

This argument was forcefully stated by George Hutchison and Kenneth Rothman of the Harvard University School of Public Health in the same issue of the *New England Journal of Medicine* as that in which the Horwitz-Feinstein analysis appeared. Hutchison and Rothman say that increased medical surveillance of estrogen users might advance the date of diagnosis of any endometrial cancers but will have little effect on the total number of cases ultimately found. This means that there will be little overrepresentation of estrogen users, especially long-term users, in the cancer group. If Horwitz and Feinstein are correct, the highest incidences of cancer should be found in women who have used the drugs for short periods of time, according to Hutchison and Rothman. But the studies that have examined how the incidence of endometrial cancer varies with length of time of estrogen use have found the opposite effect—the highest incidences in the women who have used the drugs the longest.

The validity of Hutchison and Rothman's argument rests on the assumption that all or nearly all cases of endometrial cancer will eventually be detected whether the women are under increased medical surveillance because of estrogen use or not. The investigators who support the link between cancer and estrogens say that invasive endometrial cancer will eventually progress to the point where it causes symptoms and thus will not escape notice. Horwitz and Feinstein agree that invasive cancers will probably be uncovered but they think that the early, noninvasive form of the disease may not always progress and may not be detected even at autopsy, if the uteruses are not examined for disease. There are no obvious data to prove or disprove either of these points of view.

Investigators who support a link between estrogens and endometrial cancer also cite the observed increase in the incidence of the condition with increasing dosage and duration of hormone use. Correlations such as these are usually considered good evidence in support of a cause-and-effect relationship, but Horwitz and Feinstein point out that more bleeding problems will occur in women who use higher doses or take estrogens longer. Thus, these effects could also be the result of increased detection.

Another argument in favor of a link between estrogens and endometrial cancer is the rise in the incidence of the disease that became apparent early in this decade, a few years after estrogens began to be widely used for the treatment of menopausal symptoms. More recently, however, a downturn in the endometrial can-

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cer rate has occurred in several parts of the country.

Perhaps not surprisingly, both the investigators who support and those who oppose the idea of an estrogen-cancer link manage to interpret this downturn in favor of their own theory. The supporters suggest that the downturn reflects the decreased use of estrogens occurring as a result of the reports that the drugs cause endometrial cancer. The decrease occurred very rapidly, but this is consistent with the possibility that estrogens are tumor promoters rather than true carcinogens as some investigators propose. Tumor promoters do not cause cancer by themselves but speed up the development of tumors initiated by carcinogens (*Science*, 11 August, p. 515). The effects of promoters are reversible, at least up to a point, and the tumors do not develop if exposure to the promotor stops before this point is reached.

In contrast to this point of view, Horwitz and Feinstein propose that the increase in endometrial cancer was itself the result of increased detection. More D & C's and hysterectomies have been performed in the past decade or so and this would lead to more endometrial cancers being found. Now that the excess cancers have been detected, the incidence of disease is returning to its true level.

At present, seven epidemiological studies favor a link between estrogens and endometrial cancer. Five of the seven studies have been published and two are in press at the *New England Journal of Medicine*. Because two earlier studies, which were performed in a manner similar to that advanced by Horwitz and Feinstein, also discount the existence of the link, the score now stands at seven to three in favor of a causal connection between estrogens and endometrial cancer. But Horwitz and Feinstein quote the late epidemiologist Harold Dorn on epidemiological research of this type. Dorn said: "reproducibility does not establish validity, since the same mistake can be made repeatedly," an argument that can also be cited by the other side in this dispute.

As a result of the reports linking estrogen use to endometrial cancer, the Food and Drug Administration currently requires that the label for the drugs carry a warning that they are associated with an increased risk of the cancer; the label also advises physicians to prescribe estrogen in the lowest doses and for the shortest time required to control menopausal symptoms in order to minimize that risk. The FDA is reviewing the work of Horwitz and Feinstein, a process that should take about a month, to determine whether a change in the policy on estrogen use is warranted.—JEAN L. MARX

Hair: A Diagnostic Tool to Complement Blood Serum and Urine

Hair has the potential to become a remarkable diagnostic tool. It is easily collected without trauma on the part of the donor, it can be stored without deterioration, and its contents can be analyzed relatively easily. Trace elements, in particular, are accumulated in hair at concentrations that are generally at least ten times higher than those present in blood serum or urine and may provide a continuous record of nutritional status and exposure to heavy metal pollutants. Some drugs have already been shown to accumulate in hair, and it seems likely that other organic chemicals may be identified there when sufficiently accurate analytical techniques are developed. Hair analysis thus promises to be an ideal complement to serum and urine analysis as a diagnostic tool.

Much of the original interest in analysis of hair involved its application to forensic science. Early investigators hoped that measurement of the concentrations of 10 to 15 trace elements in hair might make it possible to link a hair sample obtained at the scene of a crime with a specific individual. Subsequent work has shown that hair analysis has limited forensic value; profiles of trace element concentrations vary significantly in hairs collected from different parts of the head, and profiles obtained with many hairs change appreciably with time. In the process, though, investigators found that hair analysis can indicate exposure to certain pollutants and can serve as a probe of physiological functions.

The best results have been obtained with heavy metal pollutants such as lead, arsenic, cadmium, and mercury. Several investigators in Japan, Sweden, Canada, and the United States have shown that concentrations of these elements in the hair provide an accurate and relatively permanent record of exposure, and that there is a good correlation between concentrations in hair and concentrations in internal organs. Typical examples of such measurements were provided by Amares Chattopadyyay of Dalhousie University at the Second Human Hair Symposium, which was held in October in Atlanta.

Chattopadyyay found, for example, that the concentration of lead in hair was lowest in rural population groups, higher in urban groups, and highest in individuals who live close to lead smelters. These differences are presumed to reflect differing exposures to lead in automobile exhaust, paint, and industrial emissions. He also observed the highest concentrations of mercury and cadmium in hair from individuals with known exposure to the metals. Similar results have been reported by other investigators, but the absolute concentrations reported differ appreciably because of differences in technique (see box). Chattopadyyay and others have also shown that the approximate time of occurrence of short, intense exposures to heavy metals can be determined by sectioning hairs along their length and analyzing each section.

Several groups are thus compiling baseline data about normal concentrations of trace elements so that hair analysis can be used to monitor exposure to pollutants. The most notable effort is that of the International Atomic Energy Agency (IAEA) in Vienna. Yu S. Ryabuahin of the IAEA is collecting analytical data on more than 40 elements from laboratories in 13 countries. Several individual investigators are doing the same thing on a smaller scale. Still others, such as Harold G. Petering of the University of Cincinnati College of Medicine, are feeding the heavy metals to animals in measured quantities and monitoring concentrations in hair in an effort to correlate exposure and concentrations.

Animal hair might also be used to monitor environmental pollutants. Norman F. Mangelson and his colleagues at Brigham Young University, for example, are analyzing trace element concentrations in the hair of rodents collected in Utah's Lake Powell Recreation Area, the site of a proposed coal-fired power plant. Once they have established baseline concentrations, they plan to contin-

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