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# Oestrogen therapy and endometrial cancer

Hormone replacement therapy (HRT) is now a fashionable approach to treating menopausal symptoms. Originally short-duration oestrogen treatment was used, but more recently long-term oestrogens have come into vogue in the belief that not only will they alleviate symptoms but they may also delay the inevitable onset of some disorders of old age such as osteoporosis. Evidence supporting the use of oestrogens for the short-term relief of menopausal symptoms is, however, controversial,[1] and for the long-term prevention of osteoporosis it is as yet incomplete.[2]

So far the main hazard attributed to HRT has been uterine cancer. Evidence of an impressive association between long-term oestrogen therapy and endometrial carcinoma appeared in a series of three case-control studies[3–5] from the United States in 1975-6. All of these reported that the risk of endometrial cancer in women given HRT was between four and eight times the risk for non-users. Predictably, the studies came in for immediate criticism from opponents of the case-control approach to medical research. One editorial claimed that the studies were invalid on the grounds that they were not prospective cohort studies performed double-blind with random allocation of patients to treated and untreated groups.[6] Moreover, the studies were said to be of patients who were unrepresentative of the female population at large, since in some the control (reference) patients did not contain women who had had a hysterectomy—possibly 30% of American women in the studied age groups.[7]

Each and every one of these criticisms is invalid and shows a misunderstanding of the case-control approach as it applies to drug-related diseases. The key issue in these studies is not the representativeness of the controls in terms of the populations from which they were drawn: what matters is the comparability of cases with controls in terms of factors which may be related to the disease or the exposure being studied. Though some would argue that it would be appropriate to include among the controls a subgroup who could by definition never become cases (patients with hysterectomy cannot develop endometrial cancer), to others this may seem if not indefensible at least undesirable.

In the light of this controversy a recent further study is of some interest. Gray and his colleagues in Kentucky[8] have compared the use of HRT in a group of 205 patients with histologically proved endometrial carcinoma and 205 patients from the same gynaecological practice who had had a hysterectomy for benign disease. The use of HRT in the cancer patients had been three times greater than in the control subjects. Excess use was present among young and old, parous and nulliparous women, obese and non-obese, diabetics and non-diabetics, and those with and without hypertension. There was a clear trend towards increasing risk with length of duration of HRT use, so that the risk was increased 11-fold for those having had such treatment for 10 years or more. One reason why this study gave a lower summary relative risk than the previous ones was the use of controls who had also had a hysterectomy. This leads to the potential bias that the conditions from which these patients had suffered themselves may have been indications for oestrogen therapy. The authors were aware of this problem and made serious attempts to control it in the analyses. Nevertheless, probably they could not take it into account completely, and hence they may have underestimated the true relative risk among those using HRT for periods less than five years.

If HRT is conducive to the development of endometrial carcinoma then (after a suitable latent interval) the frequency of this tumour should be increased in areas where the treatment is in common use. That has, indeed, been reported. In a detailed study of several cancer registries in the United States Weiss *et al*[9] reported a sharp increase in the previously stable incidence rates of this tumour in the 1970s. The increase was most definite in middle-aged women, the group in which any effect of HRT would be expected.

Is a hypothetical relationship between oestrogen therapy and endometrial carcinoma biologically credible? Clearly the answer must be yes. Women with oestrogen-secreting tumours are at high risk of developing this tumour[10]; oestrogens stimulate hyperplasia of the endometrium[11]; obese women, who are at high risk of developing the tumour,[12] have higher than normal amounts of circulating oestrogens[13]; in animals parenteral stilboestrol can lead to endometrial carcinoma[14]; and in women long-term oestrogen use can lead to endometrial hyperplasia[15]—itself a condition which can be regarded as premalignant.[16,17] In a small series of 24 women receiving long-term stilboestrol therapy for gonadal dysgenesis carcinoma of the endometrium was reported in two and

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possibly three of them before the age of 36.[18] Thus there is substantial credibility for this hypothesis.

If a causal interpretation of the association is accepted, can the risks be minimised without abandoning HRT? Some workers have suggested that this could be done by prescribing oestrogens sequentially with progestogens to induce regular endometrial shedding.[19] Nevertheless, we have little hard information on which to judge this claim. Cohen and Deppe[20] have recently reported six patients who took sequential agents for oral contraception and subsequently developed endometrial carcinoma. None was obese or diabetic, but one was nulliparous and two were hypertensive. Other workers have also reported such tumours in long-term users of sequential oral contraceptives,[21 22] suggesting that as administered synthetic progestogens were not totally protective.

Thus the circumstantial evidence that HRT is associated with endometrial cancer is now so strong and comes from so many studies that it cannot be ignored. A causal interpretation of the association seems likely on the basis of the strength and magnitude of the relative risk, the absence or control of obvious confounding factors (such as age, diabetes, hypertension, obesity, and parity), the increased incidence of the tumour in association with increased use of this treatment, and the intrinsic credibility of the hypothesis.


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# Need part time be second-rate?

Part-time doctors have an unfortunate amateur image. Some of the opprobrium is a legacy of the time when a few NHS consultants spent almost every afternoon with their private patients (or on the golf course). Some comes from the conviction among dedicated enthusiasts that total commitment is needed in demanding specialties; and, finally, some comes from occasional examples of married women working part time who take a lot of time off to cope with their sick children and other real or manufactured domestic crises.

None of these objections should be allowed to justify a blanket condemnation of part-time work, and, indeed, the Royal College of Physicians of London has recently produced a report[1] encouraging women to undertake part-time training in internal medicine. Reasonably enough, the report advises women (and men whose domestic commitments make part-time work attractive) to complete the preregistration year in conventional posts, but thereafter it sees no essential reason for specialists in training to work full time.

Training may be arranged on a part-time basis in two ways. Firstly, the DHSS circular HM(69)6 gave regional hospital boards powers to establish part-time appointments in any grade from house officer to senior registrar, tailor-made to the individual. Sadly—as the report admits—when an application is made the administrative red tape may take as long as a year to untangle, and not surprisingly discouraged women doctors sometimes drift into a clinical assistantship or a sessional job in general practice. Alternatively, a full-time registrar or SHO post may be split into two five-session jobs—but again the arrangements have to be made in response to individual demand and there may be administrative delays.

Consultant appointments do not even have the backing of a Department circular for those seeking seven or fewer sessions a week. Some regions—notably Oxford—have advertised consultant posts with the comment that "doctors able to offer only seven sessions because of domestic commitments are encouraged to apply" and have appointed married women as the candidates of greatest merit. There is still, however, a suspicion in some minds that making part-time consultant appointments with so few sessions is unacceptable politically because it encourages private practice or that in some way a part-time appointment is second-best.

The remarkable aspect of these schemes is that they seem designed to cater for a tiny minority of all women doctors. In effect, the DHSS attitude seems to be that special arrangements may be made for any woman who creates a fuss and makes a personal approach to her postgraduate dean to get him to pull the right strings. Such an approach may have been appropriate when the few women who qualified as doctors were expected either to stay single or to stop work; it makes no sense when women make up 30-40% of the total student intake. Medicine—and other professions such as nursing—needs to recognise that most women want to have children and that they prefer to divide the years from 25 to 45 between their careers and their families. These practical arguments were used successfully by the BMA to persuade the EEC to recognise the importance of part-time specialist training.[2]

The college report is realistic in suggesting that women pursuing part-time training should generally avoid the most competitive specialties; but for most branches of medicine there should be many more opportunities for women wishing to work 5-7 sessions a week. There are at present wide variations in the interpretation of HM(69)6 from region to region, reflecting its permissive nature. What we need is a coherent policy for the part-time employment of a large proportion of all women doctors—but doing first-rate and not second-rate work. Such a policy should be central to any realistic projections made by the central manpower committee for the next decade.

[1] Royal College of Physicians of London, *Part-time Postgraduate Training in Medicine*. London, Royal College of Physicians, 1977, price 30p.
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