non-rachitic infants, 14 (54%) showed an increase–peak–decrease pattern of bone origin alkaline phosphatase activity with increasing postconceptional age. There was no significant change in plasma calcium or inorganic phosphorus.

Because of the difference in techniques of estimation it is not possible to compare directly our published results with those of Glass *et al.* Their recommendation of 500 U/l as an upper limit of normal cannot be directly related to our laboratory, or to any which used different methodology.

It is also difficult to define age based reference intervals for plasma alkaline phosphatase activity in preterm infants because of the non-Gaussian distribution of data. Moreover, because infants of identical postnatal age, but differing postconceptional ages, are not equivalent, it is not appropriate to use postnatal age as a basis for establishing normal values. We have noticed that alkaline phosphatase activity when measured serially in an infant will invariably exceed, at some stage, a gestational age related range (I Kovar *et al.*, unpublished data).

To avoid these problems we suggest that alkaline phosphatase activity in an individual neonate and infant should be expressed in relation to a fixed range, rather than as a gestation related mean and standard deviation; use of a percentage of an upper limit of an adult reference range permits comparison between laboratories. This then allows recommendations to be made for intervention in a given case when a fixed multiple is recorded. We agree, however, that serial plasma alkaline phosphatase activity estimation is a useful means of screening for rickets in this susceptible population.

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Skeletal changes in preterm infants

Sir,

We were interested to read the paper by Koo *et al.*[1] in which they mention that none of the infants fed exclusively on breast milk had abnormal skeletal *x*-rays.

We undertook a similar study of the possible effect of breast milk or humanised formula on infants' blood 25-hydroxycholecalciferol and parathyroid hormone concentrations.[2] It was found that parathyroid hormone concentrations at age 8 weeks (measured by radioimmunoassay which predominantly detects the C-terminal end) were normal in infants fed exclusively on breast milk, but were appreciably higher in infants receiving a formula milk in addition to breast milk. This difference was not explained by the plasma 25-hydroxycholecalciferol concentrations, which were normal and similar in both groups. We wonder whether the serum biochemical findings (calcium, phosphate, alkaline phosphatase, immunoreactive parathyroid hormone) and radiological findings in the 7 infants fed exclusively on breast milk were different from those of the 7 infants fed with the formula in the study of Koo *et al.*

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Dr Koo and co-workers comment;

We have reviewed the data from our study[1] and those published by Sann *et al.*[2] It appears there are a number of aspects which make direct comparison of the results difficult. The patients in our study who developed radiological skeletal abnormalities have more severe illnesses and have significantly lower birthweights than those with normal skeletal *x*-rays. In addition, 9 infants in our study received human milk for 2 to 37 (median 18) days—a period far shorter than the formula supplemented group of infants in the study of Sann *et al.*[2] Furthermore, the dose of vitamin D_2 supplement used in our study was 800 IU/day from age 14 days compared with the dose of 2400 IU/day from age 10 days in the study of Sann *et al.*[2]

However, we analysed our data further, using one way analysis of variance and Newman Keuls' multiple comparison procedure to determine if there were any differences between the infants with radiological skeletal abnormalities (group 1) and the infants with normal skeletal radiographs but who were fed human milk only (group 2) and those who were fed some or no human milk (group 3).

The results showed that infants in group 2 were significantly larger (birthweight 1183 ± 76 g, mean $\pm$ 1 SD) and had greater gestational ages ($30 \pm 2{\cdot}9$ weeks, mean $\pm$ 1 SD) at birth than group 1 infants ($P < 0{\cdot}05$). They also tolerated a predetermined volume of feeds (>160 ml/kg per day) significantly sooner ($7{\cdot}3 \pm 1{\cdot}9$ days of age, mean $\pm$1 SD) than group 1 infants ($P < 0{\cdot}05$). There were no significant differences in these parameters between groups 2 and 3 or between groups 1 and 3.

There were no important intergroup differences in serum calcium, phosphorus, alkaline phosphatase, total protein, 25 hydroxyvitamin D (25-OHD), and immunoreactive parathyroid hormone in the cord blood, at 5 weeks and 10 weeks postnatal age. In group 2 infants,

the serum 25-OHD levels had risen significantly ($P < 0.05$, paired t test) above cord values by 5 weeks of age, but there were no intragroup differences in the other serum variables measured. In group 1 infants, the serial changes in the serum variables measured had been reported.[1]

Although 4 of the 6 infants in our study who showed radiological skeletal abnormalities received some human milk during their hospitalisation, for reasons stated above, our data neither support nor refute the findings of Sann *et al.*[2]

Familial benign copper deficiency

Sir,

The case report by Méhes and Petrovicz[1] requires comment. They state that the serum copper of their patient was found to be 49·7 and 44·6 μg/100 ml (7·8 and 7 μmol/l) (determined by atomic absorption spectrophotometry) while the serum caeruloplasmin concentrations were 'repeatedly normal, 0·30 to 0·44 g/l.' These figures are mutually incompatible. Caeruloplasmin is a protein of fixed copper content of approximately 0·3%.[2] As the copper in caeruloplasmin is present in a fixed ratio, serum concentrations of between 0·3 and 0·44 g/l of the protein necessitate a copper concentration in the serum of not less than 90 μg/100 ml, and reaching as high as 132 μg/100 ml (20·7 μmol/l). To this must be added a small percentage of 'free copper' always present in plasma, but not exceeding 10%. Thus, if the caeruloplasmin concentrations for the patient quoted are correct his serum copper must have varied between 95 and 140 μg/100 ml (14·9 and 21·9 μmol/l), two to three times the reported figure. The only alternative explanation to an analytical error is that this patient has a mutant caeruloplasmin with only half the normal copper content: if such is the case the observation should be adequately documented.

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Dr Méhes and Dr Petrovicz comment:

The discrepancy between low serum copper and normal caeruloplasmin concentrations is certainly remarkable. Although the heterogeneity of caeruloplasmin is well-known and a significant methodical variation is also to be considered, we do not know of an explanation for this phenomenon in the family reported by us. However, since a close positive correlation between blood copper and caeruloplasmin concentrations was obtained in many hundreds of examinations of both normal and hypocupraemic subjects in our laboratory, analytical errors in the given case seem to be most unlikely.

The existence of a mutant caeruloplasmin is a possibility, but at the moment we can only speculate on this.

Hyperuricaemia as a cause of acute renal failure complicating cardiopulmonary bypass surgery

Sir,

We write in response to the interesting article by Rigden *et al.*[1] on acute renal failure complicating cardiopulmonary bypass surgery. Acute renal failure is an important and potentially very serious complication in children undergoing cardiopulmonary bypass surgery. Although the authors reported a relatively low acute renal failure rate of 5·3% in their 456 children, the mortality rate of those children with acute renal failure was still high at 50%. It is important therefore to identify the adverse predisposing factors so that preventive measures may be taken.

The three factors they identified are young age, complex cardiac lesions, and long overall bypass time. However, they failed to mention hyperuricaemia as a possible contributory factor that may cause acute renal failure in their patients. Hencz *et al.*[2] recently reported that extreme hyperuricaemia occurred in infants and children undergoing open heart surgery. We, too, in a prospective study of 97 children suffering from congenital heart disease (age ranging from 2 weeks to 14 years) found that 42% of our patients had raised serum uric acid concentrations.[3] The adverse factors which predisposed to hyperuricaemia were young age, complex cyanotic congenital heart disease with extreme polycythaemia, hypoxaemia, and low oxygen availability.

Adachi *et al.*[4] have shown that patients treated with allopurinol before open heart surgery were less likely to need DC counter shock to restart the heart beat after extracorporeal circulation. In addition, allopurinol was effective in preventing the damage to cellular structures and in minimising changes in metabolism, including a rise in serum uric acid concentrations in patients undergoing open heart surgery. Hence it is important to identify patients with hyperuricaemia before cardiopulmonary bypass surgery so that measures may be taken to prevent uric acid nephropathy causing acute renal failure.

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