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Editorial

Hormone Replacement Therapy for Women with a Past History of Breast Cancer

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It is received wisdom among oncologists that hormone replacement therapy (HRT) is contraindicated in women previously treated for breast cancer. However, recent changes in the formulation of HRT in addition to new evidence from biological research, suggest that this advice needs to be revised (Stoll, 1989). The issue involves even wider implications, since a recent conference concluded that the antioestrogen tamoxifen may be the ideal replacement therapy for some postmenopausal women at increased risk to breast cancer (Love, 1990).

Changes in the formulation of HRT have resulted from evidence linking oestrogen replacement therapy to an increased incidence of endometrial cancer. While low doses of oestrogen still remain the basis of HRT, most authorities now advise cyclical therapy, with progestogen added for one or two weeks in every four, in order to avoid the risk of endometrial cancer in women who still retain the uterus. In relation to the risk of breast cancer from such a formulation, a Consensus Conference (1987) concluded that there was no epidemiological evidence that such HRT would increase the risk.

At present, women with a history of breast cancer and complaining of menopausal symptoms are generally given a trial of the non-hormonal agent clonidine or the progestogen norethisterone. They are of limited effectiveness in relieving severe symptoms and it is time to re-examine the postulated dangers of giving HRT to women with a past history of breast cancer in relation to the following: (a) the risk of stimulating regrowth of breast cancer; (b) the risk of stimulating proliferative activity in mammary epithelial cells; (c) the biological effect of a progestogen/oestrogen combination on both types of risk.

With regard to the risk of stimulating regrowth of occult breast cancer, the effect of oestrogen is known to be dose-dependent. Low dosage of oestrogen may stimulate tumour growth whereas high dosage inhibits it (Powles, 1988) and this is confirmed in human breast cancer cell lines (Welsch, personal communication). We must, therefore, maintain the conventional advice that for women who have been treated previously for breast cancer, it is not advisable to prescribe unopposed, low dosage oestrogen, whether by mouth, vaginal cream, skin patch or implant. We must also advise that oestrogen replacement therapy be stopped if breast cancer manifests in a woman.

Such a prohibition does not necessarily apply to progestogen/oestrogen combinations. There is now considerable evidence that oestrogen-stimulated breast cancer growth can be inhibited by progestogens. In the laboratory, several reports have shown that adding progestogen to oestrogen counteracts its stimulation of growth in hormone-dependent human breast cancer cell lines such as MCF7 and T–47D (Vignon *et al.*, 1983; Allegra and Kiefer, 1985; Horwitz, 1985; Klijn *et al.*, 1989). It needs to be noted that previous oestrogen priming appears to be essential for growth inhibition by progestogens, and that given by itself, progestogen may stimulate growth in these cell lines (Klijn *et al.*, 1989; Murphy and Dotzlaw, 1989). With regard to clinical evidence, there is a very large literature reporting regression of advanced breast cancer following high dosage progestogen, both in postmenopausal and premenopausal patients. Again, the importance of oestrogen priming is shown by the observation in postmenopausal women that regression is much more likely in patients showing evidence of persistent oestrogen secretion (Stoll, 1967a).

In relation to the topic of this editorial, an important observation is that combining oestrogen with low dosage progestogen (as well as with high dosage) can cause regression of postmenopausal breast cancer (Stoll, 1967b). In 65 postmenopausal women with advanced breast cancer, 3–6 months *continuous* administration of lyndiol (a combined oestrogen/progestogen contraceptive) at contraceptive dosage, caused significant tumour regression in 22% of cases when used as secondary hormonal

inhibiting breast cancer growth in a proportion, the pill controlled menopausal symptoms in those patients in whom they were recorded when treatment was instituted.

With regard to the risk of stimulating proliferative activity in mammary cells which have already undergone malignant transformation, multiple epidemiological studies have looked for a change in the incidence of breast cancer among postmenopausal women receiving HRT (mainly oestrogen replacement therapy). Some studies have found a lowered risk of breast cancer (McDonald *et al.*, 1986; Gambrell, 1988), some an elevated risk in at least some subgroups (Hoover *et al.*, 1976, 1981; Ross *et al.*, 1980; Brinton *et al.*, 1981) while others have reported no change in the risk (Casagrande *et al.*, 1976; Hiatt *et al.*, 1984; Buring *et al.*, 1987). It is often overlooked that women complaining of severe menopausal symptoms may be a special subgroup with a hormonal make-up predisposing them to breast cancer, and few published studies have separated subgroups according to recognized risk factors. If this is done, breast cancer is shown to be more common after HRT in women undergoing a natural menopause than in those who have undergone early oophorectomy (Rohan and McMichael, 1988) or hysterectomy (Mills *et al.*, 1989). It is well recognized that a late menopause is a major risk factor for breast cancer.

A recent meta-analysis of 23 published studies found no evidence of increased risk from HRT except in those with a family history of breast cancer or in those taking the highest dosage of oestrogen (Armstrong, 1988). The question of oestrogen dosage has been highlighted in a report from the USA (Dupont *et al.*, 1989). In a large series, the administration of exogenous oestrogen (almost entirely HRT for menopausal symptoms) was found to be associated with a *lowered* risk of breast cancer in a group of women previously found to have histopathological changes of proliferative disease, even to the extent of atypical hyperplasia. The risk was reduced whether or not there was a history of breast cancer in a first degree relative. The authors point out that the lowered risk occurred only in women treated after the mid 1950s, a time when physicians in the USA reduced their dosage of natural conjugated oestrogen to 0.625 mg daily. Several reports confirm that the risk of breast cancer following HRT is increased by higher dosage of oestrogen (Hoover *et al.*, 1976, 1981; Ross *et al.*, 1980; Brinton *et al.*, 1981).

What then is the biological effect of adding progestogen to oestrogen, or the risk of stimulating proliferative activity in mammary cells which have already undergone malignant transformation? It is conventionally assumed that progestogen does not inhibit breast cell division because proliferative activity in the breasts of women using combined oral contraceptives is as high as in those with normal menstrual cycles (Meyer, 1977; Potten *et al.*, 1988). However, it is widely agreed that epithelial proliferation is the normal prelude to alveolar differentiation and secretory change in mammary tissue. Thus, while progestogens may increase cell proliferation in the oestrogen-primed breast, they also cause terminal differentiation. In this way, progestogens may act as antimitogens by directing the breast cells through the proliferative state towards a more differentiated, less cancer-susceptible state (Pike, 1985).

Very few biological observations have been made on the effect of oestrogen/progestogen combinations on the proliferation of normal human mammary cancer cells in tissue culture. Whereas Longman and Buehring (1987) found no significant effect from a combination of oestrogen and progestogen on such cells, Gompel *et al.* (1986) found that some types of progestogen could inhibit the mitogenic effect of oestradiol. It should be noted that in the latter experiments, the concentration of the agents was in the physiological range, whereas in the former, they were at much higher levels.

There are also very few epidemiological reports on the effect of HRT by a progestogen/oestrogen combination on the risk of breast cancer. One recent analysis reported that its administration for 6 or more years was associated with a fourfold increased risk but the database involved only 10 cases of breast cancer (Bergkvist *et al.*, 1989). On the other hand, three epidemiological studies report that the addition of progestogen to oestrogen in HRT can lower the risk of breast cancer in postmenopausal women (Nachtigall *et al.*, 1979; Gambrell *et al.*, 1983; Lauritzen and Meier, 1984). One of these studies noted that women not receiving HRT had a fivefold greater incidence of breast cancer compared to women on an oestrogen/progestogen formulation, while those who received oestrogen alone had an intermediate incidence (Gambrell *et al.*, 1983).

To date, only one clinical trial of HRT by an oestrogen/progestogen combination has been reported in women previously treated for breast cancer and remaining clinically free of disease (Stoll and Parbhoo, 1988). It was a Phase 2 trial in women with either severe sweats not responding to clonidine therapy (0.05 mg bd) or with symptoms of vaginal or urethral atrophy. A combination of natural conjugated equine oestrogen (0.625 mg) with norgestrel (0.15 mg) was given daily for an unbroken period of 3 months. Treatment was continued for a further 3 months if symptoms were not completely relieved.

All the treated patients showed marked improvement in flushes or genital atrophy. The patients were followed for at least 2 years and no tumour reactivation was recorded in the series during the period of observation. The combination is a widely used prescription for HRT both in Europe and the USA but in the general population, the progestogen component is given for only 7–12 days each month, whereas in the above trial it was given continuously throughout the month in order to counteract any possible mitogenic effect of oestrogen.

Thus, the available evidence suggests that a low dosage progestogen/oestrogen combination given continuously for several months is effective in the relief of severe menopausal symptoms in women treated previously for breast cancer. Moreover, considerable clinical, laboratory and epidemiological evidence suggests that low dosage progestogen/oestrogen combinations are likely to protect women both against the risk of breast cancer reactivation and also the risk of progression in premalignant lesions in the breast.

It is unlikely that epidemiological studies in the near future will be able adequately to test this hypothesis. The practical alternative is to set up clinical trials of continuous low dosage progestogen/oestrogen combinations in advanced breast cancer which has lost response to primary endocrine therapy. (A 22% response rate in the trial reported above, makes this ethical and acceptable therapy). Those formulations found to be most effective in causing cancer regression could then be investigated in the laboratory for their ability to inhibit the proliferative activity of human mammary cancer cell lines and human mammary epithelial cells. Hormone replacement therapy which controls menopausal symptoms and protects against breast cancer is on the horizon.

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