

**EXOGENOUS OESTROGENS AND OVARIAN CANCER**

SIR,—Dr Annegers and his colleagues<sup>1</sup> suggest that the data in our preliminary communication<sup>2</sup> “do not point as strongly to an increased risk of ovarian cancer with exogenous oestrogen use” as we suggested. They note that the “expected” values calculated for ovarian cancer did not take into account the proportion of women in the general population who are not at risk—namely, those with surgically removed ovaries. By adjusting for the 10% prevalence-rate of bilateral oophorectomy prevailing in the Mayo Clinic population, they estimate that our expected numbers for oestrogen-treated women are 11% too low, and that two of the three relative risks values are not statistically significant.

In case others may have been misled by our paper, we would like to emphasise the following points:

(1) We did not claim that ovarian cancer was associated with the use of exogenous oestrogens generally, but rather with specific oestrogen, diethylstilboestrol (D.E.S.). We tried to stress this by entitling the paper Stilboestrol (Diethylstilboestrol) and the Risk of Ovarian Cancer.

(2) The relative risk (R.R.) for the association between D.E.S. use and ovarian cancer was 30.0 (confidence interval, 6.2–87.7). These values are not changed by adjusting for the prevalence of oophorectomy in the general population, whether one uses the Mayo Clinic oophorectomy prevalence-rate or makes the extreme assumption that every woman in the general population with a hysterectomy has also undergone bilateral oophorectomy,

(3) Our most conservative estimate of the R.R. for all

oestrogen users was 2.4 (confidence interval, 1.0–4.8). This declines only slightly to 2.2 (0.9–4.3) when the Mayo Clinic adjustment factor for oophorectomy is used. In a more detailed discussion of the study population,<sup>3</sup> we calculated an estimate of R.R. based on the extreme assumption noted in (2) above. Even this “overadjustment” yields a 2-fold increase in risk for ovarian cancer. We see little difference in all of these estimates. The corrections have shifted the lower bound of the confidence interval below 1.0, so the values are not statistically significant at the 5% level. However, nominal levels of significance should not be overemphasised, since our risk estimate with a P value of 0.067 seems as meaningful as it was with a P value of 0.040.

(4) The associations were based on only 8 cases of ovarian cancer (including 3 for the D.E.S. group), and thus may be spurious for a number of reasons (e.g., bias, confounding, chance). Our suspicion of a causal relationship was based not on statistical probabilities but on the magnitude of the risk after D.E.S. (30-fold), plus the capacity of D.E.S. to cause ovarian tumours in dogs, and the possibility that it may explain the rising incidence of this cancer in postmenopausal women.

These findings, coupled with the magnitude of the exposure to D.E.S. in the population, led to our preliminary report in the hope that others would investigate the question. Since then, results of a follow-up of women who participated in a randomised clinical trial of D.E.S. for the prevention of miscarriage in the early 1950s has become available.<sup>4</sup> 4 women in the D.E.S. group have had ovarian cancer, compared with 1 in the placebo group. The numbers are again small, but provide further cause for concern. Annegers et al. report preliminary results from a case-control study of ovarian cancer, showing no relation to the use of exogenous oestrogens. While this is useful information, it is not relevant to the issue of the risk associated with D.E.S. exposure since an earlier Mayo Clinic survey<sup>5</sup> indicated very limited long-term use of D.E.S. in that population.

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