LETTERS TO THE EDITOR

Clotting profiles and coagulation factors

EDITOR,—Neonates who have clinical signs of a bleeding diathesis warrant a coagulation screen to detect an underlying coagulation disorder. If the specimen collected for a clotting profile clots then the test cannot be done and a repeat specimen is required. Often samples that are clotted are not repeated due to the commonly held misconception that for a specimen to clot it must have normal coagulation factor concentrations.

We aimed to test the hypothesis that if a coagulation profile specimen clots then the patient’s clotting profile must be normal. A retrospective analysis was performed, examining all neonatal clotting profile specimens that had clotted, from August 1 1996 to December 26 1998 at the Royal Women’s Hospital, Melbourne, Australia. Clotted specimens were identified and data were collected from the clotting profile of specimens repeated later the same day. The clotting profile included the prothrombin time (PT) (seconds), activated partial thromboplastin time (APTT) (seconds), fibrinogen concentration (g/l) and D-dimer (mg/l). The reference ranges for each parameter were corrected for postnatal and gestational age.

Eighteen clotted specimens were taken from 11 neonates. Only nine were repeated on the same day, two of which clotted again and blood was not re-collected. Of the remaining seven specimens, five had abnormal results. Of those five abnormal results, all had increased PT, APTT, and D-dimer (mg/l). The reference ranges for each parameter were corrected for postnatal and gestational age.

This point shows that the clinical spectrum of coagulation withdrawal in newborns includes myoclonus. Limb jerks appeared several days after birth and were suppressed by clomipramine, which suggests a withdrawal effect. Myoclonus has hitherto not been recognized, but epileptic seizures are commonly reported. However, EEGs are never performed, except for one neonate with generalised clinical manifestations and a focal epileptogenic focus. Hence, epilepsy was not unequivocally demonstrated and myoclonus may have been present in some patients.

In this case, several observations argued against epilepsy. Antiepileptic drugs were ineffective, limb jerks were stimulus sensitive, and the child remained responsive during generalised jerks. Importantly, the EEG showed no abnormalities during the generalised jerks, which proved they were not epileptic.

Recognition of myoclonus has therapeutic consequences because status epilepticus requires aggressive treatment, with phenobarbital as the first choice. However, phenobarbital is often ineffective for myoclonus and may theoretically aggravate withdrawal signs due to liver enzyme induction which facilitates clomipramine clearance. Low dose clomipramine, which allows for gradual tapering of clomipramine concentrations, seems more effective for myoclonus.

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Neonatal diabetes and severe intracerebral haemorrhage

EDITOR,—A 20 day old baby boy was referred to our hospital with a history of right sided palsy, nystagmus and seizures. He had been born by normal vaginal delivery, at 36 weeks of gestation, with good Apgar scores (8 and 9 at five minutes, respectively). He had jaundice, for which he required phototherapy for three days at the referring hospital, but was otherwise normal.

Ten days after discharge he presented again with a history of poor feeding and lethargy for one day. On examination, he looked pale with a full and tense anterior fontanelle. He was febrile and tachypnoeic. A presumptive diagnosis of sepsis/meningitis was made and he was given cefotaxime and ampicillin. Spinal tap was deferred as the fontanelle was tense. He developed intratable vomiting requiring diazepam, phenobarbitone, and phenytoin.

In view of his deteriorating condition, he was transferred to the university hospital. On arrival, he was noted to be febrile and lethargic. After stabilisation an emergency computed tomography scan of the brain was performed, which revealed cerebral oedema and a large, left sided, intracerebral bleed, with extension into the subarachnoid spaces and ventricle. Investigations on admission revealed severely deranged electrolytes. His serum glucose was 51.2 mmol/l, sodium 170 mmol/l, potassium 7.5 mmol/l, urea 39 mmol/l and creatinine 246 µmol/l. The white cell count was 17 × 10⁹/l, with a haemoglobin of 156 g/l. The platelet count was obtained from the referring hospital because our specimen had a small clot (125× 10⁹/l). The coagulation profile was normal (PT 15 seconds, APTT 203 seconds, D-Dimer > 0.5 < 1 µg/ml, fibrinogen 203 g/l). The infant was treated symptomatically with supportive care, but died on the second day of admission.

The common causes for bleeding were ruled out. There was no history of birth asphyxia or trauma. The platelet counts and coagulation profile were normal. Although the chance of arterio-venous malformation as a cause of spontaneous bleed cannot be ruled out completely, the computed tomography scan gave no indication of this. The diagnosis of neonatal diabetes was supported by concomitant hyperglycaemia (9 mmol/l), hyperosmolarity, metabolic acidosis (pH 7.29, baseline excess –16.3), dehydration and weight loss (weight at admission was 2050 g compared with birthweight of 2580 g).

Neonatal diabetes is rare. The incidence rates reported from the UK and Germany are 1 in 400 000 and 1 in 500 000, respectively. As far as we are aware, no reports have been published on the association between neonatal diabetes and intracerebral haemorrhage. However, previous reports have associated hyperglycaemia with haemorrhagic transformation of the cerebral infarct. In a recent study, Scott et al showed an increased incidence of intracerebral haemorrhage with...
admission hyperglycaemia in adults.1 In an animal model study, de Courten-Myers et al reported 25-fold more extensive haemorrhage in cats with hyperglycaemia compared with normoglycaemic cats. Similarly, Broderick et al associated hyperglycaemia with cerebral bleed in two human adults. The exact mechanism by which hyperglycaemia induces cerebral bleeding is not clear. It enhances lactic acidosis in brain tissue and the combination of hyperglycaemia and acidosis enhances endothelial damage with subsequent extravasation of red blood cells through the leaky vessels. There have been studies on the effect of glucose and acid base changes on brain ischaemia.

A causal link between hyperglycaemia and intracerebral haemorrhage in neonates may be difficult to prove, but we look forward to other prospective studies on the risks and mechanisms of brain haemorrhage in neonates with severe hyperglycaemia.

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Neonatal paracetamol poisoning

EDITOR,—Neonatal paracetamol poisoning is rare. To date, there have been no definitive therapeutic guidelines for its management. We suggest that N-acetylcysteine for paracetamol poisoning should be continued until the INR returns to normal.


Table 1
Biochemical profile of mothers and infants

<table>
<thead>
<tr>
<th></th>
<th>Neonates</th>
<th>Mothers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from ingestion (h)</td>
<td>9 18 27</td>
<td>32 48 72</td>
</tr>
<tr>
<td>Paracetamol (mg/l)</td>
<td>133 67 25</td>
<td>&lt;0.1 &lt;0.1</td>
</tr>
<tr>
<td>PT (sec)</td>
<td>44</td>
<td>147 &lt;0.1</td>
</tr>
<tr>
<td>INR</td>
<td>3</td>
<td>1.01</td>
</tr>
<tr>
<td>Bilirubin (mmol/l)</td>
<td>90 99</td>
<td>85 25 11</td>
</tr>
<tr>
<td>AST (U/l)</td>
<td>110 116</td>
<td>55 32 28</td>
</tr>
<tr>
<td>Creatinine (mmol/l)</td>
<td>52</td>
<td>52</td>
</tr>
</tbody>
</table>

“Dewatering” of the lungs

EDITOR,—The letter from Hills and Masters in response to my commentary on their paper raises some interesting points which require further comment. I stand corrected over my description of their model of the alveolus as “dry.” This was a short hand term on my part to distinguish Hills’ theory on how he has published widely from the more traditional theories of how pulmonary surfactant works.

Their letter, however, does not challenge the basic points I made in reluctantly refuting their hypothesis. These were firstly, that fetal lung liquid can be absorbed before birth—that is, before the establishment of an air–liquid interface and thus before surface forces can act—and, secondly, that we have intact pulmonary surfactant function, there is total failure of lung liquid removal when sodium ion transport is abolished. The latter finding, in particular, must make us question whether surfactant has any role in lung liquid removal at birth.

The authors make the novel suggestion in their letter that the oligolamellar structures of surfactant could be the barrier to diffusion at intercellular junctions and they claim makes the lung epithelium relatively tight and thus enhances its ability to secrete or absorb liquid through generating osmotic forces by ion movement. Before birth the pulmonary epithelium is always “tight” and restricts the passage of molecules the size of sucrose and larger. The low permeability is constant during gestation* and does not decrease (at least in the liquidtight lung) when surfactant appears near term, a finding which argues against this newly proposed function for surfactant.

Measuring permeability in the air filled postnatal lung is difficult, but the evidence suggests that there is a temporary increase in permeability over the first 12 hours after birth (probably as the result of stretch) which then reverts to near fetal permeability levels. The reason that it takes days to clear fluid from the lungs in respiratory distress syndrome (RDS) even after administration of exogenous surfactant, is because the epithelial barrier has been breached in the early stages of the disease and cannot maintain an osmotic gradient, however hard the Na+ “pump” works. Indeed, damage to the pulmonary epithelium in RDS has been shown to occur within two minutes of birth. It is the slow healing of the epithelium, hindered by persistent barotrauma and high oxygen tensions, which causes the prolonged recovery from severe surfactant deficient RDS.

A picture included in the author’s letter seems to provide evidence for the traditional theory—that surfactant rests on a very thin alveolar liquid layer and not vice versa. The thickness of this layer measured in vivo by physiological means in the air filled lung, rather than by microscopy, is indeed very small. The mean thickness being calculated at only 0.1–0.2 microns, indicating that in some areas it will be even thinner. I accept that these physiological measurements are no more able to settle the arguments about how precisely surfactant is distributed in the alveolus than can microscopy. However, for ion transport and water movement to work, there must be ready access to the
apically placed epithelial ion channels by ions in the alveolar liquid—the alveolar liquid would be better placed below any surfactant forms rather than above them. A more detailed discussion of the possible interactions between surfactant and lung liquid movement has been given elsewhere.11

The authors are to be complimented on their thought provoking suggestions, but, ultimately, all hypotheses must be supported by experimental evidence.

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Detection of heart disease in infancy

CORRECTIONS

In last month’s edition (Arch Dis Child Fetal Neonatal Ed) 1999;80, the following were inadvertently published incorrectly:

In the Letters to the Editor section, several names were omitted from Vascular ring: an important cause of upper airways obstruction (F252–3). In addition to A Sharples, I N Keengwe, I Ahmad, and O Dearlove should have been included.

The figure legends in Serum malondialdehyde concentration in babies with hyperbilirubinemia (Yigit, et al, F235–7) should have been:

Figure 1 Correlation between malondialdehyde and bilirubin concentrations in group 1.

The first author of Body composition of preterm infants during infancy (F188–91) should have been R J Cooke and not D J Rawlings, as published.


Clinicians working with children with cerebral palsy see the end result of damage which occurred many years before. To understand the causes and timing of this damage, you need to look at its origins in the fetal and newborn periods, because it is now abundantly clear that most cerebral palsy arises in prenatal life; in only a small proportion of children is there evidence of injury at birth.

The causes are by no means understood. Hypoxia and ischaemia have long been regarded as the most important, but pathologic and epidemiologic studies show that very similar forms of damage also result from maternal and placental infections, possibly mediated by cytokines crossing the placenta into the fetal brain, by metabolic disease, iodine deficiency, etc.

The contribution of very early intratuerine damage to birth asphyxia was first noted by Sigmund Freud over 100 years ago; not all birth asphyxia is what it seems. Many of these infants were set up months beforehand for a difficult birth. Dr Abraham Towbin recognised the value of studying the fetal and neonatal brain. He worked with the most eminent of neuropathologists, Paul Yakovlev, and from him learned the method of colloidin embedding. Using this technique, these tiny, fragile, and precious specimens can be embedded whole in plastic and entire brain sections cut and examined under the microscope, with unparalleled preservation of the pathologic anatomy. You won’t persuade a technician to undertake this technique today; it is far too costly, both in time and resources for modern laboratories.

This book represents a celebration of Dr Towbin’s 40 plus years in pediatric neuro-pathology. It is a meticulously documented collection of over 200 case studies accompanied by detailed obstetric and clinical histories. It is beautifully produced and the illustrations are superb. They include gross and microscopic pathology of the brain, placenta, and body organs as well as many radiographs. Most are full colour, every one is clean and crisply focused, and the legends are economical.

The weakest part of the book is Dr Towbin’s interpretation of the pathogenesis of developmental brain damage. It is idiosyncratic and he paints with a very broad brush. The clinical chapters are scarcely more informative.

But the real value of this book is that it allows us to share in a rare wealth of carefully archived material; an invaluable resource for pathologists, obstetricians, neonatologists, neurologists and developmental psychiatrists.

This book has a timely message in an age of ever-increasing litigation. Only a small proportion of developmental brain damage occurs at birth; in over 80% we still have to seek causes and establish prevention in the perinatal period.

ARCH DIS CHILD FETAL NEONATAL ED: first published as 10.1136/fn.81.1.F77 on 1 July 1999. Downloaded from http://fn.bmj.com/