What shall we do after the WHI Study and the Million Women Study?

When we look at all the data available addressing the question of HRT and potential benefit and danger we have to admit that for several evolving questions we have no definite answers: it still is a matter of what to believe. One has to believe or not believe that HRT will increase the incidence of breast cancer. One has to believe or not believe that HRT exerts some beneficial effect on the vascular system. One has to believe or not believe that HRT reduces the incidence of colon cancer. One has to believe or not believe that HRT has an effect on breast cancer mortality. As typical for matters of belief, the discussion of these topics is frequently held with religious ardour instead of scientific detachment and reserve. This is particularly true when analysing the new studies such as the Million Women Study, as demonstrated in the editorial that accompanied the paper in *The Lancet*.

The fact that we do not know the answer to these questions points to a failure within the scientific community. We have asked the wrong questions and have used the wrong tools. It is time to correct this mistake.

It seems implausible that up to the time of menopause ovarian hormones are beneficial and positive but turn to something dangerous or
evil the moment that menopause has been reached. Biochemically the same substance as produced by the ovary, i.e. oestradiol suddenly becomes something extremely dangerous. Women are advised to avoid it and are better off suffering climacteric symptoms. This very likely unwise concept is illustrated by a mind experiment. If oestradiol is as dangerous and detrimental as one has to assume when reading the advice and assessments written in the context of the WHI Study or the Million Women Study, the ovaries should be removed as soon as women have completed their reproductive career. However, this is something nobody will advocate except as treatment for existing hormone-sensitive malignant disease, i.e. breast cancer.

We have held falsely accepted beliefs and premature data as definite answers in the past and are now confronted with the HRT pendulum swinging back or being pushed back by critics of the earlier oestrogen mania. However, the same mistake must not be repeated and the rather fragile data generated by the WHI and Million Women Study must not be over-interpreted.

I think it is sensible to ask what the WHI study was designed to do. It attempted to test whether the uncritical and general prescription of HRT for all women at all ages after menopause, irrespective of menopausal complaints, would show a substantial health benefit. The question was HRT for every woman: does it bring a health benefit? The answer provided by WHI is no. When prescribing a combination of conjugated oestrogens and medroxyprogesterone-acetate (MPA) to a large cohort of postmenopausal women of all ages, there is no measurable overall benefit in survival or other characteristics recognizable after 5 years. Or the significant reduction of osteoporotic fractures and colon cancers appears to be offset by the increase in thrombotic events and detected breast cancers.

The question which the study does not answer is whether the initiation of an oestradiol/progestin combination immediately with menopause for 5–10 years will not only reduce the incidence of climacteric complaints and thus improve the feeling of well-being in this group of women but also exert a beneficial effect on cardiovascular system, fracture rate and colon cancer.

Interestingly, and nearly forgotten, is the fact that the oestradiol-only part of the study is still ongoing. This invites several interpretations.