Archives of Disease in Childhood, 1978, **53**, 604–607

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.

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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.

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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 (22) %	*1368–1500* (16) %	*1501–2000* (79) %	*≤1367* (54) %	*1368–1500* (29) %	*1501–2000* (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

born infants benefited from the monitoring and treatment facilities of an expensive intensive care unit, while those born 15 years earlier were at best kept warm in a heated crib or nursery, given oxygen by face mask or in a tent and fed by tube, pipette, Belcroy feeder or bottle, the small improvement in major handicap is rather disappointing.

It is unfortunate that so many workers use my data *from the early 1950s* to justify the conclusion that (to quote Rawlings *et al.*, 1971 as an example) 'much of the handicap found in surviving children in the past would have been avoidable with modern methods of care', since it seems likely that early starvation, which only operated for a few years, was the main cause of the very high incidence of major handicap in that era.

This is not to denigrate recent advances in neonatal care. In 1963 I wrote 'most cases of mental retardation or gross neurological abnormality probably result from developmental defect rather than from the effect of pre- or paranatal damage to a potentially normal central nervous system' and hypothesised that 'such complications (referring to the perinatal period) may have a definite, if less catastrophic, effect on later intellectual functioning and educational ability' (Drillien, 1963). Analysis of the data on early school age status of 1966–70 LBW children is incomplete, but already it seems likely that the benefits of neonatal intensive care will be demonstrated more by a reduction in minor impairment than in major handicap, if those children who suffered from the disastrous iatrogenic effects of early starvation are excluded when making comparisons by date of birth.

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'DIDMOAD' syndrome

Sir,

In the October issue of the *Archives* (1977, **52**, 796), attention was drawn to the fact that the association of diabetes mellitus, diabetes insipidus, optic atrophy, and neurosensory hearing loss is becoming increasingly recognised. We have been following a 17-year-old girl with diabetes mellitus, diabetes insipidus, and optic atrophy. To date our patient has had no evidence of high-tone neurosensory hearing loss, despite repeated audiograms. She does have a neurogenic bladder with hydronephrosis and hydroureter, a reported concomitant of the syndrome. A family history is not available as she was adopted at 6 weeks of age. She presented in early childhood with optic atrophy; at 6 years she developed diabetes mellitus; at age 15 she was diagnosed as having diabetes insipidus, and shortly thereafter a neurogenic bladder, hydroureter, and hydronephrosis.

Recently, 97 cases of this syndrome have been reported (Gunn *et al.*, 1976). Of these, 13 had the full combination of optic atrophy, diabetes mellitus, diabetes insipidus, and hearing loss and 18 had optic atrophy, diabetes mellitus, and diabetes insipidus, as did our patient; 31 had optic atrophy, diabetes mellitus, and hearing loss, and 35 had only optic atrophy and diabetes mellitus. We too feel that this condition is more prevalent than suggested by previous literature, and note the increasing frequency of new reports (Carson *et al.*, 1977; Cremers *et al.*, 1977). A high percentage of these cases may have some and not all of the components of this syndrome.

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Peritoneal dialysis and peritonitis

Sir,

Day and White (1977) reported that 42% of children dialysed developed peritonitis. All who were dialysed for more than 11 days developed peritonitis, so this is mainly related to the duration of dialysis. We have performed 75 peritoneal dialyses during the last 9 years, with an incidence of peritonitis of 12%. We ascribe this low incidence to a policy whereby we dialyse patients continuously for 40–60 hours until the blood urea is about 80 mg/100 ml (13·3 mmol/l) and other biochemical parameters are normal. The catheter is then removed and the local site dressed. Dialysis is repeated only if indicated by the biochemical parameters and the patient's clinical course. We have observed that the incidence of peritonitis is unrelated to number of dialyses. After a single dialysis, the incidence of infection was 11%, and with two or more dialyses it was 14%. Leigh (1969) concluded that peritonitis is usually related to the flora of the skin around the catheter site. With daily dialysis such flora may have more time and chance to invade the peritoneum; in our series the incidence of peritonitis was less because dialyses were shorter. Thus we suggest that peritoneal dialysis should be done as and when indicated rather than daily.