Correspondence

Drugs, infections, and congenital anomalies

Sir,

In his annotation under this title (*Archives*, 1978, 53, 93) Smithells states that all evidence to suggest a teratogenic role for sex hormones has been 'derived from retrospective studies, whereas all prospective studies published show no such effect'. This is incorrect. In a follow-up study of 50 282 pregnancies we reported an approximate doubling of the cardiovascular malformation rate in 1042 children exposed *in utero* to female hormones during the first 4 lunar months of pregnancy (Heinonen *et al.*, 1977).

Under a causal hypothesis, an association should be evident and relatively invariant regardless of whether the results are derived from prospective (or more precisely, cohort) studies, or from retrospective (case-control) studies. In fact, when different research strategies support each other, a causal inference is strengthened. The classical work of Lenz (1962) in documenting a connection between limb-reduction deformities and *in utero* exposure to thalidomide was a case-control study.

References

- Heinonen, O. P., Slone, D., Monson, R. R., Hook, E. B., and Shapiro, S. (1977). Cardiovascular birth defects and antenatal exposure to female sex hormones. *New England Journal of Medicine*, 296, 67-70.
Lenz, W. (1962). Thalidomide and congenital abnormalities. *Lancet*, 1, 45.

DENNIS SLONE and SAMUEL SHAPIRO
Drug Epidemiology Unit,
Boston University Medical Center,
10 Moulton Street, Cambridge,
Massachusetts 02138, USA.

Professor R. W. Smithells comments:

I am grateful to Drs Slone and Shapiro for calling my attention to their excellent study. It was perhaps foolish of me to attempt to summarise the evidence regarding teratogenicity of sex hormones in one sentence. Their findings (that the relative risk of congenital heart disease in infants exposed to combined oestrogen/progestogen was significantly increased ($P < 0.05$), and in infants exposed to oestrogens or progestogens was increased, but not significantly), considered in conjunction with other prospective studies which have shown no increase in malformation rates among exposed infants, lead me to believe that my classification of sex hormones as 'possible' rather than 'probable' teratogens is justifiable at present.

I certainly did not intend to disparage retrospective studies. Nearly all known human teratogens have been initially identified or suspected this way. I accept that

when case-control and cohort studies agree they strengthen each other. If I may rephrase my offending sentence, I think it is fair to say that 'the suggestions of teratogenicity (of sex hormones) mainly derive from retrospective studies, whereas most prospective studies published show no such effect'.

English law insists that the prisoner is innocent until proved guilty. Scottish law allows a verdict of 'not proven', which may be appropriate until further studies have been completed.

R. W. SMITHELLS
Department of Paediatrics and Child Health,
University of Leeds,
27 Blundell Street,
Leeds LS1 3ET.

The first feed of low birthweight infants: changing attitudes in the twentieth century

Sir,

I read the review article under this title by D. P. Davies (*Archives*, 1978, 53, 187) with particular interest, as I had just completed a brief comparison of outcome at early school age in very low birthweight (LBW) infants born 1953-55 and 1966-70, with the results shown in the Table.

Table Outcome, IQ, and type of school attended in low birthweight infants at early school age by year of birth

	Birthweight (g) and no. of cases					
	Born 1953-55 (n = 117)			Born 1966-70 (n = 264)		
	≤ 1367	1368-1500	1501-2000	≤ 1367	1368-1500	1501-2000
	(22) %	(16) %	(79) %	(54) %	(29) %	(181) %
IQ						
≥ 110	—	18	22	15	25	16
90-109	28	50	45	62	53	57
80-89	24	25	19	19	11	17
70-79	5	7	8	—	4	6
≤ 69	43	—	6	4	7	4
Total	100	100	100	100	100	100
MH/PH*	50 (22)	6 (16)	11 (79)	11 (54)	14 (29)	6 (181)

*Attending schools for mentally or physically handicapped. Numbers of cases in parentheses.

Severe restriction of fluid and calorie intake, particularly in 1953-54, was routine practice for all infants of 3 lb (1367 g) or less; earlier feeding was generally attempted above that weight. The Table demonstrates a striking improvement by date of birth only in those who were 3 lb or less at birth. In view of the fact that all 1966-70