

# Is there sufficient evidence for us to encourage the widespread use of hormone replacement therapy to prevent disease?

**A**N increasing number of women living in Britain have used hormone replacement therapy (HRT). In this month's *Journal*, Joy Townsend estimates, from government prescription data, that the proportion of women living in England aged 40 to 64 years who have used HRT increased from 2% in 1980 to 22% in 1994. Rising trends were also apparent in Scotland and Wales. These findings are supported by evidence from the Royal College of General Practitioners' Oral Contraception Study, which observed a threefold increase in 'ever' use of HRT during the 1980s.<sup>1</sup> If these trends continue, prescription costs alone may reach £150 million by the year 2000.

A number of factors are likely to be contributing to these trends. Menopausal symptoms are very common and are a frequent reason for consulting the primary care team. In the fourth National Survey of Morbidity Statistics for General Practice, 328 per 100 000 women consulted their GP for menopausal and post-menopausal symptoms — a 154% increase from the previous survey 10 years earlier.<sup>2</sup> This rise may partly be due to concurrent increases in the proportion of women who have had a hysterectomy, especially at a young age.<sup>3</sup> It may also reflect an increasing awareness of the burgeoning range of products available to alleviate symptoms. An additional powerful factor is the commercial pressure, strongly supported by some opinion leaders, to use HRT to prevent disease later in life. Currently, the focus is on preventing osteoporosis and cardiovascular disease.

In America, the lifetime probability of a 50-year-old white woman developing coronary heart disease is 46%, stroke 20%, breast cancer 10%, hip fracture 15%, and endometrial cancer 2.6%.<sup>4</sup> The magnitude and pattern of risk in British women is similar. In 1991, 68 479 women in England and Wales were certified as having died from ischaemic heart disease, 42 791 from cerebrovascular disease, and 13 786 from breast cancer.<sup>5</sup> Any treatment that could materially reduce these figures would be widely welcomed. It is not yet clear, though, whether HRT provides the desired miracle.

So far, almost all of the data regarding the cardiovascular benefits of HRT have been derived from observational studies conducted in the USA in women using unopposed oestrogen (predominately conjugated equine oestrogen). Most studies have found a reduced risk of coronary heart disease among oestrogen users compared with non-users: perhaps 35–45%.<sup>4</sup> This apparent benefit, however, may be due to selection processes whereby HRT is prescribed and maintained preferentially to healthier women rather than because of direct biological effects of the drugs themselves. Certainly studies have shown that HRT users differ from non-users in a number of ways that could affect their risk of heart disease.<sup>1,6,7</sup>

These potential biases are avoided in randomized clinical trials. Examination of cardiovascular events reported during clinical trials studying other, short-term, aspects of HRT do not suggest a large cardiac benefit from the numerous products studied (mainly opposed preparations that combine oestrogen with progestogen).<sup>8</sup> The uncertainty, however, will not be resolved until results are published from several large trials currently underway that use cardiovascular endpoints. Unfortunately, this information will not be available until the

turn of the century at the earliest. Meanwhile, randomized trials with surrogate endpoints<sup>9</sup> need to be interpreted cautiously, since the measured biological markers may not reflect the mechanism by which HRT exerts its effects. These studies cannot, therefore, provide substantial support for the observational data, nor can they inform us whether opposed preparations have the same cardioprotective effects as unopposed oestrogen. Depending on which marker is examined, additional progestogens may or may not diminish the benefits of oestrogen.<sup>9</sup> Recent observational studies that have suggested similar cardioprotective effects of the various preparations had insufficient statistical power to reliably detect differences between preparations.<sup>10,11,12</sup>

Even if the cardioprotection is found to be real, and unaffected by the addition of progestogen, the public health impact of current patterns of HRT use may still be modest. The evidence suggests that the cardiac benefits occur mostly in current users. For optimum impact, HRT would need to be used when most cardiac events occur, that is, after the age of 60. Thus, for primary prevention of non-fatal myocardial infarction, perhaps 106–187 women need to take HRT for 10 years to avoid one event if HRT is started at the age of 50, compared with only 27–49 women if treatment is started at the age of 60.<sup>13</sup> Most women currently use HRT for short durations, usually during the perimenopausal period. Barriers to long-term treatment include a commonly expressed reluctance on the part of non-hysterectomized women to receive preparations that might continue, or restart, regular vaginal bleeding; short-term side effects such as nausea and breast tenderness; and concerns about long-term adverse effects such as breast cancer. Women already known to have cardiovascular disease may be more motivated to use HRT for secondary prevention; the number who need to be treated to avoid a second event is also smaller than for primary prevention.

New insights into the possible relationship between breast cancer and HRT have been provided by a recent re-analysis of 90% of the worldwide epidemiological data about this issue.<sup>14</sup> Among current and recent (stopped within previous five years) users of HRT, there appears to be a small increased risk of breast cancer: about a 2.3% increase in relative risk for each year of use. This level of risk is similar to that associated with a delay in the age of menopause. The only factor to modify the risk of breast cancer in HRT users was the woman's weight as the effects of prolonged use are more pronounced in lighter than in heavier women. The cancers found in current and recent users are more likely to be localized without spread to axillary lymph nodes or more distant sites. These observations may reflect screening or detection bias, a true biological effect, or a mixture of these effects. Any excess in risk of breast cancer among HRT users is lost within five years of stopping, so the cumulative risk associated with the patterns of HRT use represented by the studies in the re-analysis (predominantly short-term use, at or shortly after the menopause, mostly oestrogen-only preparations) will be low. More information is needed about the risk of breast cancer associated with other patterns of use, such as the use of combined HRT formulations for prolonged periods by older women.

There is more information about the skeletal benefits of HRT. Observational studies show a reduced risk of hip, vertebral, and

wrist fractures among HRT users.<sup>15</sup> These findings are supported by randomized controlled trials which show that HRT protects against postmenopausal bone loss while treatment continues. Maintenance of bone mass for even a few extra years during the perimenopausal period is probably enough to materially affect the lifetime risk of fracture, although the exact length of treatment required remains unclear.

There can be little doubt that HRT is useful for the relief of menopausal symptoms relating to oestrogen deficiency. More information, however, is needed about the overall balance of risks and benefits associated with each HRT preparation used for varying durations by women at differing levels of disease risk. Only when such data are available can the primary health care team help women make fully informed decisions about whether to use HRT to prevent disease.

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# Medicine and the arts: let's not forget the medicine

There has been much talk recently in medical publications of the role of the arts and humanities in medicine. This discussion has focused largely on the perception that doctors have become less 'humane' in their approach to patients,<sup>1</sup> and that the scientific aspects of medicine in evidence-based practice are now outweighing the personal. In a recent issue of the *BJGP*, Dr Malcolm Rigler gave an eloquent and appealing account of his medical practice in Dudley.<sup>2</sup> He points to this sense of concern in the profession (and particularly in general practice) about our relevance in the context of the ills of modern society and proposes a direct use of the arts in medical practice as an answer. The Chief Medical Officer (who has a personal interest in the arts in medicine)<sup>3</sup> chaired a meeting of interested parties at Richmond House in December 1996. At this meeting, three main groups of people with interests in different applications of the arts in medicine were identified: those who were using the arts in therapy; those who saw a role for the arts in community schemes involving health promotion; and those (mostly university-based) who wanted to see more arts and humanities courses in the education of medical undergraduates.

The education group differs from the first two in its focus on *practitioners* and the *manner* of their practice rather than on the *recipients* (patients) and the *content* of the therapy they receive. This is an important distinction and is central to the discussion of the role of the arts and humanities in medicine. The distinction will become clearer if we look at the fundamental question that

Rigler poses in his paper: 'What does it actually mean to practise good medicine?'

Rigler's answer is that good medicine is anything we can do to alleviate people's suffering, whatever its cause. Others in the profession have attempted to answer this question by producing statements of 'core values'.<sup>4</sup> Indeed, there has been an outbreak of 'core values' statements from medical schools as they attempt to redefine the end product of the educational process. The problem with both answers is that neither seems to say much about practising medicine.<sup>5</sup>

So what does it really mean to practise good medicine, and what part might the arts play in enhancing this practice? The problem in answering the first part of this question is that the practice of medicine involves so many different activities that an all-embracing definition is difficult to establish.<sup>6</sup> It might help here to turn to the philosopher Plato, who classifies medicine as a *techne*, i.e. a craft in common with other crafts, such as cookery, bricklaying, or navigation.<sup>7</sup> For Plato, the good doctor is 'good at' something, and that 'something' is benefiting people in matters of health, in the same way as the cook is good at supplying flavour to our food or the navigator is a useful person to have around on a sea voyage. Being a doctor involves the exercise of specific skills relating to treatment and diagnosis. It may be that the doctor has to try to offer advice relating to personal problems, but this is not part of the skill of the physician. This aspect of a doctor's role (particularly the general practitioner's)