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SIR—The Collaborative Group on Hormonal Factors in Breast Cancer[1] present data showing an increasing risk of developing breast cancer in women who use hormone replacement therapy (HRT). In this, as well as in similar epidemiological studies, one fundamental bias is not considered: HRT is prescribed without reflection and monitoring and without individualisation for the particular patient.

HRT is substitution and balancing of a deficient endocrine situation. Before and after starting HRT, some basic clinical questions should be considered, which has so far not been done. Is the patient really suffering from a hormonal deficiency? Which steroid is missing, and does HRT induce normal or supraphysiological hormone concentrations? Some physicians prescribe hormones as if they were vitamins. A free lunch of hormones for patients who do not need them stimulates many intracellular events in endocrine-dependent tissues. Furthermore, is oestrogen substitution the first choice of HRT in every patient? It is well known that menopause often starts with a progesterone deficiency and an oestrogen excess.

An unreflected addition of oestrogen induces side-effects, reduces patient compliance, and may also be responsible for cell transformation. The most important clinical point and the greatest bias in such studies is the uncontrolled conduct of HRT. Sexual steroids are transcriptional factors, they do not need the second messenger pathway and have an immediate access to genome and transcriptional machinery. No ethical committee today would approve a therapy with new transcriptional factors in such an uncontrolled and light-minded design as is seen with HRT. In another context, a higher risk for endometrial cancer was registered in patients with combined therapy than in patients with no therapy at all.[2] Supraphysiological oestradiol concentrations were suspected to be involved in this problem.

Recently, a highly significant relation between oestrogen-induced bone mass and the risk of breast cancer was published.[3] The researchers postulated that high bone density may indicate the effect of cumulative oestrogen exposure.

It is the dosage that makes a pharmaceutical product into either a poison or a remedy. This fact should henceforth be recognised in clinical practice as well as in the interpretation of epidemiological papers.

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1 Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52 705 women with breast cancer and 108 411 women without breast cancer. *Lancet* 1997; **350:** 1047–59.
2 Beresford SAA, Weiss NS, Voigt LF, McKnight B. Risk of endometrial cancer in relation to use of oestrogen combined with cyclic progestagen therapy in postmenopausal women. *Lancet* 1997; **349:** 458–61.
3 Zhang Y, Kiel DP, Kreger BE, et al. Bone mass and the risk of breast cancer among postmenopausal women. *N Engl J Med* 1997; **336:** 611–17.

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