

Medicine as an art demands constant evaluation, weighing new treatments against old practices, benefits against risks, successes against failures. On occasion, the evidence leads to different conclusions. Nowhere is this more evident than in the management of the cancer patient.

OPINIONS will present the views of specialists on a wide spectrum of controversial subjects. It is hoped that the frank expression of ideas will provide a framework within which our readers may form their own opinions.

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POSTMENOPAUSAL ESTROGENS AND ENDOMETRIAL CANCER

The menopause is a natural physiologic state, in which the ovaries cease to function. Delaying this phenomenon by the prophylactic use of estrogens is regarded by some physicians as a modern therapeutic advance, permitting the woman to remain youthful, healthy and "feminine forever." Others, including myself, are concerned by increasing evidence that long-term estrogen therapy may be correlated with the development of endometrial cancer. Supportive data for the estrogen-cancer hypothesis is substantial and, although further analysis is necessary, difficult to discount.

Experimental evidence that estrogen is a powerful growth-stimulating agent in the female genital tract dates back at least to the 1920s. This suspicion was further enhanced in the next 20 to 30 years by numerous accounts of endometrial cancer (and, incidentally, the breast as well) in women who were exposed to estrogen.

During this time, in 1947, my colleagues and I demonstrated conclusively that adenomatous hyperplasia, a precursor of endometrial cancer, could be produced in humans and lower animals by continued estrogenic stimulation. Crossen and Loeb also noted such a change in the endometrium of aged mice given estrogen; Meissner and Sommers induced endometrial hyperplasia in rabbits. This correlation is now well known. We have also seen adenomatous hyperplasia of the endometrium in young women who have failure of ovulation, such as those with Stein-Leventhal disease, infertility or those under the stimulus of functioning ovarian tumors. The incidence of true endometrial cancer is also higher in these patients, especially in postmenopausal women.

My interest in the hormone relationship of endometrial cancer was further generated by a great deal of circumstantial evidence. Repeated studies revealed that women with endometrial cancer appeared to show a greater prevalence of obesity, nulliparity, infertility and dysfunctional bleeding than patients with other neoplasms of the uterus or with controls. These are all conditions wherein estrogen may constantly stimulate the uterus without progestational neutralization, which ordinarily occurs with ovulation in the normal cycling woman. Reports of therapeutic benefit with progestagens in patients with ad-
vanced endometrial cancer\textsuperscript{19,20} and evidence of reversibility of adenomatosus hyperplasia and carcinoma in situ of the endometrium by Kistner\textsuperscript{21} and our group\textsuperscript{22} again point up an endocrine trigger for progressive endometrial change in some patients. The mode of action of progestational substances is not yet clearly known, although there can be no doubt of some effect. Much work remains to be done in the field of molecular biology. With the advent of better steroid technology, it has already been demonstrated that postmenopausal women with carcinoma of the endometrium, especially those who are obese, can convert an adrenal steroid, androstenedione, to estrone at a greater rate than do controls.

All of these studies clearly indicate that estrogens are a potent substance, and one that should be used judiciously, not prophylactically, in postmenopausal patients. This viewpoint has been dramatically supported by three epidemiologic studies conducted in the last year or so.

In Seattle, a history of estrogen use or non-use was compared in 317 patients with endometrial cancer and 317 controls. Estrogen users were found to be 4.5 times more likely to develop endometrial cancer than non-users. A group in Los Angeles reviewed the histories of 94 women with cancer of the endometrium and 188 women without such a history, and concluded that the risk of endometrial cancer was 7.6 times higher in those who had taken conjugated estrogens. Risk increased with duration of use, and was 13.9 times greater in women who had been on estrogens for seven or more years than in non-users. The third study, at a California retirement community, showed that women who had used estrogens were eight times more likely to develop endometrial cancer than non-users. Risk appeared to increase with dosage. These epidemiologic studies have confirmed my opinion that estrogen may act as a stimulant to seedling, dormant areas in the endometrium, perhaps already established, allowing them to grow into true cancer.

Supportive evidence continues to mount. Most striking is the finding by Herbst and colleagues that women given stilbestrol (a non-steroidal estrogen) in early pregnancy have adolescent female offspring who now show a high incidence of benign changes in the cervix and vagina, and a small incidence of adenocarcinoma of the vagina.\textsuperscript{23} This occurs at a time of life almost unknown in patients without a history of maternal ingestion of estrogen in pregnancy.

Furthermore, a small group of young women with Turner’s syndrome have recently been found to develop endometrial cancer following estrogen therapy to stimulate growth of their secondary sex characteristics. And, in the last year, there have been several reports of women taking sequential oral contraceptives who have carcinoma of the endometrium at a relatively young age, when otherwise not usually expected.

Accepting the conclusion that the risk of endometrial cancer is increased by long-term estrogen therapy in postmenopausal patients, I recommend the following guidelines.

- Women who require estrogen to control flushes or atrophic vaginitis—and these are the minority of women in the menopause—can be given estrogens safely on a short-term basis, under medical control.
- The prophylactic use of estrogens for all postmenopausal women to preserve youth, for cosmetic effect or for the prevention of coronary disease, is without hard evidence and, in my opinion, not justified.
- The use of estrogen for the prevention of osteoporosis, while it may play a role, clearly involves a greater risk than diet or exercise, which also play a role.

The current vogue of estrogen therapy
to keep postmenopausal women "young" and vigorous is based on a myth that has sadly been dispelled for those women who now have endometrial cancer.

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