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.

References

1 Greenberg C, Inman WHW, Weatherall JAC, Aldestein AM, Haskey JC. Maternal drug histories and congenital abnormalities. *Br Med J* 1977;**ii**:853–6.
2 Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *Journal of the National Cancer Institute* 1959;**22**:719–48.
3 Breslow NE, Day NE. *Statistical methods in cancer research. Vol 1. Analysis of case-control studies.* Lyon: IARC Scientific Publications, 1980: 165–6.
4 Golding J, Vivian S, Baldwin JA. Maternal antinauseants and clefts of lip and palate. *Hum Toxicol* 1983;**2**:63–73.
5 Leck I. Causation of neural tube defects: clues from epidemiology. *Br Med Bull* 1974;**30**:158–63.
6 Weatherall JAC. A review of some effects of recent medical practices in reducing the numbers of children born with congenital abnormalities. *Health Trends.* London: HMSO, 1982;**14**:85–8.
7 Nevin NC. Neural tube defects. *Lancet* 1981;**ii**:1290–1.
8 Stein SC, Feldman JG, Friedlander M, Klein RJ. Is myelomeningocele a disappearing disease? *Pediatrics* 1982;**69**:511–4.
9 Windham GC, Edmonds LD. Current trends in the incidence of neural tube defects. *Pediatrics* 1982;**70**:333–7.
10 Field B, Kerr C, Mathers CD. Incidence of neural tube defects. *Dev Med Child Neurol* 1982;**24**:861–2.
11 Danks DM, Halliday JL. Incidence of neural tube defects in Victoria, Australia. *Lancet* 1983;**i**:65.
12 Nora JJ, Nora AH, Blu J, *et al.* Exogenous progestogen and estrogen implicated in birth defects. *JAMA* 1978;**240**:837–43.
13 Robinson SC. Pregnancy outcome following oral contraceptives. *Am J Obstet Gynecol* 1971;**109**:354–8.
14 Royal College of General Practitioners Oral Contraception Study. The outcome of pregnancy in former oral contraceptive users. *Br J Obstet Gynaecol* 1976;**83**:608–16.
15 Vessey M, Meisler L, Flavel R, Yeates D. Outcome of pregnancy in women using different methods of contraception. *Br J Obstet Gynaecol* 1979;**86**:548–56.
16 Cuckle HS, Wald NJ. Evidence against oral contraceptives as a cause of neural tube defects. *Br J Obstet Gynaecol* 1982;**89**: 547–9.
17 Heinonen OP, Slone D, Shapiro S, eds. *Birth defects and drugs in pregnancy.* Littleton: Publishing Sciences Group, 1977.
18 Smithells RW, Sheppard S, Schorah CJ, *et al.* Apparent prevention of neural tube defects by periconceptional vitamin supplementation. *Arch Dis Child* 1981;**56**:911–8.
19 Smithells RW, Nevin NC, Seller MJ, *et al.* Further experience of vitamin supplementation for prevention of neural tube defect recurrences. *Lancet* 1983;**i**:1027–31.
20 Mulinare J, Cordero JF, Erickson JD. Vitamin use and the occurrence of neural tube defects (NTD's). *Teratology* 1981;**23**:54A.
21 Nelson MM, Forfar JO. Associations between drugs administered during pregnancy and congenital abnormalities of the fetus. *Br Med J* 1971;**i**:523–7.
22 Milkovich L, van den Berg BJ. An evaluation of the teratogenicity of certain antinauseant drugs. *Am J Obstet Gynecol* 1976;**2**:244–8.
23 Smithells RW, Sheppard S. Teratogenicity testing in humans: a method demonstrating safety of Bendectin. *Teratology* 1978; **17**:31–6.
24 Shapiro S, Heinonen OP, Siskind V, Kaufman DW, Monson RR, Slone D. Antenatal exposure to doxylamine succinate and dicyclomine hydrochloride (Bendectin) in relation to congenital malformations, perinatal mortality rate, birth weight, and intelligence quotient score. *Am J Obstet Gynecol* 1977;**128**:480–5.
25 Harron DWG, Griffiths K, Shanks RG. Debendox and congenital malformations in Northern Ireland. *Br Med J* 1980;**ii**:1379–81.
26 Patterson DC. Congenital deformities associated with Bendectin. *Can Med Assoc J* 1977;**116**:1348.
27 Donnai D, Harris R. Unusual fetal malformations after antiemetics in early pregnancy. *Br Med J* 1978;**i**:691–2.
28 Azad Khan AK, Truelove SC. Placental and mammary transfer of sulphasalazine. *Br Med J* 1979;**ii**:1553.
29 Newman NM, Correy JF. Possible teratogenicity of sulphasalazine. *Med J Aust* 1983;**1**:528–9.
30 Craxi A, Pagliarello F. Possible embryotoxicity of sulfasalazine. *Arch Intern Med* 1980;**140**:1674.
31 Slone D, Siskind V, Heinonen OP, Monson RR, Kaufman DW, Shapiro S. Aspirin and congenital malformations. *Lancet* 1976;**i**:1373-5.

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Commentary

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Reports of an apparent protective effect of folic acid, with[1] or without[2] other vitamins, against recurrence of neural tube defects have led to a lively debate[3–5] 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-Hill[7] 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.

References

1 Smithells RW, Nevin NC, Seller MJ, *et al*. Further experience of vitamin supplementation for prevention of neural tube defect recurrences. *Lancet* 1983;**i**:1027–31.

2 Laurence KM, James N, Miller MH, Tennant GB, Campbell H. Double-blind, randomised controlled trial of folate treatment before conception to prevent recurrences of neural-tube defects. *Br Med J* 1981;**282**:1509–11.

3 Dobbing J. (ed.) *Prevention of spina bifida and other neural tube defects*. London: Academic Press, 1983.

4 Elwood JM. Can vitamins prevent neural tube defects? *Can Med Assoc J* 1983;**129**:1088–91.

5 Wald NJ, Polani PE. Neural-tube defects and vitamins: the need for a randomised clinical trial. *Br J Obstet Gynaecol* 1984;**91**:516–23.

6 Mulinare J, Cordero JF, Erickson JD. Vitamin use and the occurrence of neural tube defects (NTDs). *Teratology* 1981;**23**:54A.

7 Bradford-Hill A. The environment and disease: association or causation? *Proceedings of the Royal Society of Medicine* 1965;**58**:295–300.