Sir,

I would like to present our experience with copper deficiency in neonates of very low birthweight and to comment on the paper by Sutton et al.1 Over the previous two years we diagnosed five cases of neonatal copper deficiency (birthweight: 740–1200 g, gestational age 26–34 weeks) at the postnatal age of 8–20 weeks. Three neonates had bone changes, but all had anaemia and severe neutropenia in the absence of infection. Only two neonates had required prolonged periods of ventilation and parenteral nutrition. All had received a milk formula with a relatively high copper content. At the time of diagnosis their serum copper concentration was <0-4 μmol/l (2-5 μg/100 ml) and their caeruloplasmin concentration was <1-5 g/l (1-4 mg/100 ml). They were treated with 5 mg/day of copper sulphate solution (1% solution) for six months with excellent results. The earliest and most sensitive indicator to treatment was the response of the neutrophil count (increase in 48 hours after treatment and return to normal in two weeks). With this experience and reviewing previous reports I should like to make the following comments.

(1) Although serum copper and caeruloplasmin concentrations provide some information, they do not adequately reflect the copper stores of the body. Therefore treating very low birthweight infants with copper sulphate because of low serum copper and caeruloplasmin concentration in the absence of any other finding is questionable.

(2) The most sensitive and early index of copper deficiency is in our experience haematological. Bone changes will eventually occur in all patients, but they are a relatively late finding. In preterm neonates anaemia is a common finding of varied aetiology and can be masked by transfusion. Severe neutropenia in the absence of infection, on the other hand, is an unusual and impressive finding. I would agree with Sutton et al that facilities for copper and caeruloplasmin estimation should be available to neonatal units. I think, however, that these variables should be measured in all very low birthweight neonates over the age of 4–6 weeks. If selective measurements are preferred, I would favour neutropenia to be the indicator rather than the findings suggested by Sutton et al, which are either relatively late (osteonoporosis) or unusual (oedema).

(3) With respect to treatment I think that neither the dose of copper sulphate nor the length of treatment is presently known. In the absence of balance studies involving at least copper and zinc I would not favour the administration of excessively high doses of copper over a very short period as described by Sutton et al. It is probable that in order to replenish copper stores a longer period of copper administration is necessary.

Reference

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Dr Sutton and co-workers comment:

We were interested to hear of this experience of copper deficiency in Greece and assume that the caeruloplasmin concentrations were less than 0-15 g/l (0-14 mg/100 ml) rather than as stated in the letter.

We agree that neutropenia is a useful finding in copper deficiency, but feel that we should try to make a diagnosis before this stage is reached. Growth failure and oedema were present up to four weeks before significant neutropenia or anaemia was seen, and osteoporosis was reported at an earlier stage also. We would dispute the statement that bone changes are a relatively late finding and would suggest that this may be a consequence of the rather insensitive methods of detection.

With regard to treatment, there is an unfortunate error in the dose of copper that we used which should read 4 μmol (254 μg) copper/kg/day. This was based on the experience of Yuen et al and has proved to be satisfactory when given for 1–2 weeks in the six cases we have treated. This dose is approximately four times the minimum daily requirement for the preterm infant, and we would not consider it excessive. The dose of 5 mg per day of copper sulphate (presumably pentahydrate solution, equivalent to 1-25 mg of elemental copper) given by Dr Dellagrammaticas is approximately five times the amount we used. There is no evidence that this amount of copper needs to be given for such a prolonged period, and indeed, as there is competition for absorption with other essential elements it might be detrimental.

Our intention was to increase the general awareness of copper deficiency so that ideally it can be prevented by adequate supplementation, or at least diagnosed at an early stage to reduce the risks from the metabolic effects of a deficiency state. We would therefore strongly disagree with the suggestion by the author of the letter that neutropenia should be the indicator for diagnosis.

Posthaemorrhagic hydrocephalus in new born term infants

Sir,

Dr Hill and Morgan1 draw attention to the occurrence of intraventricular haemorrhage in previously well, full term infants but in their discussion of aetiology fail to mention the possibility of α₁-antitrypsin deficiency. Readers of this journal will know of the association between α₁-antitrypsin deficiency and a bleeding diathesis in the newborn2 and of the occurrence of intracranial haemorrhage in such infants.3 4 We have also seen α₁-antitrypsin deficiency presenting as intracranial haemorrhage in a previously well, full term infant who had received vitamin K at birth. We would suggest that the diagnosis of α₁-antitrypsin deficiency is considered in full term infants presenting with intracranial haemorrhage.

References
Copper and the preterm infant

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Arch Dis Child 1985 60: 1107
doi: 10.1136/adc.60.11.1107

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