Prediction of acute renal failure after birth asphyxia

D S Roberts, G B Haycock, R N Dalton, C Turner, P Tomlinson, L Stimmer, J W Scopes

Abstract

Twenty one babies of 34-41 weeks' gestational age with birth asphyxia (5 minute Apgar score <5 or umbilical artery pH ≤7.2) were studied during the first two days of life to find out whether the urinary excretion of tubular markers of renal function is of value in the early diagnosis of acute renal failure. Urinary retinol binding protein, myoglobin, and N-acetyl-β-D-glucosaminidase (NAG), expressed as a ratio with urinary creatinine, were measured and excretion profiles repeated at 3-6 days in 15 infants and at 7-14 days in 11 infants. Plasma creatinine concentration, creatinine clearance, plasma myoglobin concentration, and fractional sodium excretion were measured where possible in asphyxiated infants. Control data were obtained from 50 healthy infants: 28 gave urine samples alone, 17 urine and blood, and five blood alone. Normal urinary values were derived from 17, 25, and three infants, respectively, for the three time periods. The number of control samples was limited for ethical reasons.

Four asphyxiated infants had acute renal failure (group 1), four had tubular dysfunction without glomerular disturbance (group 2) and 13 had normal renal function (group 3). Group 1 were clearly identified by greatly increased urinary retinol binding protein (>27 000 μg/mmol creatinine) and myoglobin (>1500 μg/mmol creatinine) excretion measured in the first two days of life. In control infants the range of excretion of retinol binding protein within the same time period was 3 to 967 μg/mmol creatinine and urinary myoglobin was undetectable. Excretion of NAG failed to discriminate between groups 1 and 2. Acute renal failure occurred only in infants who had heavy myoglobinemia. Tubular dysfunction in group 2 was transient and not accompanied by plasma electrolyte disturbances.

We conclude that measurement of urinary excretion of retinol binding protein or myoglobin after birth is helpful in the early diagnosis of acute renal failure.

Acute renal failure is a recognised complication of birth asphyxia; it carries a poor immediate prognosis and may result in permanent renal damage in up to 40% of survivors.1-4 The recent reports of increased urinary excretion of β2-microglobulin in infants with evidence of intrauterine fetal distress (meconium stained liquor) by Cole et al, and in sick infants by Tack et al, led these authors to suggest that subclinical, hypoxic, renal damage may be a relatively common, underdiagnosed finding.7 8

The early recognition of acute renal failure is particularly important in asphyxiated infants with hypoxic encephalopathy, in whom a stable biochemical milieu is vital, because it facilitates the administration of appropriate fluid and electrolyte replacement. The diagnosis is frequently difficult to make, however, because many of the clinical and biochemical findings that are helpful in establishing the diagnosis of acute renal failure in adults and children are unreliable in neonates. The presence or absence of oliguria may be misleading as 7% of healthy babies fail to pass urine until the second day of life,9 and non-oliguric acute renal failure has been reported in neonates. The plasma creatinine concentration on day 1 is a poor guide to an infant's renal function, because it mainly reflects the maternal creatinine concentration.11 12 A further difficulty in the interpretation of the plasma creatinine concentration is that the methods of measurement in common use (modifications of the colorimetric Jaffé reaction) are subject to errors from interfering chromogens such as bilirubin and pyruvate,13 substances that are likely to be present in increased concentrations in the blood of sick infants. The value of indexes such as the urine:plasma concentration ratio of sodium, creatinine, and urea are limited by the overlap that exists between infants with functional (prerenal) failure, and those with intrinsic renal failure.14-16

The fractional excretion of sodium or renal failure index may be of diagnostic value, but both need to be interpreted with caution in the preterm,17 and in infants who have been given a saline challenge or treated with diuretics or aminophylline.

Myoglobinuria is a cause of renal failure in adults,18 and a strong correlation between the duration of postnatal oliguria and the severity of myoglobinemia has been reported in asphyxiated infants.19 The presence of myoglobinuria may therefore be a useful indicator of acute renal failure.20

This study was designed to investigate the value of measurements of the excretion of retinol binding protein, myoglobin, and N-acetyl-β-D-glucosaminidase (NAG) during the first two days of life as predictors of clinically important acute renal failure after birth asphyxia, and to follow the excretion profiles into the second week of life.

Patients and methods

Twenty one infants who had had an episode of birth asphyxia, defined as a 5 minute Apgar
score of 5 or below, or an umbilical artery pH of 7.2 or below at delivery, were studied in the neonatal units of these hospitals. The study was approved by the ethics committees of both hospitals and parental consent was obtained in all cases. Infants were managed according to the standard protocols used in the two units, no modifications being made as a result of participation in the study.

Causes of birth asphyxia included severe shoulder dystocia, intrapartum cord traction, and haemorrhage. Sepsis was implicated in the cause in only one infant, delivered in poor condition at 36 weeks, whose cultures yielded *Listeria monocytogenes* after 48 hours’ incubation.

All infants were of 34 weeks' gestational age or above. This lower limit was chosen because nephrogenesis is complete by this time and comparisons are not usually complicated by developmentally determined differences in renal function.21 Gestational age was assessed from the menstrual history, ultrasonography, or by the clinical criteria of Dubowitz et al.22

Wherever possible, infants were studied on several occasions during the first two weeks of life and results grouped into three postnatal time periods: 1–2 days, 3–6 days, and 7–14 days. All infants were studied within the first two days of life and measurements were repeated between 3–6 days in 15, and in the second week of life in 11 infants. It was not possible to repeat measurements in some infants because of death or discharge.

A total of 50 non-asphyxiated infants served as controls for the study; 28 provided urine samples, 17 both urine and blood samples, and five urine samples alone. Seventeen control urine specimens were available for analysis during the first two days of life, 27 during the 3–6 day period, and three during the period 7–14 days. With the exception of two infants who provided urine samples on different days, non-asphyxiated infants were studied on a single occasion.

Blood samples from all infants were obtained when blood was drawn for clinical purposes, and data are limited for this reason. The numbers of individual analyses are shown in table 1. Plasma was separated immediately and stored at −20°C until analysis. Urine was collected by the method of Tarlow and also stored at −20°C.23 None of the infants studied was treated with aminoglycosides, which may affect tubular function.24 25

Glimmer function was estimated by the plasma creatinine concentration and endogenous creatinine clearance (calculated as urine creatinine concentration × urine flow rate (ml/min)/plasma creatinine concentration). Tubular performance was assessed by the urinary concentrations of retinol binding protein, NAG, and myoglobin, divided by the urinary creatinine concentration. Fractional excretion of sodium (calculated as the urine:plasma sodium ratio/urine:plasma creatinine ratio) was also measured, and results are reported when data were not administrated.

Sodium was estimated in plasma and urine by flame photometry. Creatinine was measured in plasma by high performance liquid chromatography with cation exchange (HPLC),26 and in urine by an automated, reaction rate version of the Jaffé reaction.27 Retinol binding protein and myoglobin were measured in urine by enzyme linked immunosorbent assays (ELISA) using rabbit antiserum (Dako Ltd).28 (Retinol binding protein ELISA: P Tomlinson, personal communication, myoglobin ELISA: D Roberts, unpublished observations). Myoglobin in plasma was also estimated by ELISA. The limit of detection for both assays was 2 μg/l. NAG

### Table 1

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Number of infants in each group providing samples for each analysis at each time period</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Analysis</strong></td>
<td><strong>Asphyxiated infants (n=21)</strong></td>
</tr>
<tr>
<td><strong>Time period (days)</strong></td>
<td><strong>Time period (days)</strong></td>
</tr>
<tr>
<td>1–2</td>
<td>3–6</td>
</tr>
<tr>
<td>Retinol binding protein</td>
<td>21</td>
</tr>
<tr>
<td>Urinary myoglobin</td>
<td>21</td>
</tr>
<tr>
<td>N-acetyl-β-D-glucosaminidase</td>
<td>21</td>
</tr>
<tr>
<td>Urine output</td>
<td>19</td>
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<tr>
<td>Plasma creatinine</td>
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<tr>
<td>Creatinine clearance</td>
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<tr>
<td>Plasma myoglobin</td>
<td>20</td>
</tr>
<tr>
<td>Fractional excretion of sodium</td>
<td>19</td>
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</table>

*Wilcoxon rank sum test with Bonferroni correction.

### Table 2

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Clinical data of infants studied on days 1–2. Values are expressed as geometric mean (range)</th>
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<tbody>
<tr>
<td><strong>Analysis</strong></td>
<td><strong>Asphyxiated infants (n=21)</strong></td>
</tr>
<tr>
<td><strong>Gestational age (weeks)</strong></td>
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<tr>
<td><strong>Birth weight (g)</strong></td>
<td>3400 (2200–4800)</td>
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<tr>
<td><strong>Appar score:</strong></td>
<td></td>
</tr>
<tr>
<td>At 1 minute</td>
<td>2–3 (0–7)</td>
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<tr>
<td>At 5 minutes</td>
<td>4·1 (0–9)</td>
</tr>
</tbody>
</table>

### Table 3

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Results of biochemical tests done during first two days of life. Values expressed as geometric mean (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control infants (n=17)</strong></td>
<td><strong>Asphyxiated infants</strong></td>
</tr>
<tr>
<td><strong>Urineary excretion of:</strong></td>
<td></td>
</tr>
<tr>
<td>Retinol binding protein (μg/mmol creatinine)</td>
<td>75 (3–967)</td>
</tr>
<tr>
<td>N-acetyl-β-D-glucosaminidase (μmol substrate/hour/mmol creatinine)</td>
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</tr>
<tr>
<td>Fractional sodium excretion (%)</td>
<td>Not detectable</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min/kg)</td>
<td>0·2 (0·1–0·5)</td>
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<tr>
<td>Plasma concentrations of:</td>
<td>Not measured</td>
</tr>
<tr>
<td>Creatinine (μmol/l)</td>
<td>75 (59–93)</td>
</tr>
<tr>
<td>Myoglobin (μg/l)</td>
<td>48 (32–56)</td>
</tr>
<tr>
<td>Urine output (ml/kg/hour)</td>
<td>Not measured</td>
</tr>
</tbody>
</table>

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Asphyxiated infants divided into three groups. The relevant biochemical data of the study infants on days 1–2 are shown in Table 3. The upper tolerance limits of normal for retinol binding protein and NAG were defined as the geometric mean plus two logarithmic SDs for the respective set of control data. These were 2968 μg/mmol creatinine and 465 μmol substrate/hour/mmol creatinine, respectively. Myoglobin was undetectable in the urine of healthy newborns on days 1–2.

When the urinary retinol binding protein: 

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Figure 1: Urinary concentration of retinol binding protein measured during the first two days of life in control (open symbols) and asphyxiated infants (closed symbols). Asphyxiated infants were divided into three subgroups according to the degree of retinol binding protein excretion. The scale is logarithmic, and the bar indicates the mean and tolerance limits of normal.

Figure 2: Plasma creatinine concentrations with increasing postnatal age in control subjects (open symbols) and the three subgroups of asphyxiated infants (closed symbols—group 1: circles, group 2: triangles, and group 3: squares). The horizontal bars indicate the mean for each group.

Figure 3: Creatinine clearance according to birth weight, and urine output, measured during the first two days of life in the three subgroups of asphyxiated infants (group 1: circles, group 2: triangles, and group 3: squares). The scale is logarithmic, and the horizontal bars indicate the mean for each group.
creatinine ratio of asphyxiated infants (measured in the first two days of life) was displayed graphically, the values were noted to be divided into three distinct subgroups (fig 1). Group 1 (n=4) had concentrations that were 15-44 times above the upper tolerance limit of normal. Group 2 (n=4) had concentrations that were 2-8 times above the upper tolerance limit of normal, and group 3 (n=13) had concentrations that were within the normal range.

All infants in group 1 had acute renal failure. Glomerular function was normal in groups 2 and 3. Throughout the rest of this paper the asphyxiated infants are considered in these three subgroups.

Plasma creatinine values in control infants and in the asphyxiated infants studied serially are shown in fig 2. Infants in group 1 already had greatly increased plasma creatinine concentrations during the first two days of life, which increased further towards the end of the first week and then declined during the second week. Infants in groups 2 and 3 showed the expected decline in plasma creatinine concentration with increasing postnatal age.

Creatinine clearance during the first two days of life, expressed according to birth weight, was correspondingly reduced in group 1; all these infants were oliguric at the time of initial assessment with urinary flow rates of less than 1 ml/kg/hour (fig 3).

Tubular dysfunction was confirmed in groups 1 and 2 by the fractional excretion of sodium (fig 4).

In control infants the mean urinary excretion of retinol binding protein and myoglobin, and the fractional excretion of sodium were constant during the first two weeks of life; NAG excretion showed a slight rise with increasing postnatal age. Myoglobin was detected in the urine of only one control infant, between 3 and 6 days: the concentration was at the limit of the assay and the infant did not show the highest concentration of retinol binding protein or of NAG in the control group. In infants in group 1 the mean excretion of all markers declined towards their respective normal ranges with increasing time after the episode of asphyxia, the retinol binding protein most slowly. The same was true of group 2 with the exception of NAG, the mean excretion of which remained unchanged. Excretion of all markers in group 3 was comparable with control values throughout the first two weeks of life (fig 5, 6, and 7).

Free myoglobin seems to be handled by the kidney as a low molecular weight protein, in a similar way to retinol binding protein. In the presence of an increased filtered load (a raised plasma concentration) it appears in the urine in detectable quantities in the presence of tubular dysfunction, as indicated by an increased urinary retinol binding protein concentration.

Plasma myoglobin concentration was greatly increased in infants in group 1 (fig 8), but concentrations decreased in all groups with increasing postnatal age.

**Discussion**

The measurement of various tubular markers of renal function has proved useful in the diagnosis and surveillance of a number of renal disorders. Low molecular weight proteins, such as β2-microglobulin and retinol binding protein, are freely filtered at the glomerulus and almost completely reabsorbed by the proximal tubular cells in health, so that when tubular dysfunction is present, increased quantities appear in the urine. The report of raised urinary β2-microglobulin concentrations in infants with meconium stained liquor who were otherwise well led to the suggestion that subclinical tubular damage was present in a proportion of these infants, and that measurement of low
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Figure 6. Urinary excretion of N-acetyl-β-D-glucosaminidase (NAG) with increasing postnatal age in control subjects (open symbols) and asphyxiated infants (closed symbols—group 1: circles, group 2: triangles, and group 3: squares). The scale is logarithmic and the horizontal bars indicate the mean for each group.

Figure 7. Urinary excretion of myoglobin with increasing postnatal age in control subjects (open symbols) and asphyxiated infants (closed symbols—group 1: circles, group 2: triangles, and group 3: squares). The scale is logarithmic and the horizontal bars indicate the mean for each group.

molecular proteinuria might be a useful adjunct in the assessment of their renal function.

Comparison data from studies in adults have shown that urinary retinol binding protein concentration correlates well with that of β₂-microglobulin, and that it is of equal sensitivity in the detection of tubular dysfunction. We chose to measure retinol binding protein because it is stable at lower urinary pH values at which degradation of β₂-microglobulin occurs, and the need for manipulation of urinary pH on voided specimens is eliminated.

Excretion of retinol binding protein in neonates is higher than in adults. Our control infants achieved a mean retinol binding protein excretion in the first two days of life of 75 µg/mmol creatinine, with similar values in the second week of life, in contrast to a reported mean concentration of 7-7 µg/mmol creatinine in adult men. This tenfold difference is not a spurious increase in the retinol binding protein concentration as a result of the lower urinary creatinine concentrations found in infants; the absolute urinary retinol binding protein concentrations in the infants were greater, with a maximal recorded value of 4000 µg/l, compared with the maximal normal adult value reported in the above study of 540 µg/l. This presumably reflects reduced proximal tubular reabsorption in neonates.

The mean retinol binding protein excretion reported here for control infants with gestational ages of more than 34 weeks is similar to the value obtained by Clark et al., but out upper tolerance limit of normal is roughly five times higher and reflects a greater range of retinol binding protein excretion values in the group studied.

We identified three groups of asphyxiated infants according to their urinary retinol binding protein:creatinine ratio. The four infants with acute renal failure had the highest excretion (range 27 759–81 112 µg/mmol creatinine) and there was clear discrimination between these infants and the others. In turn, infants in group 2 (3721–15 243) were clearly differentiated from those in group 3 (6–1418). Infants with acute renal failure also had the heaviest myoglobinuria (range 1526–13 195 µg/mmol creatinine) and, as with retinol binding protein, were sharply distinguished from the others. Those in group 2 had detectable, but lesser, degrees of myoglobinuria (0–4–430). Gross pigmenturia, giving a brown colour to the urine, was seen in all infants in group 1, and in the infant from group 2 who had the highest myoglobin concentration of that group. In three infants from group 3 myoglobin was detected in the urine, but the values were at the limit of detection. Our results are in agreement with those of Kojima et al.

Tubular dysfunction was confirmed by the fractional excretion of sodium, which was grossly abnormal in group 1 (mean 31–9%) mildly increased in group 2 (1–7%), and normal in group 3 (0–3%). That in control infants was below 1% and in sodium balance studies the fractional excretion of sodium in healthy infants of similar gestational age with a sodium intake of ≤2.5 mmol/kg/day has been reported to be normally less than 1%.
NAG is a lysosomal enzyme of a molecular weight that precludes its filtration at the glomerulus, it is also rapidly cleared from the circulation by the liver so that increased urinary excretion is a consequence of intrinsic renal damage. NAG excretion was considerably increased in infants with acute renal failure (range 1135–13 484 μmol substrate/hour/mmol creatinine) and in infants with tubular dysfunction and no glomerular disturbance (692–7736). This presumably reflects a similar initial degree of tubular cell damage in the two groups. NAG is clearly a sensitive measure of tubular damage, but not specific enough to discriminate the infants with acute renal failure.

In the infants who were studied serially, retinol binding protein, NAG, and myoglobin excretion declined in group 1, retinol binding protein more slowly than either NAG or myoglobin, and all remained above the normal range into the second week of life. In one infant, measurements were repeated at the age of six weeks and urinary retinol binding protein and NAG were still greatly increased, suggesting that tubular recovery, if it occurs at all, is slow. The increased excretion of NAG in the second week of life is probably not the result of continued tubular cell exfoliation, but of increased lysosomal activity in surviving cells; tubular reabsorption of low molecular weight proteins occurs by endocytosis, the proteins then fusing with lysosomes within which they are digested. Urinary NAG concentrations were highest in those infants with the greatest excretion of retinol binding protein and myoglobin, suggesting that this persistent use is the result of a stimulated exocytosis similar to that shown in animal experiments. The similar continued rise in urinary NAG, with more or less constant mean values throughout the two week postnatal period in infants in group 2, supports this suggestion. In these infants retinol binding protein and myoglobin excretion steadily declined, and by the second week remained high in only one infant; measurements were repeated in the third week in this infant and all results were then normal. This indicates that tubular dysfunction in these infants is transient. Infants in group 3 had concentrations comparable with those in control infants throughout the study.

Our single criterion for the diagnosis of acute renal failure was a plasma creatinine concentration of over 130 μmol/l for at least two days. The presence of oliguria was not required so we did not overlook infants with non-oliguric acute renal failure. Similar plasma creatinine concentrations have been used as diagnostic criteria in other studies. We measured plasma creatinine using high performance liquid chromatography because the method is specific; with modified Jaffé techniques various chromogens present in plasma interfere with the reaction resulting in overestimations or under-estimations of the creatinine concentration that cannot be predicted for any individual measurement and may produce errors in excess of 100%. Within two days, the plasma creatinine concentrations in infants in group 1 were considerably raised (mean 257 μmol/l). The mean values were similar in groups 2 and 3, comparable to our limited control data, and within the expected range for infants of similar postnatal age reported by other workers. Creatinine clearance expressed according to birth weight, was correspondingly reduced (mean 0.01 ml/min/kg) in group 1. The clearances measured in groups 2 (0.8), and 3 (1.2), are similar to those described by Coulthard in a review of published data on glomerular filtration rates expressed by birth weight in healthy newborns.

All infants in group 1 were oliguric in the first two days of life with urinary flow rates of less than 1 ml/kg/hour. One infant from group 3 had a reduced urine output, the remainder had flow rates in excess of 1 ml/kg/hour.

Severe muscle damage associated with subsequent renal failure is well documented in adults, and the same phenomenon probably occurs in neonates. Birth asphyxia is associated with rhabdomyolysis in the first few days of life, the severity of which is—in turn—related to the duration of postnatal oliguria. Plasma myoglobin concentrations, measured in the first 2 days of life in our asphyxiated infants, ranged from 21 to 7625 μg/l. The infants with acute renal failure had the highest concentration, and the infant who required dialysis had the highest of all. These concentrations are similar to those reported by Kasik et al., and similar to those seen in adults with acute rhabdomyolysis and acute renal failure. At birth, infant muscle contains roughly 10% of the adult myoglobin content; the plasma concentrations achieved by several of the asphyxiated infants therefore indicate considerable muscle breakdown.

If the normal range of plasma creatinine at birth and an expected daily rise above 18 μmol/l
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in the presence of acute renal failure are considered, the plasma creatinine concentrations in our infants represent an extremely rapid rise. Such a rise has been reported in myoglobinuric renal failure in adults, and is the result of the release of large quantities of intracellular creatine from damaged muscle. Our results show that an asphyxial insult may be associated with tubular dysfunction, but that acute renal failure supervenes only in the presence of high plasma concentrations of myoglobin: the exaggerated rise in plasma creatinine in our infants, coupled with the heavy myoglobinemia and myoglobinuria, suggests that these infants had rhabdomyolysis induced renal failure.

Our identification of infants with no glomerular disturbance but with detectable tubular dysfunction confirms previous reports, although this was a less common occurrence in our study (19%) than in others. Plasma myoglobin concentrations in these infants were lower than in those with acute renal failure, evidence that they sustained less severe asphyxial damage. These infants undoubtedly have a degree of tubular dysfunction that is clinically unsuspected but which can be shown with sensitive tests. The higher mean fractional excretion of sodium in this group of infants has implications for electrolyte balance, although we found no significant differences in the plasma sodium and potassium concentrations between these infants and those without tubular dysfunction during the time periods 1–2 and 3–6 days (Wilcoxon rank sum test with correction factor).

In conclusion, 62% of the infants studied, who were over 34 weeks’ gestational age and had an episode of birth asphyxia, showed no apparent impairment of renal function, 19% had overt acute renal failure, and a further 19% had tubular dysfunction indicated by an increased excretion of tubular proteins, but without any associated glomerular disturbance. These figures do not represent the absolute incidence of renal damage in our units because the numbers presented here include infants not born in the hospital and exclude those who received treatment with aminoglycoside antibiotics.

Infants with acute renal failure were clearly identified by their increased excretion of retinol binding protein and myoglobin. Urinary retinol binding protein:creatinine ratios in excess of 27,000 μg/mmol creatinine, and urinary myoglobin:creatinine in excess of 1500 μg/mmol creatinine seem to be of diagnostic value. NAG excretion, although a sensitive indicator of tubular injury, is not specific for acute renal failure.

Plasma creatinine concentration, creatinine clearance, and fractional excretion of sodium defined the group with acute renal failure, but all have some disadvantage that affects their potential diagnostic value. The HPLC method we used, which measures ‘true’ plasma creatinine is of restricted availability; creatinine clearance is subject to the added inaccuracies incumbent upon timed urine collections and incomplete bladder emptying and the measurement of the fractional excretion of sodium requires simultaneous blood and urine samples and cautious interpretation when diuretics or a saline load have been administered.

The measurement of retinol binding protein or myoglobin is simple, inexpensive, and can be carried out on random samples of urine. We suggest that the measurement of retinol binding protein or myoglobin should be incorporated into the management of asphyxiated infants at birth, as they give an early indication of the adequacy of renal function.

We thank the parents and participating infants for their help and understanding. We thank sisters B Clarkson-White and B Nicholson and all staff of the neonatal units of St Thomas’s and Guy’s Hospitals for their help and patience.

This study was supported in part by the Children Nationwide Medical Research Fund. D S Roberts was supported by St Thomas’s Hospital Research Endowment Fund.

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Arch Dis Child 1990 65: 1021-1028
doi: 10.1136/adc.65.10_Spec_No.1021

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