LETTERS TO THE EDITOR

Neonatal symptomatic thromboembolism in Germany

EDITOR,—We read with interest the article by Ulrike *et al.*¹ They diagnosed hereditary thrombophilia in seven out of 35 (20%) neonates investigated; the cerebral arteries were involved in seven of 79 (9%) of cases in the study. Tests were not available at the time of the study to detect resistance to activated protein C.

In another study of 37 children with venous and arterial thrombosis, 5.1% of a control group, 52% with venous thrombosis, and 38% with arterial thrombosis, had the factor V mutation associated with activated protein C resistance (APCR).² In this study cerebral artery thrombosis occurred in 14 neonates, suggesting that APCR and other defects of the protein C pathway may have a major role in neonatal cerebral thrombosis.

Of those with APCR, most cases of venous thrombosis (60%) and 28% of cases with arterial thrombosis were associated with exogenous risk factors, and the authors therefore suggested that an acquired risk of thrombo-embolic disorders masks the coagulation deficiency in most patients with an inherited pre-thrombotic state. However, arterial thrombosis occurred in the absence of risk factors in both studies.

The genetic defect causing APCR is a point mutation of the factor V gene, often referred to as factor V Leiden. The mutation is often present in heterozygous form in 5% of white European and North American populations. It is detected in 20% of cases of deep vein thrombosis and in 50 to 60% of pregnancy associated venous thromboses. The odds ratio for increased risk of venous thrombosis is 7 for heterozygotes and 80 for homozygotes. Although typically associated with venous thrombosis, recent studies of children³ and adults⁴ have suggested a possible role for APCR in arterial thrombosis.

We recently diagnosed heterozygosity for the Leiden mutation in a 2 year old boy with APCR (1.21; normal range 2.08–3.62), who has cerebral palsy but not other adverse neonatal risk factors. Investigations for abnormalities of protein C, S, antithrombin III and anticardiolipin antibodies were normal. At 8 weeks he had a divergent squint; at 3 months he developed infantile spasms and hypsarrhythmia which were quickly controlled with Vigabatrin. A computed tomogram indicated a well defined cerebral infarct in the left posterior occipital region. He currently has a right hemianopsia and mild right hemiparesis.

It was thought that the cerebral infarction occurred in utero or perinatally, but the history did not indicate any explicable event or risk factor. His mother had recurrent deep vein thrombosis and pulmonary embolism at an early age. Both she and the father were screened for thrombophilia, as well as the child. Interestingly, the father and child were both heterozygous for factor V Leiden, but the mother was not. The mother may have another, as yet, unidentified cause of thrombophilia, so the child could have several risk factors for thrombosis.

The question is whether the presence of heterozygosity is relevant to the aetiology of

cerebral palsy in this case. Although heterozygosity is common, we feel that it would be unwise to preclude a possible connection. We believe that not only are further studies warranted to investigate the prevalence of APCR and other defects of proteins C and S in neonates with thrombosis, but also in children who have cerebral palsy as a result of vascular thromboses that have occurred at an undetermined time, often in utero. How many children with unexplained cerebral palsy or cerebral palsy with relatively minor risk factors, are heterozygous for APCR? If there is an association, it may afford some comfort to parents and clinicians, that there is, at least in some cases, a potentially inherited risk factor for cerebral palsy.

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High serum immunoreactive trypsin not caused by cystic fibrosis

EDITOR,—In the course of neonatal screening for cystic fibrosis, a boy had raised immunoreactive trypsin values 112 pg and 73 µg/l (normal reference values <70 µg/l) at 6 and 28 days of age. His birthweight had been 3.6 kg (50th centile) at 41 weeks of gestation, and at 6 weeks his weight was 3.77 kg (< third centile). His length was 54 cm (25th centile) and head circumference 37.5 cm (25th–50th centile). He was alert and cheerful, not dehydrated or wasted. Respiratory and gastrointestinal systems were functioning normally.

Initial investigations showed a serum sodium of 163 mmol/l, urea 8.7 mmol/l, potassium 4.7 mmol/l, and bicarbonate 24.4 mmol/l; creatinine was 53 µmol/ml and urinary sodium, 17 mmol/l. Matched serum/urinary osmolalities were: 322/70 and 318/53 mosmol/kg, and there was no response to 10 mg of nasal desmopressin (matched serum/urinary osmolalities 317/58 mosmol/kg). An initial sweat test at 6 weeks obtained only 10 mg of sweat, but at 20 weeks the sweat chloride was 15 mmol/l and sodium 15 mmol/l (288 mg sweat). Faecal chymotrypsin was 149 µg/g (normal 120). DNA analysis was negative for DF508, G551D, and R553X mutations. Chest x ray picture and renal ultrasound scan were both normal. Serial measurements of urinary osmolality and urinary arginine-vasopressin (AVP) showed low osmolalities with inappropriately high AVP values (fig 1), with a flat dose response curve, confirming the diagnosis of nephrogenic diabetes insipidus.

Raised serum immunoreactive trypsin in infants who do not have cystic fibrosis has been reported in DF508 heterozygotes,¹ and in hypoxic insult to the fetal pancreas, congenital viral infections, trisomy 18 and 13, renal insufficiency, congenital heart disease and spina bifida.² Nephrogenic diabetes insipidus is yet another cause for falsely high serum values, but the mechanism for this is unclear.

Figure 1 Dose response curve of urinary osmolality (mmol/kg) to log urine AVP excretion rate, corrected for osmolality clearance (pg/min/Cosm).

Dehydration does not seem to be the entire explanation as the immunoreactive trypsin value had become almost normal by day 28, when the serum osmolality was still high.

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Effects of bolus tube feeding on cerebral blood flow velocity in neonates

EDITOR,—We read with interest the paper by Nelle *et al.*¹ The authors report that nasogastric bolus feeding in preterm infants provokes a considerable decrease in cerebral blood flow velocity (CBFV) while blood pressure and heart rate remain unchanged. In this study 20 to 40 ml of milk were delivered over 5 minutes to infants with a mean postmenstrual age of 35 weeks.

Was the feeding tube inserted before tube feeding or was it indwelling? Insertion itself could have significantly affected CBFV, heart rate, and oxygen saturation during the feeding period.²⁻⁴

What position were the infants in during the study? There are clear differences in oxygen saturation and heart rate between the prone and supine positions.⁵

Figure 1 Incidence of quiet and other than quiet sleep states in 11 healthy preterm infants (birthweight 1278 ± 168 g and gestational age 5 ± 2 weeks) before, during, and up to 20 minutes after feeding in the first, second, and third postnatal weeks. Note significant increase in quiet sleep state after feeding.

Apart from the periods when the infants woke up because of the blood pressure measurements, it is difficult to see how the infants remained in a quiet sleep state throughout the investigation. Behavioural state significantly affects CBFV.⁶ We recently studied the effects of orogastric feeding with infants in the prone position.⁷ After feeding (recorded until 20 minutes postprandially), most of the infants were in quiet sleep state, but before or during feeding the quiet sleep state was recorded in only a few infants (fig 1). This increase in the incidence of the quiet sleep state after feeding had a beneficial effect on oxygenation.⁷

We agree that a 10% postprandial decrease in CBFV over 10 minutes is considerable when associated with oxygen desaturation. But it is debatable whether such a decrease is due to the insufficient increase in cardiac output. In our experience, the duration of milk infusion in this study was rather short for the amount of milk given. Fast gastric filling could have caused the greater stimulation of vagal afferents⁷ with an ensuing transient decrease of CBFV.⁴ The authors did not report any cardiorespiratory instability in association with feeding, as reported by others.^{2,3} We found no significant influence of intermittent orogastric tube feeding on CBFV in healthy preterm infants.⁷

Transcranial Doppler ultrasonography allowed Nelle *et al* to perform continuous CBFV measurements over the 1 hour period. However, the authors limited the information by analysing just the first five Doppler curves at the beginning of each recorded minute. In our opinion, this made the recordings similar to those assessed by conventional duplex Doppler ultrasound scanning.

Transcranial Doppler sonography has established the concept of slow variability of CBFV in neonates. During slow variability, physiological state dependent CBFV fluctuations of 25% per minute have been reported.⁶ Accordingly, if transcranial Doppler ultrasound measurements are analysed in the same way as duplex Doppler measurements, important information may be lost.

We suggest analysing the mean values of consecutive one minute recordings, if absolute values of CBFV are to be presented and if the

expected change in CBFV takes place over a longer (10–60 minute) periods of time. For changes in CBFV that occur over a shorter (<10 minutes) or longer (>60 minutes) periods of time, mean values of other time units may be more appropriate (means of 5 second, or 10 second, or 5 minute periods, etc.).

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Dr Nelle *et al* respond:

An indwelling feeding tube was inserted at least 4 hours before taking the measurements in all infants. Thus a vagal response to tube insertion at the time of the measurements was unlikely.¹ One minute after the start of tube feeding, CBFV fell to 34.8 (15.4) cm/s ($p < 0.05$) and increased after 2 minutes to 37.7 (13.2) cm/s, and changed little during the following 3 minutes.

Measurements were carried out when the infants were in the supine position. The Doppler probe was fixed 30 minutes before

starting the measurements, and care was taken to ensure that nursing or other routine care was not performed for at least an hour before investigations began. During measurements, infants were in the quiet sleep state, as reported.

We agree that behavioural state² has a significant impact on CBFV. That is why we kept the environment as quiet and tranquil as possible, but we cannot rule out the possibility that some infants woke up during blood pressure measurements.

Haxhija and Rosegger question whether a decrease in CBFV is due to insufficient increase in cardiac output. Mean blood flow velocities in various intestinal arteries increase after tube feeding by about 100% in both full term and premature infants.³ To maintain cardiac output and blood pressure, the perfusion of other organs has to decrease in response to feeding.⁴ In preterm infants, peripheral (muscular and cutaneous) blood flow remains unchanged after feeding.⁵ Thus the increase in splanchnic blood flow in preterm infants after feeding requires either a substantial rise in cardiac output⁶ or redistribution of regional blood flow in favour of the splanchnic area at the expense of other organs.

We agree that gastric filling, as used in our study, could have stimulated vagal afferents and might have impaired CBFV.⁷

Lucas *et al*⁸ found that plasma concentrations of gut hormones were significantly increased 30 to 60 minutes after starting feeding, rising well above plasma concentrations found in adults. Gastrointestinal hormones have an important role in local intestinal perfusion, thereby altering systemic and cerebral circulation.

We analysed only the first five beats at the beginning of each recorded minute, because we were not aiming to study CBFV variability within each minute. Rather, we wanted to study minute by minute changes in CBFV after tube feeding. This is not feasible, using Doppler devices. Nevertheless, our results suggest that under certain conditions—that is, infants at risk of cardiovascular or cerebrovascular disease, bronchopulmonary dysplasia, or apnoea-bradycardia syndrome—tube feeding may cause adverse outcomes, and this should be borne in mind when used in critically ill neonates.

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Measures of visual function in minimum datasets

EDITOR,—We strongly support Johnson's recommendation for a standard minimum dataset for follow up studies,¹ which includes information on visual function. There are very limited data available on the incidence of severe visual impairment and blindness among children in the UK. Estimates have often been based on the national registers of partial sight and blindness. However, these have documented limitations in terms of detail and completeness and can only provide rates of registration of visual deficit.²

We understand the rationale for a minimalist approach to collection of readily available data, but propose an alternative to the suggestion of recording only whether the child is blind or sees light. Blindness can be difficult to define and measure in young children. Even among children at high risk of severe visual defects, inability to perceive light and other levels of blindness³ are not common. Moreover, blindness per se is not always the outcome of greatest interest. We therefore suggest that the ability to fix and follow a light should be recorded. This can be assessed in most young children, including those with other disabilities.

If a less minimalist approach to the minimum dataset were adopted, particularly for older children, the corrected visual acuity in each eye, together with the method of measurement, should be recorded. This information should be readily available for children thought to have a visual defect as they are likely to have undergone an ophthalmic assessment. This would improve the comparability of follow up studies and their usefulness in planning educational and other services without unduly expanding the minimum dataset.

Finally we suggest that whether the child has been registered as partially sighted or blind should be recorded. We believe that these refinements of the proposed measure of visual function would improve the usefulness of routinely collected data on visual morbidity among children at high risk of visual defects.

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Lactate and anion gap in asphyxiated neonates

EDITOR,—We read with interest the article by Deshpande about blood lactate and acid base status in neonates. We agree with the authors about the lack of correlation between blood pH and lactate. Nevertheless, in a retrospective study we found that the anion gap $[(Na+K) - (Cl+HCO_3)]$ was a reliable marker, and correlated well with blood lactate for at least 36 hours.

From January 1990 until December 1992, 155 asphyxiated neonates were admitted after acute fetal distress. All were mechanically ven-

tilated and none had received bicarbonate. Mean gestational age was 36 weeks (range 26-42), (57% preterm; 20% small for gestational age). Sixteen per cent died and 12% had an abnormal neurological examination on discharge. We measured: umbilical arterial pH at birth and arterial pH, bicarbonate, anion gap and lactate at time 1 (T1) (mean 4 hours after birth), and in the sickest, at T2 (mean 14 hours) and T3 (mean 37 hours). We used the Spearman Rank test for correlations.

Lactate correlated with the anion gap throughout, but not with arterial pH. There was a decreasing correlation with bicarbonate over time (table 1). Umbilical pH correlated with lactate at T1 ($p=0.0041$). The blood lactate concentration at T1 did not seem to influence mortality or morbidity. Interestingly, an anion gap above 20 mmol/l at T1 was associated with an increased neonatal mortality (19% vs 9%) and neurological abnormalities detected on discharge (18% vs 4%). Nevertheless, the positive predictive values (PPV) of death at T1 was very poor: 20% for lactate > 2 mmol/l, and 13% for anion gap > 20 mmol/l. The negative predictive values were, respectively, 70% and 63%. The best PPV was obtained by either lactate > 2 mmol/l or anion gap > 20 mmol/l, associated with an Apgar score < 4 at 1 and 5 minutes (66% in both cases).

Table 1 Correlation (Spearman test) between blood lactate values and anion gap, arterial pH and bicarbonate at T1 (4 hours), T2 (14 hours) and T3 (37 hours)

	T1	T2	T3
Anion gap	<0.0001	<0.0001	0.0034
pH	NS	NS	NS
HCO ₃	<0.0001	0.0283	NS

Metabolic acidosis is a marker of birth asphyxia,² but is poorly correlated with outcome.³ To our knowledge, correlation of blood lactate with the anion gap has not been studied before in neonates. Although lactate was not correlated with anion gap in adults,⁴ we speculate that the excretion of lactate in case of lactic acidemia⁵ might be immature in neonates, then avoiding the reabsorption of chloride.

Our results suggest that the anion gap is a useful and easily performed biological reflection of neonatal asphyxia.

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Is ibuprofen a useful treatment for patent ductus arteriosus?

EDITOR,—I am delighted to find that Van Overmeire *et al*¹ have acquired evidence to support the view that ibuprofen may be a useful treatment for patent ductus arteriosus (PDA). However, their paper may mislead. Their study suggests that there is no more than a 30% difference in the efficacy of indomethacin and ibuprofen for closing PDA. Unfortunately, a 30% difference is often seen as adequate to prove the superiority of one treatment over another, rather than to demonstrate equality.

Since our original publication,² we have also acquired data which further support the contention that ibuprofen is a suitable treatment for PDA. Using these data to perform power calculations, we found that a total study number of 380 is required to demonstrate that the difference between the rate of PDA closure with each drug is no greater than 10% at the 5% level with 80% power. Such a result would be of far greater value for clinical purposes.

In order to define precisely the value of indomethacin for closure of PDA, we are currently preparing a multicentre randomised double blind control trial which will have sufficient power to settle this question once and for all. We would be delighted to discuss this further with interested research groups.

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Van Overmeire and colleagues respond:

We only showed that in a small number of patients ibuprofen seems to be as efficient as indomethacin in closing PDA by day 3 of life. There is no doubt that, as we pointed out in our paper, a larger number of infants should be studied before definitive conclusions in the equal efficacy of both drugs can be drawn. We believe that although ibuprofen seems to be a promising alternative to indomethacin, its efficacy as well as its side effects should be studied further in controlled trials before it can be used in routine practice.

Since we first started our clinical studies with ibuprofen, about 150 patients have been randomly allocated; the data obtained seem to confirm our earlier reported results.

We are currently running a larger multicentre controlled trial in which we compare, not only the efficacy, but also less frequently occurring side effects. Moreover, many other factors will be studied (haemodynamic, cerebrovascular, circulatory, pharmacological, etc). We believe that ibuprofen remains a promising drug, worthy of study in neonates, and we welcome further discussion about clinical trials and other aspects of the drug from interested research groups.