disease, degree of hydration, fever, and other drugs. Study designs and data analyses controlling for all these variables are difficult and sometimes impossible in very sick patients. The studies of Nahata *et al*[3] and Toumanen *et al*[4] included many patients with these confounding variables. Nahata *et al* studied 10 children with infection of the central nervous system, four of whom received phenobarbital or phenytoin, or both; these are both known to induce hepatic enzymes. One child also received acetaminophen. Toumanen *et al*[4] studied 44 children with bacterial meningitis, 11 of whom had seizures requiring anticonvulsants. All 44 children were feverish (38·5 to 41°C). In contrast, four of our five patients had epiglottitis, an illness of rapid onset and short duration. They had previously been in good health and had not received any medication before presenting with breathing difficulty. When studied 48–72 hours after chloramphenicol had been started, all five were well hydrated and only one was feverish (38·1°C). Nahata *et al*[3] reported an increase in chloramphenicol and chloramphenicol succinate kinetics in their 10 children. The mean area under the curve (mg/l/hour) and plasma half life t 1/2 (hours) for their patients when first studied were similar to those in our patients (105·7 and 3·0 compared with 112·2 and 3·0). These authors repeated their kinetic studies two to 17 days after the first and found that the mean area under the curve and t 1/2 had decreased to 79·5 and 2·3, respectively, compared with 28·7 and 1·2 in our patients (48–72 hours after the first study). They found that patients who had the greatest area under the curve at the time of the first study had the greatest decline. We found no such correlation. The mean (SD) change in the area under the curve among our patients was 74·1 (6·9)%, the patient with the smallest initial area under the curve had a 77·7% change and the patient with the largest had a 73·5% change.

It is possible that the changes we observed in chloramphenicol pharmacokinetics were independent of acetaminophen. We agree with Dr Choonara that information on the pharmacokinetics of chloramphenicol after acetaminophen therapy or the use of control patients who concurrently received acetaminophen and chloramphenicol followed by chloramphenicol alone would have been ideal. Hepatic microsomal enzyme activation may take days to weeks to return to the preactivated level after withdrawal of the inducing agent.[5] The decrease in the urinary excretion of free chloramphenicol with an inverse relative increase in the glucuronide conjugate, and the magnitude of change in the kinetic profile of the drug in our patients who were studied on two occasions with 72 hours allowed us to conclude that a chloramphenicol-acetaminophen interaction existed as we had no other clear explanation for these changes. Our conclusion also remains that therapeutic drug monitoring is necessary whenever drugs with a narrow therapeutic index such as chloramphenicol are used.

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Neonatal typhoid fever

Sir,

In a recent article, Chin *et al* concluded that 'infants with mild *Salmonella typhi* enteritis do not require (antibiotic) treatment.[1] Diarrhoea is a common feature of typhoid fever in children, but is rarely associated with fluid depletion.[2] It should not, however, be inferred that the finding of *S typhi* in a stool culture is of no clinical importance; a positive stool culture, even in a healthy contact, is often followed by a typical septicaemic illness seven to 10 days later.[3] Typhoid fever is usually a milder disease in children than in adults, but life threatening complications and even deaths have been reported, especially among young, malnourished infants.[3] The use of antibiotics has resulted in a considerable reduction in the morbidity and mortality of typhoid fever;[3] thus treatment of all cases of acute *S typhi* infections seems to be indicated.

According to Chin *et al* the duration of the carrier state of *S typhi* is not shortened by treatment with antibiotics. In addition, chloramphenicol probably does not shorten the carriage time of *S typhi* in treated patients.[3] The problem is that the reference cited by Chin *et al* to support this statement is not relevant. The study mentioned was carried out among children suffering from uncomplicated, non-bacteraemic gastroenteritis caused by salmonella strains other than *typhi* and *paratyphi*, an entity totally different from typhoid fever.[4]

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Dr Chin and Dr Tarlow comment:

We thank Dr Yagupsky for his interest in our article. We did not imply that the finding of *S typhi* in a stool culture should be ignored. This is a potential health hazard as was pointed out in our paper. Typhoid fever can indeed be a life threatening condition as exemplified by our first case. We agree that the introduction of antibiotic treatment has reduced the mortality of typhoid fever. We do not, however, feel that all infants (including those with minimal gastrointestinal symptoms) require oral antibiotics. Although a septicaemic infection may occur later in some patients with mild symptoms, antibiotic treatment does not completely prevent a major clinical relapse after treatment has been stopped. It is not our policy to treat all healthy contacts, even if their stool cultures are positive.

Although the paper by Nelson *et al*[4] did not refer specifically to the use of antibiotics in *S typhi* infection, the randomised prospective double blind study did show that oral antibiotics were of no benefit to infants and children with acute salmonella gastroenteritis.[1] Furthermore, the treated patients had an increased risk of symptomatic relapse. We are not aware of any recent or similar study relating to *S typhi* gastroenteritis. Lastly, one must not forget that non-typhoid salmonella infections can also cause serious complications in infants.

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Incidences of childhood coeliac disease and transient gluten intolerance move discrepantly in UK and Sweden

Sir,

Current criteria for the diagnosis of childhood coeliac disease were formulated by the European Society for Paediatric Gastroenterology and Nutrition. Coeliac disease was defined as a lifelong disorder in which the small intestinal mucosa is abnormal as a result of exposure to gluten in the diet. The mucosal damage improves on treatment with a gluten free diet but recurs within two years of reintroduction of gluten. In some cases, however, this gluten challenge does not bring about a mucosal relapse within the two year period. These children have so called transient gluten intolerance. In an earlier study we reported an incidence of transient gluten intolerance of 19% among children with an initial flat small intestinal mucosa that resembled that seen in coeliac disease.[1]

Since 1975 the incidence of coeliac disease seems to have decreased sharply in the UK[2] while the high incidence in Sweden has remained unchanged. On the other hand, we have observed a steep decline in the number of children with transient gluten intolerance diagnosed during the same period. This is in accordance with the findings of Walker-Smith who reported no new cases of transient gluten intolerance in children born after 1975 at the Queen Elizabeth Hospital for Children.[3]

The fact that the incidences of childhood coeliac disease and transient gluten intolerance are moving discrepantly in the United Kingdom and Sweden is interesting but puzzling, and suggests that factors other than gluten ingestion are involved in the pathogenesis of coeliac disease.

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