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LETTERS TO THE EDITOR

Metabolic acidosis in premature babies

Sir,- Walter recently reviewed metabolic acidosis in newborns, however little mention was made concerning volume expansion as a possible treatment strategy. 1 In particular the role of human albumin solution (HAS) in ventilated, premature babies was not discussed.

We have studied the effect of an infusion of 15 ml/kg of 4.5% HAS, over 30 minutes, in 19 consecutive low birthweight infants receiving mechanical ventilation with a metabolic acidosis. Arterial blood was taken before and after 15 minutes after volume expansion for the measurement of pH, base deficit, bicarbonate, and lactate (table). During the study ventilatory requirements remained stable.

The significant rise in pH (p<0.01) and significant decrease in base deficit (p<0.0001) was mirrored by a significant decrease in serum lactate (p<0.001), interestingly there was no change in serum bicarbonate (paired t test).

This study shows that lactate accumulation, probably the result of hypovolaemic tissue hypoxia, is a cause of metabolic acidosis in premature babies. This acidosis is acutely rectified by the infusion of a volume expander.

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Traumatic neonatal intracranial bleeding and stroke

Sir,- Extending the concept of posterior cerebral artery compression associated with intracranial hypertension to other arterial distributions in the expanding neonatal skull requires reasonable proof. We believe that discrepancies in the radiological and clinical data presented by Govaert et al limit the strength of their final suggestion. 1

Direct demonstrations of arterial injury associated with intracranial hypertension are not presented. Several computed tomograms are misinterpreted, for example fig 1 does not show a 'basal convexity' haematoma while anatomically inaccurate interpretations are given for fig 6B. In fig 3, the haematoma is located at the level of the tentorium while the computed tomogram demonstrates a hypodensity in the territory of the proximal middle cerebral artery. This anatomical discrepancy is continued in the schematic drawing. Either the initial (case 5) or follow up (case 6) computed tomograms are not presented and consequently adequate conclusions may not be reached concerning the aetiology of the computed tomogram abnormalities. Finally, alternative clinical explanations for the computed tomogram findings such as a watershed infarct in case 1 or intraparenchymal injuries in cases 2 and 7 are ignored or discarded without sufficient cause.

Most of these infants demonstrated several neuroradiological abnormalities. Ascribing long term sequelae to one or the other may be inaccurate and legally treacherous. More importantly, the natural but inappropriate desire to correct surgically any potential problems implied by these data should be resisted until newer techniques such as magnetic resonance angiography can confirm the authors' speculations.

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Dr Govaert and coauthors comment:

We welcome the interest raised by our article on traumatic neonatal intracranial bleeding and stroke. The essence of our observation was the existence of hypoperfusion within the region of the middle cerebral artery ipsilateral to extracerebral haemorrhage. In the first case of our small series of seven an interval of at least two days between traumatic vacuum delivery (with subgaleal bleeding and subtemporal subdural haematoma) and subsequent hypoperfusion within the middle cerebral artery on that side suggested the possibility of vasospasm as an intermediary mechanism. This was not demonstrated with an angiographical technique and therefore we used the term hypothesis to describe that finding.

We would agree that 'basal convexity haematoma' may be a misnomer. In the absence of generally accepted defining criteria for various types of subdural bleeding we use the term to refer to supratentorial subdural haemorrhage not related to bridging veins of the superior sagittal sinus or central tentorial injury near the great cerebral vein. Usually these collections are under the tempo-occipital lobe and along the temporal lobe convexity, as was the case in our first patient. The sections used in fig 1 do not show the 'typical' site of bleeding as visible in other sections.

In fig 3 (case 4) a basal subdural haematoma is associated with hypodensity of the mesial temporal lobe. According to all anatomy books we consulted this area is perfused by the posterior cerebral artery. This would not exclude concurrent hypoperfusion of branches of the middle cerebral artery, but we felt our computed tomogram did not show this with certainty. The hypodense areas depicted in fig 1 (case 1) cannot be a watershed arterial infarct according to the same references. It is plainly within the region perfused by the middle cerebral artery.

Some initial or follow up scans were not presented because there is a limitation to the use of scans in an article. We therefore chose to use the most representative scans. The patient in case 6 (fig 5) did not have a follow up scan, because it is our practice to perform scans only on clinical indication.

In case 2 (fig 2) there were three major reasons why we felt the haemorrhage to be

Effect of 4-5% HAS infusion in 19 low birthweight infants. Results are mean (SE)

<table>
<thead>
<tr>
<th>pH</th>
<th>Base deficit (mmol/l)</th>
<th>Serum bicarbonate (mmol/l)</th>
<th>Serum lactate (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before infusion</td>
<td>7.258 (0.023)</td>
<td>8.98 (0.82)</td>
<td>17.37 (0.62)</td>
</tr>
<tr>
<td>After infusion</td>
<td>7.328 (0.025)</td>
<td>7.53 (0.79)</td>
<td>17.44 (0.71)</td>
</tr>
</tbody>
</table>

extracerebral: (i) there was little evidence of midline shift, which in view of the size of the bleeding would argue against its location within the brain substance; (ii) this was almost a 'chance' finding in an apparently healthy neonate, suggesting very little brain damage in itself; and (iii) there was no residual tissue loss on follow up ultrasound scan.

In case 7 (fig 6) the text describes a cerebral contusion, which in my view is synonomous with intracerebral haemorrhage of some sort. This detail was not big enough to explain the amount and type of tissue loss seen on follow up.

Finally there seems to be little doubt that in patients 1, 5, and 7 obvious mechanical difficulties during delivery, in the absence of clinical signs of hypoxic-ischaemic encephalopathy or bacteraemia, preceded tissue loss within an arterial region of the cerebrum (twice the middle cerebral artery). Whether or not this observation is legally treacherous we tend to leave to solicitors and judges as a matter of eternal debate. From a medical point of view the association stands.

### Brain uptake of amino acids in intravenously fed preterm infants

**Snr.—**Up to 500 000 infants, mostly preterm, in Britain alone have received the intravenous amino acid solution, Vamin 9 (Kabi Pharmacia). Hyperphenylalaninaemia is often induced by Vamin 9,1 2 resulting in speculation about brain damage,2 as in phenylketonuria (PKU). In PKU cerebral damage probably follows excessive brain weight uptake of phenylalanine with competitive suppression of uptake of other neutral amino acids to perhaps critically low levels.2

To explore whether such deranged brain uptake of amino acids might occur in intravenously fed preterm infants, sequential plasma samples were analysed for amino acids as described previously3 in 336 preterm infants below 2800 g birth weight under-going neonatal care. Brain fluxes of amino acids were calculated from amino acid profiles using a rat model experimentally derived by Pratt.3

Infants were divided into three groups: (1) those never receiving Vamin 9, (2) those who received Vamin 9, and (3) infants on Vamin 9 who developed hyperphenylalaninaemia (peak plasma phenylalanine >300 μmol/l). The table shows data on mean plasma concentrations and calculated mean brain uptake values for neutral amino acids (excluding tryptophan which was not measured). These are compared with corresponding values for normal children and those with untreated and treated PKU.3

<table>
<thead>
<tr>
<th>Amino acid</th>
<th>Group 1 (No Vamin)</th>
<th>Group 2 (Vamin-9)</th>
<th>Group 3 (Vamin-9; peak phenylalanine &gt;300 μmol/l)</th>
<th>Group 4 (Normal children)</th>
<th>Group 5 (Untreated PKU)</th>
<th>Group 6 (Treated PKU)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P</td>
<td>F</td>
<td>P</td>
<td>F</td>
<td>P</td>
<td>F</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>69 5-9</td>
<td>125 5-9</td>
<td>463 5-9</td>
<td>68 7-3</td>
<td>1496 45-0</td>
<td>335 30-1</td>
</tr>
<tr>
<td>Methionine</td>
<td>22 1-7</td>
<td>33 1-7</td>
<td>92 1-7</td>
<td>50 3-1</td>
<td>11 0-2</td>
<td>10 0-3</td>
</tr>
<tr>
<td>Histidine</td>
<td>137 4-5</td>
<td>144 4-9</td>
<td>240 4-7</td>
<td>74 5-6</td>
<td>47 1-0</td>
<td>99 2-7</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>57 1-9</td>
<td>72 1-7</td>
<td>55 1-8</td>
<td>43 0-4</td>
<td>129 1-9</td>
<td></td>
</tr>
<tr>
<td>Threonine</td>
<td>238 1-4</td>
<td>214 1-6</td>
<td>252 1-5</td>
<td>92 0-9</td>
<td>67 0-2</td>
<td>217 0-9</td>
</tr>
<tr>
<td>Tyrosine</td>
<td>144 4-2</td>
<td>225 4-1</td>
<td>824 4-1</td>
<td>50 3-9</td>
<td>40 0-9</td>
<td>86 2-6</td>
</tr>
</tbody>
</table>

The marked brain uptake of phenylalanine, seen in PKU, did not occur in any of the groups of preterm infants. Furthermore, competitive suppression of methionine, histidine, isoleucine, threonine, and tyrosine seen in untreated PKU was not seen in Vamin 9 fed preterm infants. Hypertryrosinaemia, commonly seen in preterm infants, did not appear to result in increased brain uptake of tyrosine. These findings probably reflect the concomitant increase of competing amino acids during intravenous nutrition,3 in contrast to the isolated hyperphenylalaninaemia in PKU.

Some caution is required in extrapolating results of an animal model to preterm infants in whom alterations, for example, in cerebral flow and blood brain permeability could theoretically influence the results; and the absence of tryptophan data could have affected our calculations. Nevertheless, these concerns are theoretical and kinetics of cerebral amino acid uptake have been shown generally to apply across species, including man.5

Recently we showed that hyperphenylalaninaemia induced by Vamin 9 was not associated with an adverse developmental outcome at 18 months.1 The data presented here provide a potential explanation, as it is unlikely that hyperphenylalaninaemia could have damaged the brain if cerebral uptake of amino acids was unaffected. These preliminary data, therefore, do not provide a biological basis for the view that Vamin 9 could damage the brain.6

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(Sadly Dr Pratt died before completion of this work)


### Mean plasma values; μmol/l (P) and estimated mean brain fluxes; nmol per min/g brain (F). Groups 1–3 are values in preterm infants; groups 4–6 are values published for comparison