A Physiological Approach to Ovarian Cancer

Several years ago, George Crile, of the Cleveland Clinic, observed that his clinic had removed only 11 thyroids that year, and that they had done more than 5000 thyroidectomies annually in the 1920s. The reason for the change was that they found that there was rarely any reason to remove the gland; even thyroid cancers of most types could be controlled safely by using a thyroid supplement, to reduce the growth-stimulating action of the pituitary hormone.

Since many physicians still believe that destruction of the thyroid gland, by radiation or surgery, is an appropriate treatment for thyroid disease, it isn't surprising that there is so little attention given to the possibility of physiologically controlling the more aggressive ovarian cancers. The recent report that ovarian cancer is more common among women who have taken gonadotrophins, to promote fertility, will probably bring increasing attention to the physiology of ovarian tumors.

Around menopause, the pituitary gonadotrophins increase. Menopausal estrogen treatment shouldn't be called "estrogen replacement therapy," because the amount given is typically about 15 times higher than occurs in younger women. The reason for the use of such high doses is that the dose is increased until the pituitary gonadotrophins are suppressed. The reason for the menopausal increase in pituitary hormones is that the nerve cells which regulate their secretion have been killed or desensitized by their past exposure to estrogen; it is their reduced sensitivity that requires the very large doses of estrogen to suppress secretion of the gonadotrophic hormones.

Clonidine (normally used for high blood pressure) can be used as a skin patch, to control menopausal flushing; progesterone and DHEA prevent osteoporosis. After those issues have been taken care of, the question of pituitary hyperfunction should be considered, in relation to preventing ovarian cancer. (Combinations of safe substances including progesterone and naloxone can probably be worked out empirically.) A variety of other possibilities exist, including Gonadotrophin Inhibiting Substance, and antagonists to the specific gonadotrophin release hormones. Normalizing the menopausal gonadotrophins would have far-reaching effects, possibly improving the immune response.(1)

For years, it has been known that nuns have a high incidence of ovarian, breast, and endometrial cancer. Women who have children, or who take oral contraceptives that might suppress ovulation, are believed to have a lower incidence of ovarian cancer because of reduced exposure to the gonadotrophins. (Though cancers of liver, breast, and other organs are reported to be more frequent among pill users; prolactinomas seemed to become epidemic after the pill was introduced.)

Normal factors in the physiological control of the ovaries include an interaction between the thyroid and the gonadotrophins; the combination of hypothyroidism and stimulation by gonadotrophins can cause ovarian cysts to develop. Small amounts of estrogen can increase both FSH and LH, and large amounts of progesterone decrease both FSH and LH.(2)

If ovaries are removed from their normal location, and transplanted into the spleen, so that their secretions go directly to the liver where they are inactivated, they produce tumors because they are subject to "hypersecretion of gonadotrophic hormones."(3) Other experiments support the idea that ovarian tumors develop from excess pituitary stimulation. For example, removal of one ovary was essential to produce a tumor in the other ovary even after it had been irradiated.(4) Similarly, no tumors developed in irradiated ovaries transplanted into other mice, irradiated or not, as long as they had their own ovaries, which kept the pituitary functioning normally.(5)

Progesterone and estrogen "receptors" can be demonstrated in some ovarian tumors, and by analogy with breast and uterine tissue, in which progesterone generally retards cell division and estrogen stimulates it, hormones have been investigated as possible therapies for ovarian cancer. Although in vitro studies show that there might be a direct action on the tumor cells,(6) the reports of positive responses in patients treated with progesterone or synthetic progestins(7) are more interesting, since the most logical approach involves normalization of the pituitary gonadotrophins.

If it is true that a "deficiency" of the so-called "essential" fatty acids suppresses gonadotrophin secretion,(8) then a diet lacking those estrogen-promoting(9) substances should be both protective and therapeutic for ovarian cancer (assuming that the results seen with progestin therapy are produced by gonadotrophin inhibition.) If our purpose is to delay the menopausal rise of the gonadotrophins, then it is interesting that lipid peroxidation of polyunsaturated fatty acids (which increases with age) can be intimately involved in loss of progesterone forming ability by human steroidogenic tissues.(10) That is, aging decreases the ability of certain brain cells to inhibit the pituitary gonadotrophins, and it also tends to decrease the steroidogenic tissues' ability to produce the regulatory steroids.

After menopause, estrogen is produced less by the ovary than by other tissues, including fat cells. Breast cancer cells can produce their own estrogen. This means that estrogen is one of the "cancer hormones" which, secreted by the tumor, promotes the growth of the tumor and also has a systemic pro-cancer action. Ovarian tumors, too, can cause great systemic hormonal imbalances, which should be investigated routinely in a physiological approach to the disease. After menopause, estrogen is largely produced by conversion of "androgenic" steroids from the adrenal glands. It would be desirable to be able to inhibit the conversion of the adrenal steroid precursor to estrogen. Newton, et al.(11)

showed that progesterone inhibits the conversion of the precursor to estrogen, and P.K. Siiteri showed a similar effect for thyroid hormone.

A diet low in polyunsaturated fats facilitates thyroid hormone secretion, transport, and tissue response to it, and would minimize the stress-related or age-related inhibition of progesterone formation by lipid peroxidation. Vitamin E and vitamin A also protect against lipid peroxidation, and vitamin A is specifically involved in progesterone synthesis. Vitamin A also has a variety of anti-estrogen functions,(12) that are often considered to be relevant to protection against cancer.(13)

All of these dietary and hormonal approaches to normalizing the pituitary gonadotrophins and controlling ovarian cell division are things which also tend to optimize the immune response. A slight deficiency of iron is probably protective against cancer, since there are several ways that iron can promote cancer, apart from its role in damage to the immune system and the steroidogenic system by lipid peroxidation.(14)

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