Dr McKenzie comments:

We agree with Dr Weinberger that ideally the starting dosage of theophylline should be small, blood levels checked, and dosage built up. However, many of our patients live some distance from the hospital and we feel that it would be impracticable to recall these children frequently to measure levels and adjust dosage. We prefer to titrate our patients by starting with a high dosage, checking levels, and then raising or lowering the dosage as necessary. Only 2 of 65 children who started theophylline treatment with slow-release preparations in the dosage we recommended (McKenzie and Baillie, 1978) had side effects that might have been attributable to theophylline, but in neither was the blood level >20 $\mu\text{g/ml}$.

We found that the incidence of nausea and vomiting in children treated with choline theophyllinate or plain theophylline (the preparation used in the Hammersmith/Denver study (Hambleton *et al.*, 1977)) was high (McKenzie *et al.*, 1978) and that compliance, as others have found (Eney and Goldstein, 1976), was poor. These side effects may occur even when levels are within the therapeutic range or below it. We now rarely use these compounds, preferring the slow-release preparations.

We agree that serum levels may be more constant in those children with fast clearance rates if the slow-release preparation is given every 8 hours. However, it must be remembered that the efficacy of theophylline is proportional to the logarithm of the blood level (Mitenko and Ogilvie, 1973). Trough levels <10 $\mu\text{g/ml}$ may give satisfactory control for many children and an extra dose just to raise the blood level would therefore be unnecessary.

References

- Eney, R. D., and Goldstein, E. O. (1976). Compliance of chronic asthmatics with oral administration of theophylline as measured by serum and salivary levels. *Pediatrics*, **57**, 513–517.
- Hambleton, G., Weinberger, M., Taylor, J., Cavanaugh, M., Ginchansky, E., Godfrey, S., Tooley, M., Bell, T., and Greenberg, S. (1977). Comparison of cromoglycate (Cromolyn) and theophylline in controlling symptoms of chronic asthma. *Lancet*, **1**, 381–385.
- McKenzie, S., and Baillie, E. (1978). Serum theophylline levels in asthmatic children after oral administration of two slow-release theophylline preparations. *Archives of Disease in Childhood*, **53**, 943–946.
- McKenzie, S. A., Edmunds, A. T., Baillie, E., and Meek, J. H. (1978). Clinical applications of serum theophylline measurement by high pressure liquid chromatography. *Archives of Disease in Childhood*, **53**, 322–325.
- Mitenko, P. A., and Ogilvie, R. I. (1973). Rational intravenous doses of theophylline. *New England Journal of Medicine*, **289**, 600–603.

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Incidence of dental caries in coeliac children

Sir,

Referring to the letter on this subject (*Archives*, 1979, **54**, 166), we have submitted a paper entitled 'Gastroenteritis, coeliac disease, and enamel hypoplasia' to the *British Dental Journal*. One of the problems in such a study was the difficulty in obtaining, for histological section, teeth with enamel hypoplasia. The hypoplastic lesions are often destroyed by dental caries. We were lucky to obtain specimen teeth, in spite of the fact that we have been observing coeliac children for 20 years.

The lesions that were on the permanent incisors and on the first permanent molars were produced at the end of the first year of life. It is possible to detect the lesions before the teeth erupt by means of x-rays. This allows appropriate preventive or therapeutic measures to be instituted as soon as the tooth erupts.

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Mr Fulstow comments:

I should like to thank Mr Miller and Mr Smith for their comments and I look forward to reading their paper in the *British Dental Journal*.

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Fucidic acid in Gunn rats. No influence on serum bilirubin concentration

Sir,

When drugs which compete with bilirubin for albumin-binding sites are injected into homozygous Gunn rats there is a decline in the level of serum bilirubin. After long-acting sulphonamides, for instance, serum bilirubin decreases to between 10 and 20% of the baseline concentration (Ballowitz and Hanefeld, 1976). The displaced, now unbound (free), bilirubin moves out of the plasma mainly into adipose tissues, including the brain, where it may lead to kernicterus. This was first described for sulphisoxazole (Gastrisyn) by Johnson *et al.* (1959).

During the last decade several other drugs that are commonly used in nurseries have been subjected to appropriate tests (Brodersen, 1974; Yearly and Davis, 1974; Rayner *et al.*, 1978). Fucidic acid was not among them, as this substance is not often prescribed during the first days of life. However, we recently had to infuse this antibiotic into a newborn baby suffering from severe staphylococcal sepsis and osteomyelitis, the staphylococci being resistant to most other antibiotics.

We therefore tested IV 'fucidin soluble' ampoules (Thomae GmbH Biberach a.d. Riss, Germany) in 3- to 5-day-old homozygous, jaundiced Gunn rats. We also

gave them an oral suspension 'z 141-EXT 7'+ (not yet available in Germany) containing 5 g fucidic 2·2 imido-ethanol per 100 ml. The IV dose was 10–50 mg/kg, the oral dose—given by gavage—50 to 2000 mg/kg. LD₅₀ of the 2 preparations, which we investigated in 3- to 5-day-old, heterozygous, nonjaundiced Gunn rats, differed markedly. It was between 50 and 100 mg/kg after IV and 1000 mg/kg after oral application. There was no effect on levels of serum bilirubin. Half an hour after IV and 3 hours after oral administration, the highest doses decreased the levels of serum bilirubin to about 80% of the baseline concentration (7·1–9·3 mg/100 ml; 121–159 µmol/l), a similar decline to that which occurs after a saline injection.

We conclude that neither fucidic acid nor the stabilisers in the intravenous preparation is a strong competitor for albumin-binding sites.

References

- Ballowitz, L., and Hanefeld, F. (1976). Effect of drugs on infant Gunn rats under phototherapy. *Birth Defects (Original Article Series)*, 12, No. 2, 61–80.
- Brodersen, R. (1974). Competitive binding of bilirubin and drugs to human serum albumin studied by enzymatic oxidation. *Journal of Clinical Investigation*, 54, 1353–1364.
- Johnson, L., Sarmiento, F., Blanc, W. A., and Day, R. (1959). Kernicterus in rats with an inherited deficiency of glucuronyl transferase. *American Journal of Diseases of Children*, 97, 591–608.
- Rayner, H. L., Schacter, B. A., and Israels, L. G. (1978). In *Handbook of Experimental Pharmacology*, pp. 273–332. Edited by G. V. R. Born, O. Eichler, A. Farah, H. Herken, and A. D. Welch. Springer: Berlin.
- Yeary, R. Q., and Davis, D. R. (1974). Protein binding of bilirubin: comparison of *in vitro* and *in vivo* measurements of bilirubin displacement by drugs. *Toxicology and Applied Pharmacology*, 28, 269–283.

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Spina bifida and maternal Rh blood type

Sir,

Spina bifida cystica (myelomeningocele) is a relatively common birth defect (one in 500 to one in 200 live births) whose aetiology is not known, although it has been suggested that a patient's children and siblings have an increased risk (Bergsma, 1973). Unfortunately, preventive measures, other than genetic counselling to affected families and prenatal screening for high α -fetoprotein levels in patients at risk, are nonexistent. We should like to report the results of a pilot retrospective study on children with spina bifida, whose parents are members of the Houston chapter of the Spina Bifida Association of America. We examined 28 cases and found that more mothers had Rh- blood type in this population compared with the general population ($\chi^2 = 6.45$, confidence interval 0.02%). We found about twice as many mothers with Rh- blood type in our sample (i.e. incidence 15%) (Wiener, 1954). We are currently planning to study a much larger sample and we hope to determine the Rh-blood type of parents and all siblings, and compare the incidence of Rh-blood incompatibility, Rh haemolytic disease, early postnatal jaundice, and transfusions. We have found no reports that suggest a possible relationship between maternal Rh-blood type and spina bifida.

References

- Bergsma, D., editor (1973). *Birth Defects: Atlas and Compendium*, p. 646. National Foundation March of Dimes Original Article Series. Williams and Wilkins: Baltimore.
- Wiener, A. S. (1954). *Rh-Hr Blood Types: Applications in Clinical and Legal Medicine and Anthropology. Selected Articles in Immunohematology*, p. 7. Grune and Stratton: New York.

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