CORRESPONDENCE

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Hormone replacement treatment

SIR,—Dr Paul Belchetz reviewed the advantages and risks of oestrogen replacement therapy and pointed to the advantages of percutaneous or subcutaneous routes of delivery.[1] Even so, a casual reader could be forgiven for concluding that oral therapy with so called "natural oestrogens" is safe, but is it?

These oestrogenic preparations are natural to horses rather than humans, and, furthermore, they undergo substantial change in the gut and liver before entering the systemic circulation. Can we really be reassured that oral oestrogens reduce the risk of cardiovascular morbidity?

Unfortunately, in the published case-control and cohort studies comparison is not between like and like. Study groups invariably contain more health conscious women, at low risk from death from all causes other than suicide.[2] There are fewer smokers or obese or hypertensive women and their exercise and dietary habits are likely to be more favourable than those of the controls. Even so, the Framingham study showed an increase in cardiovascular morbidity.[3] This long running study included more older patients and should not be ignored. Why should oral oestrogens, given together with 12 days of progestogen, not carry similar risks to oral contraceptive steroids? Given the available alternatives, should we not be circumspect, especially for women judged to be at high risk?

Nor should we underrate the potential for inducing breast cancer. Too few studies continued long enough to give meaningful results. The Louisville study, however, suggests an increasing risk when oestrogens are taken for more than 12 years and that the risk increases with duration of use.[4] This accords with what we know of the natural biology of the disease. All patients, especially those with a first degree family history, should know of this possible risk and cooperate with careful follow up examinations, including mammography. Anyone who is now more confused may find more help by reading Hunt *et al.*[2]

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1 Belchetz P. Hormone replacement treatment. *Br Med J* 1989; **298**:1467-8. (3 June.)
2 Hunt K, Vessey M, McPherson K, Coleman M. Long term surveillance of mortality and cancer incidence in women receiving hormone replacement therapy. *Br J Obstet Gynaecol* 1987;**94**:620-35.
3 Wilson PWF, Garrison RJ, Castelli WP. Postmenopausal estrogen use, cigarette smoking and cardiovascular morbidity in women over 50. The Framingham study. *N Engl J Med* 1985;**313**:1038-43.
4 Hoover R, Gray LA, Cole P, MacMahon B. Menopausal estrogens and breast cancer. *N Engl J Med* 1976;**295**:401-5.

AUTHOR'S REPLY,—To identify oestrogens commonly used in hormone replacement treatment as "natural" is not necessarily to equate them with better but simply to differentiate from the components of oral contraceptives. The proof of the pudding is in the eating and the studies cited do seem to indicate long term cardiovascular protection. The fact that equilin is natural for the horse rather than women does not in itself disqualify its use. There are certainly theoretical reasons to prefer preparations which deliver oestradiol into the systemic circulation, as was clearly emphasised. The important work by Hunt and her colleagues was referred to explicitly and is a source of many important data. The topic is bound to remain contentious, but when an accumulation of evidence produces a general consensus on matters as important as cardiovascular morbidity and mortality and prevention of osteoporosis, not to mention physical and psychological wellbeing, I believe it is responsible to come off the fence. The advice must necessarily be qualified by a realisation that absolute knowledge is unattainable and it is imprudent and unethical not to highlight areas of special concern.

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SIR,—Dr Paul Belchetz rightly argues that this treatment with oestrogen deserves wider use.[1] And as women have falls more often after the age of 45[2] the antiosteoporosis benefits could be considerable, even if the treatment began before the menopause. But there are concerns about the progestogen, which is given to protect the intact uterus from endometrial carcinoma. As Dr Belchetz says, "Current wisdom dictates that it (progestogen) is given for 10 to 12 days each month." Current wisdom may be wrong, or at least half right. The type of progestogen used and its route of administration require more attention.

Most of the studies that show a benefit in circulatory disease have used unopposed oestrogen. There are metabolic grounds for believing that the progestogens (chiefly norethisterone and levonorgesterel) currently used in hormone replacement preparations could undo the good work of oestrogen by their adverse effects on lipids (particularly high density lipoprotein cholesterol).[3] In the younger age group a contraceptive effect cannot be promised and in women past the menopause the withdrawal bleeds are not always acceptable. Moreover, women frequently report loss of the benefits, or even the development of a "premenstrual syndrome," just during the time the progestogen is being given. Professor Malcolm Pike hypothesises (personal communication, 1989) that its effect in suppressing the oestrogen induced rise in sex hormone binding globulin might nullify a potential reduction in risk of breast cancer.

We urgently need a progestogen only pill or other systemic treatment releasing one of the new progestogens with less relative binding affinity for the androgen receptor—that is, 3-keto-desogestrel or gestodene. These would permit the oestrogen to have its potentially beneficial effects on lipids and sex hormone binding globulin. Possibly the best option of all, however, would be the use of a progestogen releasing intrauterine device simultaneously with systemic oestrogen.[4] This would virtually eliminate the systemic dangers of progestogens, the "premenstrual" symptoms, and (normally) all uterine bleeding. It is a tenable hypothesis that the uterus would be protected against endometrial cancer, and, when relevant, the contraceptive effect would be particularly high in this age group. But the important point is that this intrauterine "contraceptive" would be valuable even when contraception itself was not required.

May I reinforce pressure on the relevant manufacturers: we urgently need them to produce these 3-keto-desogestrel-gestodene only treatments and progestogen releasing intrauterine devices. The latter are needed not only to replace the Progestasert but also the levonorgestrel releasing devices whose future development has been blocked.

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1 Belchetz P. Hormone replacement treatment. *Br Med J* 1989; **298**:1467-8. (3 June.)
2 Winners J, Morgan CA, Evans JG. Perimenopausal risk of falling and incidence of distal forearm fracture. *Br Med J* 1989;**298**: 1486-8.
3 Larosa JC. Effect of estrogen replacement therapy on lipids: implications for cardio-vascular disease risk. *J Reprod Med* 1985;**30**(suppl 10):811-3.
4 Bowen-Simpkins P. Contraception for older women. *Br J Obstet Gynaecol* 1984;**91**:513-5.

SIR,—Dr Paul Belchetz contended that in the face of the relatively low level of prescribing in Britain and the "flood of material in the media . . . promoting the treatment" we need to "look hard at the risks and benefits of hormone replacement therapy."[1]

A focus of his brief review was the potential benefits of oestrogen treatment in relation to cardiovascular disease. It is true that there is now a substantial body of evidence suggesting a strong protective effect.[2] There was, however, no reference to the fact that these data are derived almost exclusively from studies of women taking *unopposed* oestrogens. As most women with intact uteri are now prescribed oestrogens opposed by a progestogen it is important to acknowledge that we do not yet know whether the use of opposed oestrogens in the perimenopausal and postmenopausal period will have a similar protective