

obtain any evidence of a teratogenic effect for any of the considerable number of drug groups examined.

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Dr D A Cahal died in 1983.

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Commentary

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Reports of an apparent protective effect of folic acid, with¹ or without² other vitamins, against recurrence of neural tube defects have led to a lively debate³⁻⁵ and to the initiation of further intervention studies. These further studies are likely to take many years to complete and may be no easier to interpret at the end of the day than those already published.

Meanwhile, indirect illumination of this important area of preventive paediatrics is welcome. Winship *et al* have extended a study originally designed to examine the possible teratogenicity of drugs and have found a remarkable *negative* association between folic acid and central nervous system anomalies, particularly with folic acid prescribed in the trimester *before* the last menstrual period. This

is in notable contrast to most prescribed drugs which, in this and similar case-control studies, usually show an odds ratio in excess of unity for drugs taken in the first trimester of pregnancy. Few other studies have considered drugs taken before conception, but Mulinare *et al*⁶ reported a broadly comparable study from the United States. They found a similar negative association between 'vitamins' taken either before or during early pregnancy, or both, and neural tube defects in white mothers, especially in the poorer social classes.

The Winship study deals with a rather different population from those of the intervention studies. Their study group comprises central nervous system anomalies. This includes not only neural tube defects but also isolated hydrocephaly and microcephaly which are of very mixed aetiology. Only 17 of 764 mothers had had previous infants with central nervous system anomalies, whereas the intervention studies so far have dealt entirely with recurrences. Their control group is matched for general practice, which is the best way to avoid problems arising from the differing prescribing habits of doctors, but this effectively precludes any other kind of matching. As the authors point out, general practitioner records cannot provide a complete account of drug consumption, but as the controls are matched by practice, the comparison of cases with controls is valid.

Those who regard statistics as one degree worse than damned lies will note that the odds ratio derives from 1 case and 7 control mothers who took folic acid in the trimester before the last menstrual period. These small numbers doubtless contribute to the lack of formal significance. A repeat of the study

for a year later than 1981 might yield larger numbers of preconceptional vitamin takers.

The seeming absence of effect from folic acid prescribed in the first trimester is not surprising because most of these prescriptions are issued after the time of neural tube closure, which is usually within 6 weeks of the last menstrual period.

When considering whether an association suggests a causal relation, Bradford-Hill⁷ listed a number of criteria including consistency. So far there is remarkable coherence in the evidence from many sources suggesting that vitamin deficiency is related to human neural tube defects. There is to date no evidence that is inconsistent with the hypothesis. The study of Winship *et al* provides further support.

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