The incidence of renal calcification in preterm infants

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Abstract
A total of 79 infants born at less than 32 weeks' gestation were studied with serial renal ultrasound scans to assess the incidence of nephrocalcinosis. Twenty one infants developed renal calcification giving an overall incidence of 26-6% in the study group. Affected infants were significantly smaller (mean (SD) birth weight 940 (323) g) and significantly less mature (mean (SD) gestation 26-9 (1-9) weeks). In 17 patients the calcification was represented by hyperechogenic renal pyramids alone, and in four patients renal calculi were demonstrated. Factors associated with renal calcification included hypophosphataemia, hypercalcemia, hypercreatininaemia, and prolonged oxygen requirement during the first month of life. Multivariate analysis showed that the strongest clinical indicator of calcification was duration of oxygen treatment. Infants who still required oxygen treatment at 28 days had a 62% chance of developing renal calcification.

The tendency for calcium salts to deposit in the human renal tract has plagued mankind and provided employment for lithotomists for over 2000 years. Improved survival among preterm infants has resulted in a greater recognition of the complications of their medical management, which includes a risk of renal calcium deposition. The first reports of renal calcification appeared in 1982, and subsequent reports continued to link it with hypercalciuria and frusemide administration. Improvements in diagnostic ultrasound resulted in the increased recognition of this problem, and in 1988 Jacinto et al reported an incidence of 64% in infants below 1500 g birth weight.

This report was the first to describe the occurrence of renal calcification in the absence of frusemide treatment. Despite the suggestion that two out of every three infants below 1500 g birth weight are likely to be affected, reports of renal calcification continue to be sporadic. Only three cases have been described in Britain, all of whom have been treated with frusemide.

Factors that may contribute towards renal calcification include renal insufficiency, parenteral feeding, prolonged immobility, and bone demineralisation, all of which are commonly encountered in the sick preterm infant.

In view of the conflicting reports of the incidence of calcification in the face of known risk factors this study was designed to determine the incidence of and possible contributory factors towards renal calcification in preterm infants.

Patients and methods
All infants born before 32 completed weeks’ gestation and admitted to our neonatal intensive care unit within 24 hours of birth were eligible for the study. Infants born elsewhere and transferred after 24 hours of age were excluded, as were those who were discharged or died before 7 days of age. Recruitment occurred only after the first week of life. The study protocol was approved by the local ethics committee.

Clinical data was recorded for the duration of each infant's admission. This included diagnosis, gestation, birth weight, duration of ventilation and oxygen treatment, aminoglycoside, steroid, and diuretic treatment, and prescribed and actual intakes of enteral and parenteral feeds.

Weekly intakes of calcium and phosphate were calculated from prescribed supplements if parenterally fed and using published concentrations of calcium and phosphate if milk fed. Human expressed breast milk was assumed to contain 8.75 mmol/l of calcium and 4.85 mmol/l of phosphate.

Blood specimens were collected at least daily during periods of intensive care, and no less than weekly as the patients improved, to assess calcium, phosphate, and creatinine concentrations. Beyond 28 days of age serum alkaline phosphatase activity was measured once a week. Apart from creatinine, all biochemical analyses were performed using a Technicon autoanalyser in a clinical laboratory with staff experienced in handling neonatal specimens. Serum and urine creatinine estimation was by the Jaffe reaction.

After 7 days of age random urine specimens were collected at weekly intervals to measure calcium, phosphate, and creatinine concentrations. Calcium to creatinine ratios were calculated and tubular reabsorption of phosphate was determined using serum biochemical results from specimens obtained the same morning. Urine specimens were generally collected into a urine collecting bag but if this proved impractical then specimens were extracted from soaked napkins as described by Roberts and Lucas. Over 80% of specimens were collected into urine bags, or extracted immediately from the napkin, with the remaining specimens divided equally between the two groups.

Renal ultrasound scans were performed employing initially an ATL scanner with 5 MHz probe, substituted with an Ultramark IV scanner and 10 MHz probe shortly after commencing the study. Scans were repeated on a weekly basis until discharge and hard copy prints were obtained and assessed by one of us (AS) for presence of calcification. Strict criteria.
Table 1  Infants with renal calcifications

<table>
<thead>
<tr>
<th>Case No</th>
<th>Sex</th>
<th>Gestation (weeks)</th>
<th>Weight (g)</th>
<th>Frusemide given</th>
<th>Age at diagnosis (days)</th>
<th>Size of calcification</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>26</td>
<td>986</td>
<td>Yes</td>
<td>41</td>
<td>R+L</td>
<td>Alive</td>
</tr>
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<td>2</td>
<td>M</td>
<td>26</td>
<td>612</td>
<td>No</td>
<td>37</td>
<td>L</td>
<td>Died</td>
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<td>3</td>
<td>M</td>
<td>25</td>
<td>718</td>
<td>Yes</td>
<td>66</td>
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<tr>
<td>4</td>
<td>M</td>
<td>28</td>
<td>820</td>
<td>Yes</td>
<td>82</td>
<td>R+L</td>
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<tr>
<td>5</td>
<td>M</td>
<td>26</td>
<td>1132</td>
<td>No</td>
<td>53</td>
<td>R+L</td>
<td>Alive</td>
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<tr>
<td>6</td>
<td>F</td>
<td>26</td>
<td>726</td>
<td>Yes</td>
<td>55</td>
<td>R+L</td>
<td>Alive</td>
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<tr>
<td>7</td>
<td>F</td>
<td>27</td>
<td>1192</td>
<td>Yes</td>
<td>36</td>
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<tr>
<td>8</td>
<td>M</td>
<td>24</td>
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<td>No</td>
<td>37</td>
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<td>F</td>
<td>29</td>
<td>620</td>
<td>Yes</td>
<td>34</td>
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<td>Alive</td>
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<td>11</td>
<td>F</td>
<td>30</td>
<td>1856</td>
<td>Yes</td>
<td>55</td>
<td>R+L</td>
<td>Alive</td>
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<td>F</td>
<td>24</td>
<td>760</td>
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<td>32</td>
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<td>13</td>
<td>F</td>
<td>28</td>
<td>1300</td>
<td>Yes</td>
<td>46</td>
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<td>Alive</td>
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<td>14</td>
<td>M</td>
<td>28</td>
<td>1178</td>
<td>No</td>
<td>43</td>
<td>R</td>
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<tr>
<td>15</td>
<td>F</td>
<td>29</td>
<td>1400</td>
<td>Yes</td>
<td>35</td>
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<td>Alive</td>
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<tr>
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<td>27</td>
<td>758</td>
<td>Yes</td>
<td>41</td>
<td>R+L</td>
<td>Died</td>
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<td>17</td>
<td>F</td>
<td>27</td>
<td>850</td>
<td>No</td>
<td>47</td>
<td>R+L</td>
<td>Alive</td>
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<td>F</td>
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<td>812</td>
<td>Yes</td>
<td>47</td>
<td>R+L</td>
<td>Alive</td>
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<td>19</td>
<td>M</td>
<td>26</td>
<td>1220</td>
<td>Yes</td>
<td>37</td>
<td>R+L</td>
<td>Died†</td>
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<tr>
<td>20</td>
<td>M</td>
<td>31</td>
<td>580</td>
<td>Yes</td>
<td>27</td>
<td>R+L</td>
<td>Alive</td>
</tr>
<tr>
<td>21</td>
<td>F</td>
<td>27</td>
<td>726</td>
<td>No</td>
<td>53</td>
<td>R+L</td>
<td>Died</td>
</tr>
</tbody>
</table>

*Patient had solitary kidney.
†Patient died three weeks after discharge.
R, right; L, left.

Table 2  Mean (SD) duration of respiratory illness

<table>
<thead>
<tr>
<th>Variable</th>
<th>Calcification (n=21)</th>
<th>Normal (n=58)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilation (days)</td>
<td>41 (25)</td>
<td>8 (12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Oxygen (days)</td>
<td>79 (31)</td>
<td>18 (20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Admission (days)</td>
<td>85 (30)</td>
<td>53 (17)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

were employed in making a diagnosis of renal calcification.8 There had to be areas of hyper-
echogenicity visible in either the renal pyramids or renal pelvis on at least two consecutive scans, and
even highly suspicious echoes were ignored unless accompanying acoustic shadowing was seen.

Statistical analysis was performed using Student's t test for normally distributed data
and the Mann-Whitney U test for skewed data. Multivariate analysis was performed by
computer employing the SPSSx statistical program.9 Results are given throughout as
mean (SD) unless otherwise stated.

Results

Over a 10 month period in 1989, 83 infants born at less than 32 weeks' gestation were admitted
and survived beyond the first seven days of life. Of these patients four died or were discharged
before the first renal ultrasound scan and are thus excluded from further analysis. Twenty one
of the 79 remaining infants developed renal calcification giving an overall incidence of
26.6%. Renal calcification was bilateral in 18 cases and unilateral in three, one of whom had
a solitary kidney. Calcification was detected at a mean age of 47 (14) days and affected boys
and girls equally. Among the unaffected group four patients died while still at risk of developing
renal calcification. There were four deaths in the affected group, and one late death after
discharge from hospital.

Infants in whom calcification developed showed significant differences in birth weight
(mean 940 (323) g compared with 1212 (362) g, p<0.002) and gestation (mean 26·9 (1·9) weeks
compared with 28·8 (2·1) weeks, p<0.001). Details of affected patients are given in table 1.

Altogether 15 (71%) of the infants who developed calcification were prescribed regular
frusemide treatment, compared with only 10 (17%) of the unaffected infants (p=0.001). The
mean total dosage given was considerably higher in the group with calcification (138·5
(152) mg) than in the unaffected infants (28·1 (10·8) mg), although two patients prescribed
frusemide had developed calcification before starting treatment. The mean total dose of frus-
semide prescribed before calcification was first detected was only 22·8 (23·2) mg.

All of the affected infants were ventilated for hyaline membrane disease, compared with 79% of
the normal infants. Duration of ventilation and subsequent oxygen treatment were signifi-
cantly longer in the affected group, all of whom went on to develop bronchopulmonary dysplasia
(table 2).

Serum urea and creatinine concentrations were both significantly greater in the affected
patients indicating a greater degree of renal insufficiency. Despite the very high values in
some cases no patient required dialysis and by 4 weeks of age there was no difference between
the two groups (fig 1).

There was no significant difference in either calcium:creatinine ratio (4·4 (4·1) compared
with 4·0 (2·9), p=0·47) or phosphate:creatinine ratio (1·5 (1·8) compared with 1·3 (1·7), p=
0·33) as measured on a molar:molar basis on specimens collected at 7 days of age. From 2
weeks of age, however, infants who subse-
sequently developed renal calcification had signifi-
cantly higher urinary calcium excretion. The
difference was significant until week 6 after
which small numbers of normal patients affected the statistical analysis (fig 2).

To ensure that the higher calcium:creatinine ratios in the affected group did not simply
reflect diminished renal function with poor
urinary concentration, mean values for urinary
calcium and creatinine concentrations were also
calculated for the first month of life. These
showed both significantly higher urine calcium

http://adc.bmj.com/ Arch Dis Child: first published as 10.1136/adc.66.4_Spec_No.412 on 1 April 1991. Downloaded from http://adc.bmj.com/ on August 23, 2022 by guest. Protected by copyright.
concentrations (3·12 (1·9) mmol/l compared with 2·27 (1·8) mmol/l, p<0·01) and significantly lower urine creatinine concentrations (810 (381) μmol/l compared with 1016 (502) μmol/l, p<0·01), both of which would contributed to the higher calcium:creatinine ratios.

Intakes of calcium, phosphate, and fluids were recorded for all patients during the first four weeks of life. The prescribed calcium intake was significantly less in the group with nephrocalcinosis for each of the first four weeks, though a difference in phosphate intake became apparent only after the first week. However, all of the parenterally prescribed calcium would enter the circulation, though only around 33% of calcium administered orally as preterm formula would be absorbed. Therefore estimation of the actual calcium intake for the two groups showed no difference during the first month of life. Fluid intake was significantly lower in the group with nephrocalcinosis during the second and third weeks of life only (table 3).

The affected patients were more reliant on parenteral feeding as a source of fluid intake, with a delay in institution of milk feeds. The mean age at introduction of milk feeds was 11 (9) days in the unaffected patients but 30 (12) days in those who developed calcification (p<0·001).

The maximum recorded serum calcium and minimum recorded serum phosphate both showed significant differences between the two groups, although the minimum recorded calcium was not different (fig 3). Alkaline phosphatase activity, an indicator of osteopenia of prematurity, was consistently higher in the group with nephrocalcinosis. Mean maximum alkaline phosphatase activity in the nephrocalcinosis group was 1670 (770) IU/l compared with 890 (430) IU/l for the unaffected group (p<0·001).

Figures 4 and 5 show typical ultrasound appearances of hyperechogenic renal pyramids and a renal calculus. Both were detected using the Ultramark 4 scanner and persisted for several months, and were still present on discharge from the neonatal unit.

Table 3 Mean (SD) mineral and fluid intakes kg/day

<table>
<thead>
<tr>
<th>Intake</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescribed calcium (mmol)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephrocalcinosis</td>
<td>0·90 (0·27)</td>
<td>0·94 (0·28)</td>
<td>0·94 (0·46)</td>
<td>1·18 (0·56)</td>
</tr>
<tr>
<td>Normal</td>
<td>1·08 (0·35)</td>
<td>1·57 (0·65)</td>
<td>1·89 (0·82)</td>
<td>2·06 (0·86)</td>
</tr>
<tr>
<td>Estimated calcium (mmol)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephrocalcinosis</td>
<td>0·89 (0·26)</td>
<td>0·91 (0·24)</td>
<td>0·83 (0·09)</td>
<td>0·86 (0·20)</td>
</tr>
<tr>
<td>Normal</td>
<td>0·87 (0·20)</td>
<td>0·87 (0·24)</td>
<td>0·88 (0·18)</td>
<td>0·89 (0·18)</td>
</tr>
<tr>
<td>Phosphate (mmol)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephrocalcinosis</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Normal</td>
<td>0·55 (0·21)</td>
<td>0·67 (0·25)</td>
<td>0·74 (0·33)</td>
<td>0·91 (0·34)</td>
</tr>
<tr>
<td>Fluid (ml)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephrocalcinosis</td>
<td>134 (35)</td>
<td>141 (34)</td>
<td>145 (22)</td>
<td>147 (19)</td>
</tr>
<tr>
<td>Normal</td>
<td>137 (25)</td>
<td>137 (21)</td>
<td>154 (15)</td>
<td>153 (23)</td>
</tr>
</tbody>
</table>

NS* Statistical analysis performed using Mann-Whitney U test, except those marked* where Student’s t test used; NS=not significant.

*Estimated calcium intake equals all parenteral calcium plus 33% prescribed calcium in oral feeds.
The incidence of renal calcification in preterm infants

Figure 3 Mean maximum recorded serum calcium (A), minimum recorded serum calcium (B), and minimum recorded serum phosphate (C) concentrations during the first four weeks of life for infants with normal and calcified kidneys, showing mean (SD); NS = not significant.

Figure 4 Ultrasound scan of a neonatal kidney demonstrating hyperechogenic renal pyramids (white arrows) with accompanying acoustic shadowing (black arrows). This patient was not treated with frusemide.

Discriminant analysis was performed using SPSSx statistical package. The presence of nephrocalcinosis was the dependent variable and serum calcium, phosphate, and creatinine concentrations, gestation, frusemide and oxygen treatment; age at introduction of milk feeds, and duration of admission acted as independent variables. The most significant predictor of calcification was duration of oxygen treatment with a residual variance of just 0.38. Addition of the three next variables (milk feeds, admission, and serum phosphate) decreased this only slightly to 0.31.

Computation of partial correlation coefficients showed that the association between calcification and oxygen treatment remained highly significant (coefficient 0.6, p<0.001) even after controlling for gestation and frusemide treatment.

Discussion

The original reports of renal calcification in preterm infants were often coincidental findings on routine chest or abdominal radiographs and as such probably reflected a more severe form. Prospective studies and improvements in diagnostic ultrasound have allowed earlier detection in larger numbers. Different diagnostic criteria are probably responsible for the even higher incidence reported by Jacinto et al. and would also account for the appreciable difference in reported mortality which varies between 0 to 70%.

All studies seem to confirm that it is the smaller, more immature infant who is susceptible to calcification; the mean gestation of our patients corresponds well to those reported by both Ezzedeen et al. and Gilsanz et al. Boys and girls appear to be equally at risk, the higher number of girls in our series simply reflecting the increased proportion of girls in the study group (13 out of 21 compared with 32 out of 58, p=0.25).

The mean age at diagnosis was 47 (14) days with a range from 32 to 82 days. Most cases (n=15) were detected in the fifth, sixth, or seventh week of life. Where our findings differ significantly is in the apparent effect of frusemide. Although affected patients are more likely to have received frusemide, there is no difference in the mean total dose given before detection of calcification and the mean total dose given to unaffected patients. This appears to suggest that frusemide is prescribed for infants who are already at risk of renal calcification because of other factors, and the suggestion that frusemide...
induced hypercalciuria is the predominant factor in aetiology is an oversimplification of the complex interaction of risk factors in these infants.

Assessment of urinary calcium excretion suggests that all preterm infants begin life with relative hypercalciuria. Although this tends to improve in the unaffected group, the tendency in the group with calcification is for a progressive increase in renal calcium excretion. This hypercalciuria is regularly detected before the introduction of frusemide, after which individual patients may show either increases or decreases in calcium. The measurement of calcium:creatinine ratios on random specimens of urine has previously been validated, but there is no doubt that 24 hour urine collections give a more accurate indication of calcium excretion. The extraction of specimens from wet napkins may also lead to errors in estimation of urinary calcium, although prompt collection of urine once voided will minimise this problem. Nevertheless this potential source of error may account for the relatively high values obtained in our patients compared with the figures previously reported by Karlen et al.

A further problem related to the use of calcium:creatinine ratios is that the figures obtained by Karlen et al represent healthy infants with normal renal function, and hence a normal ability to concentrate urinary creatinine. Due to renal impairment the sick preterm infants in our study showed diminished urinary creatinine concentration, more noticeably in the group with nephrocalcinosis. Although to interpret a high calcium:creatinine ratio in such circumstances as indicative of hypercalciuria may be wrong, it would appear that both higher calcium excretion and lower creatinine excretion contribute to the increased ratios.

We did not assess urinary stone inhibitors in this study. There is, however, some evidence suggesting that urinary citrate tends to fall with rises in urinary calcium, and urinary magnesium is also lower in infants with nephrocalcinosis who are receiving frusemide. The role of urinary uric acid excretion in the aetiology of renal calcium deposition in preterm infants remains unclear.

In order for urinary crystallisation and stone formation to occur the urine must be supersaturated with calcium. Given a constant rate of calcium excretion urinary calcium saturation will be greater at times of low urinary production. We have not measured urine output in our patients, although it would seem likely that the raised serum creatinine concentrations in affected infants may have been accompanied by varying degrees of oliguria. Ezzedeen and colleagues identified oliguria (<1.5 ml/kg/hour) as a risk factor for renal calcification found in 59% of their cases, although no data are provided for suitably matched controls. If facilities are available for accurate monitoring of urine output, particularly during the initial period of intensive care, then a documented period of oliguria may well be a further indicator of infants at risk of nephrocalcinosis.

Similarly acidosis has been suggested as a further risk factor for nephrocalcinosis, in view of the resulting increase in calcium excretion. However both metabolic and respiratory acidosis occur so commonly in sick preterm infants, whom we have already identified as the group at risk of renal calcification, that the presence of a low pH is unlikely to increase significantly the ability to identify potentially affected infants.

Hypercalciuria is a recognised consequence of hyperphosphataemia, which we have demonstrated in our patients throughout the first month of life. There has been considerable interest in the role of phosphate intake in the aetiology of osteopenia of prematurity, and it would appear that it is similarly implicated in renal calcium deposition. Exact phosphate requirements in sick preterm infants are difficult to establish, but recent reports suggest 1.4 mmol/kg/day may be the optimal figure.

The currently used parenteral feeding regime on our unit provides only half this amount, and may be partly responsible for the high incidence of nephrocalcinosis. Ensuring adequate phosphate intake would not only reduce hypercalciuria, it may also eradicate osteopenia of prematurity. The solubility of phosphate in parenteral feeding solutions causes problems in administration, however, and caution is needed when prescribing phosphate supplements in the presence of appreciable hypercalciuria. Too much phosphate may result in the anticipated calcium deposition occurring renal rather than skeletal.

The high alkaline phosphatase activity that we found in our patients is not surprising given the intricate association between the skeleton and renal tract in calcium and phosphate homoeostasis. The role of vitamin D in this association is difficult to establish. Vitamin D supplementation (2400 units/day) were given orally to infants once enteral feeds were established, and hence they were introduced at a significantly earlier age in unaffected patients (22 (15) days compared with 52 (23) days, p<0.001). Infants on parenteral feeds were prescribed a mean of 160 units per day of vitamin D intravenously. If vitamin D contributed towards the
hypercalciuria one would expect to find affected infants receiving more rather than less vitamin D. During the first weeks of life in sick preterm infants the vitamin D requirement is not clear, however, and the low doses administered in our patients still exceed (on a unit/kg basis) the apparent requirement of 30 units/kg recommended by Koo. 18

Relative immobility is common to all infants in the neonatal period, but by 8 weeks of age the bone mineral content of term infants begins to rise. 19 For a sick preterm infant ventilated and in an incubator it may be several weeks before his movements approximate to those of a term infant, and this relative immobility may well contribute towards the hypercalciumia. Equally the prolonged periods of parenteral feeding may be responsible. Intravenously administered calcium and parenteral feeding have been associated with renal stone formation in older patients, 20 and there are theoretical reasons for concern over oxalate precursors in parenteral feeds. 21 Though enteral feeds in sick infants are not without risk, the greater intake of phosphate that they allow is just one reason why their early introduction should be considered.

We have shown that the duration of oxygen treatment, and hence the presence of chronic lung disease, acts as a very useful indicator of the risk of renal calcification. Many different facets of neonatal management may be responsible for this increased risk, including the use of frusemide. Rare disorders such as primary hyperparathyroidism and a variant of Bartter's syndrome should be considered, 22 particularly in the absence of chronic lung disease, but most sick, preterm infants have sufficient calcific stimuli that the addition of frusemide is not necessary to induce renal calcification.

Long term follow up of affected patients is needed to assess the significance of this calcification. Complications of renal calculi, such as infection, obstruction, and haematuria are well recognised. There is understandable concern about long term renal function in the presence of nephrocalcinosis, but in the small number reported by Ezvedden et al other complicating factors make interpretation of his findings difficult. 9 Four of our affected patients had acute tubular necrosis with oliguric renal failure, the effects of which must also be considered in subsequent follow up.

While awaiting data on the sequelae of nephrocalcinosis in preterm infants, efforts should be directed towards reducing urinary calcium saturation. In addition further work is required to establish the role of urinary inhibitors of stone formation. Controlled trials are needed to compare the effects of different diuretic treatments and different phosphate intakes on the incidence of nephrocalcinosis.

We thank the nursing staff of the neonatal intensive care unit at Liverpool Maternity Hospital; Dr T. McKendrick for helpful advice and criticism; and the Alder Hey Children's Kidney Fund for financial support.