flow. We do not disagree that in mature animals (and possibly humans) the major cerebral arteries may show vasoactivity in response to changing patterns of flow, but we can find no data from the work of Drayton and Skidmore to support this assertion in the premature infant. The onus is on them to show that their method for measuring CBF correlates with any other independent method either in humans or in animals before we can accept that major cerebral arteries mediate cerebral autoregulation in the preterm neonate.

References

- ¹ Drayton MR, Skidmore R. Vasoactivity of the major intracranial arteries in newborn infants. *Arch Dis Child* 1987;**62**: 236-40.
- ² Evans DH. Can ultrasonic duplex scanners really measure volumetric flow? In: Evans JA, ed. *Medical ultrasound*. London: IPSM, 1986.
- ³ Walther FJ, Siassi B, Ramadan NA, Ananda AK, Wu PYK. Pulsed Doppler determinations of cardiac output in neonates: normal standards for clinical use. *Pediatrics* 1985;**76**:829-33.

M I LEVENE, D H EVANS, L N J ARCHER,
and D SHORTLAND
Departments of Child Health and
Medical Physics,
Leicester University School of Medicine,
Leicester LE1 5WW

Drs Drayton and Skidmore comment:

Our finding of a large increase in cerebral artery blood velocity during the first 48 hours of life but no change in a measure of cerebral blood flow (CBF) has important implications for simpler Doppler techniques of assessing the cerebral circulation. Levene *et al* question whether limitations of our volumetric technique could explain the absence of any apparent increase in CBF.

It is true that if there had been progressive and unidentified constriction of the aortic isthmus over the 48 hours, CBF might indeed have risen. We know of only two detailed studies of sequential changes in the size of the isthmus both of which conclude that there is a progressive but slow relative increase in the diameter of the isthmus from birth.^{1,2} The isthmus has a different embryological origin from the ductus arteriosus, and is histologically indistinguishable from the rest of the aortic arch, which decreases the likelihood that it constricts in a similar manner to the ductus itself.³ M mode measurement of the diameter of the isthmus in our infants was frequently impossible but measurements from the real time image did not suggest that there were any progressive changes in diameter over the time course of our studies. The oval section of the aortic isthmus may introduce a small but constant error in our calculations but this is irrelevant to this discussion of change in velocity and flow.

In our opinion the basis for their calculation of potential error in our technique is inappropriate. Our own calculations, available from us on request, give a potential error in mean CBF of 9% for the preterm group and 16% for the term group, both well below the percentage change observed in cerebral artery velocity.

We may approach the same problem empirically by

using the dispersion in our data that incorporates error and variation from all sources to calculate the confidence limits for any change. We can thus be 95% certain that any change in CBF between 1.5 and 48 hours was between +32% and -30% for the preterm group and +28% and -33% for the term group.

Levene *et al* conclude from the work of Kennedy *et al* that there is an increase in CBF in the first few days of life in dogs born at term. Their results, however, showed no increase in CBF over the first six days of life. Furthermore, Cooke *et al*, using venous occlusion plethysmography in the term human infant, showed quite clearly that CBF was constant between three and 24 hours and that in fact flow was rather higher during the first two hours.⁴

Contrary to the statement of Levene *et al*, nowhere in our paper have we suggested that 'the major cerebral arteries perform the main role in regulating blood flow'. Clearly in the normal brain perfusion is closely coupled to metabolic demand in the tissues and important local mechanisms regulating flow must exist. We do contend that the regulation of CBF is unusual in occurring at more than one arterial level including the major cerebral arteries. The quoted work of Ahmann *et al* suggests that in the anterior cerebral arteries of only three preterm infants studied the vessels had an immature muscle coat, whereas in eight infants of a wide range of gestations studied by ourselves the muscle wall was well developed. It seems illogical that Levene *et al* are prepared to accept that the major cerebral arteries of mature animals and humans are vasoactive, but are unwilling to accept the same for neonates. Our technique has been carefully validated in vitro. Appropriate animal models for validation in vivo are not currently available to us and we do not believe that acceptable gold standards for the measurement of CBF in the newborn human exist. We believe that investigators who rely on the use of mean cerebral artery blood velocity as a measure of CBF may be misled.

References

- ¹ Rosenberg HS, Klima T, Henderson SR, McNamara DG. Maturation of the aortic isthmus. *Cardiovascular Research Center Bulletin* 1971;**10**:47-56.
- ² Pattern BM. *Pathology of the heart and blood vessels*. Springfield: Charles C Thomas, 1968:80-5.
- ³ Rosenberg HS. Coarctation of the aorta: morphology and pathogenetic considerations. In: Rosenberg HS, Bolande RP, eds. *Perspectives in pediatric pathology I*. Chicago: Year Book Publications, 1973:339-68.
- ⁴ Cooke RWI, Rolfe P, Howat P. Apparent cerebral blood-flow in newborns with respiratory disease. *Dev Med Child Neurol* 1979;**21**:154-60.

Interaction between chloramphenicol and acetaminophen

Sir,

Dr Choonara¹ raises the possibility that the changes in chloramphenicol pharmacokinetics observed in our study² were unrelated to acetaminophen.

The pharmacokinetics of chloramphenicol could be influenced by many factors including age, underlying

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.

References

- 1 Choonara IA. Interaction between chloramphenicol and acetaminophen. *Arch Dis Child* 1987;**62**:319.
- 2 Spika JS, Davies DJ, Martin SR, Belamy K, Rex J, Aranda JV. Interaction between chloramphenicol and acetaminophen. *Arch Dis Child* 1986;**61**:1121–4.

- 3 Nahata MC, Powell DA. Chloramphenicol serum concentration falls during chloramphenicol succinate dosing. *Clin Pharmacol Ther* 1983;**33**:308–13.
- 4 Toumanen EI, Powell KR, Marks MI, Laferriere CI, Alt-miller DH, Sack CM, Smith AL. Oral chloramphenicol in the treatment of *Haemophilus influenzae* meningitis. *J Pediatr* 1981;**99**:968–74.
- 5 Benet LZ, Scheiner LB. "Pharmacokinetics: The dynamics of drug absorption, distribution and elimination". In: *Goodman and Gilman's The pharmacological basis of therapeutics*. Gilman AG, Goodman LS, Rall TW, Murad F (eds), 7th ed., New York, Macmillan Publishing Company. 1985. p. 3–34.

J S SPIKA and J V ARANDA
McGill University,
Montreal Children's Hospital,
Montreal,
Quebec, Canada H3H 1P3

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

P YAGUPSKY
Department of Paediatrics,
Soroka Medical Centre,
Ben-Gurion University of the Negev,
Beer-Sheva, Israel

References

- 1 Chin KC, Simmonds EJ, Tarlow MJ. Neonatal typhoid fever. *Arch Dis Child* 1986;**61**:1228–30.
- 2 Duggan MB, Beyer L. Enteric fever in young Yoruba children. *Arch Dis Child* 1975;**50**:67–71.
- 3 Mandal BK. Typhoid and paratyphoid fever. *Clin Gastroenterol* 1970;**8**:715–35.