Renal function in sick very low birthweight infants: 2. Urea and creatinine excretion

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Abstract

Plasma urea and creatinine concentrations and urea and creatinine clearances and excretion were measured in a sample of 40 infants of 25.5–33 weeks' gestation, birth weight 720–2000 g, between the ages of 0.5 and 33 days. Creatinine excretion rate was between 60 and 120 $\mu\text{mol/kg/day}$ in the first five postnatal weeks (mean 90.5) and was independent of sex or growth retardation. This can be used in clinical practice to estimate instantaneous urine flow rate V , if the creatinine concentration is measured in a randomly voided urine sample, from the formula $V=90.5/\text{urine creatinine}$, with 95% confidence limits $\pm 39\%$. There is a wide range of plasma creatinine at all gestations and ages decreasing from range 75–130 $\mu\text{mol/l}$ in the first two days to 35–80 $\mu\text{mol/l}$ at 3 weeks of age. Plasma urea is a poor indicator of glomerular filtration rate (GFR) in sick preterm infants. GFR (ml/min/kg) can be estimated from plasma creatinine from the formula $\text{GFR}=69.2/\text{plasma creatinine}$ but this estimate is imprecise with 95% confidence limits $\pm 46\%$. Urea:creatinine clearance ratio was usually less than 1.0 (range 0.18 to 1.5) and was lower when the urine flow rate was low. Urea excretion was up to 17 mmol/kg/day in the first two weeks, higher in the more immature infants. These high levels were paralleled by a high plasma urea concentration, up to 18 mmol/l . A high plasma urea is not necessarily associated with renal failure or dehydration.

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The clinical management of sick preterm infants requires meticulous attention to many aspects of physiology and to the daily prescribing of water, salts, and nutrition. Renal physiology often receives scant attention because plasma creatinine is the only accessible index of renal function, and even this may be unreliable because of interfering substances in routine methods. Although urine is easily obtainable it is rare for neonatal units to measure urinary indices of renal function routinely. In prescribing intravenous water and electrolyte treatment it may be useful to have a day to day, or even more frequent, estimate of renal excretion of water, sodium, potassium, etc. Such an estimate may be obtained without the tedium and inaccuracy

of timed urine collections by relating urine concentration to creatinine, provided creatinine excretion rate is not scattered too widely. The few reports of creatinine excretion so far are not encouraging in this respect^{1–6} but most have relied on timed urines for their measurement. Plasma urea is a poor guide to glomerular function in all subjects but has received little attention in the sick preterm newborn.

The purpose of the present investigation was: (1) to establish a normal range for plasma creatinine in sick infants less than 33 weeks' gestation at various ages using a creatinine method which measures true creatinine without interference; (2) to establish a normal range for creatinine excretion and thereby derive formulas to estimate glomerular filtration rate (GFR) and urine flow rate from plasma and urine creatinine; and (3) to investigate the usefulness of plasma urea as an indicator of renal function by examining the relationship between urea and creatinine clearance and between plasma urea and urea excretion.

Patients and methods

This study was part of a wider study of glomerular and tubular function in very low birthweight infants. Altogether 40 infants were chosen who could be studied in the first postnatal week, and later if possible. Gestation at birth was 25.5–33 weeks, birth weight 720–2000 g. Further clinical, experimental, and laboratory details are given in part 1.⁷

Plasma creatinine and urea concentrations were measured sequentially in 40 infants up to age 3–33 days. Urine flow rate was measured on 124 occasions in 39 infants by a continuous infusion Polyfructosan-S (PF-S, Laevosan-Gesellschaft) clearance method,^{8,9} between the ages of 0.5 and 33 days. Urine flow rate (urine volume or renal water excretion rate, ml/day) was calculated by:

Urine flow rate = PF-S infusion rate / urine PF-S concentration

Creatinine excretion rate ($\mu\text{mol/day}$) was calculated by:

Creatinine excretion = urine flow rate $\times$ urine creatinine concentration

Urea and sodium excretion rates (mmol/day) were similarly calculated. Plasma and urine creatinine were measured by a modification⁸ of a resin adsorption method^{10,11} which avoids the positive interference of non-creatinine chromogen and the negative interference of

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bilirubin. The resin adsorbs creatinine but not substances that normally interfere with the Jaffé creatinine assay. Approximately 6 mg Dowex 50W-X8(H) 200–400 mesh ion exchange resin is added to the samples. After 15 minutes the resin is washed twice and the creatinine eluted with 600 µl alkaline picrate. The optical density of the supernatant is measured at 515 nm. The reaction is linear and for a plasma creatinine of 100 mmol/l optical density is 0.068. The coefficient of variation is 4.4% at 69 µmol/l and 2.4% at 499 µmol/l. Yield for creatinine added to plasma or urine was 95–105%. Bilirubin, glucose, proteins, and ketones did not interfere.

Plasma urea was measured by an enzymatic colorimetric method on a Technicon RA-1000 multichannel discrete autoanalyser where ammonia is produced from urea by a urease enzyme and combines with 2-oxoglutarate and NADH to yield L-glutamate and NAD. The coefficient of variation is 2.7% at 2.5 mmol/l and 1.1% at 17 mmol/l. Urine

urea concentration was measured on a Technicon SMAC 3 system by a photometric method which depends on the formation of a chromophore by the combination of urea with diacetyl in acidic solution in the presence of ferric ions and thiosemicarbazide. The coefficient of variation is 0.7% at 12 mmol/l and 4.5% at 2 mmol/l. Urine sodium and potassium were measured by photometry (Instrumentation Laboratories 913) and osmolality by cryoscopy (Gonotec Osmomat 030), all with a coefficient of variation of <1%.

Urine flow and sodium, creatinine, and urea excretion rates were expressed as ml, mmol, or µmol/kg/day. Weight rather than surface area was used because it is physiologically more appropriate in immature infants¹² and it is more accessible in routine practice. Birth weight was used unless the baby had regained his birth weight and was growing in which case latest weight was used. Factoring by a weight less than birth weight causes false overestimation of renal functions.^{7 13}

Figure 1 Plasma creatinine concentration (resin adsorption method) as a function of postnatal age for two gestational groups (n=367). Sequential measurements are joined for six individuals.

Figure 2 Creatinine excretion rate as a function of postnatal age (n=123). Repeated measurements in individuals are included. The dotted horizontal lines are the mean (90.5 µmol/kg/day) ± 2 SDs for all measurements.

Results

PLASMA CREATININE

Plasma creatinine as a function of age is shown in fig 1. This scattergram and all other figures include a mixture of cross sectional and longitudinal data. There is a wide variation at all ages with an overall decline during the first two to three weeks. Points are joined for six individuals studied for longer than two weeks. In some infants the creatinine has reached a trough by the third week, but in others it is still declining. There is an initial steep decline in the first week in most infants, although this is sometimes preceded by an initial increase. This is presumably because the result in the first day or two reflects maternal creatinine.^{14 15} There is a wide overlap between the ranges in the two groups shown. Means and their 95% confidence limits were calculated for the two groups at the ages: <2 days, 3rd day, 4th day, 4–7 days, 7–14 days. Only at the 4th day and 4–7 days were there significant differences between the means shown in the table.

CREATININE EXCRETION RATE

Creatinine excretion rate as a function of postnatal age is shown in fig 2. At all postnatal and all postconceptional ages there is a broad

Mean plasma creatinine concentration (µmol/l) at various postnatal ages in infants of two gestational age groups. The 95% confidence intervals for the means are shown in parentheses

Age	25.5–29 weeks	>29–33 weeks
<2 days	101 (94 to 108) [n=17]	103 (95 to 111) [n=12]
3rd day	98 (90 to 106) [n=17]	94 (88 to 100) [n=14]
4th day	97 (90 to 104) [n=19]	84 (76 to 92) [n=13]
4–7 days	88 (84 to 92) [n=20]	82 (77 to 87) [n=13]
7–14 days	82 (72 to 92) [n=18]	75 (66 to 84) [n=13]

range of excretion rates, the range being wider in the first week when more observations were made. Multiple estimations in individual babies were averaged for the first week postnatal and for after the first week. Mean creatinine excretion in the first week (30 babies) was $91.9 \mu\text{mol/kg/day}$, and mean excretion after 1 week was $89.4 \mu\text{mol/kg/day}$. There was no significant difference between these. The difference between first week creatinine excretion and later creatinine excretion in individual babies had a range of -32 to $+32 \mu\text{mol/kg/day}$, mean 2.5 (95% confidence interval -6 to $+11$). Creatinine excretion increases significantly with postconceptional age within the range 26–33 weeks, from $81 \mu\text{mol/kg/day}$ at 26 weeks to $102 \mu\text{mol/kg/day}$ at 33 weeks. No

inference can be made outside this range of postconceptional age. Infants whose birth weight was less than the 50th centile for gestational age had the same excretion rates as those with birth weights greater than the 50th centile.

Mean overall creatinine excretion was $90.5 \mu\text{mol/kg/day}$ (62.8 nmol/l min) with a SD of $14 \mu\text{mol/kg/day}$. The distribution is normal. The approximate 95% tolerance interval (mean ± 2 SDs) is 62.5 to $118.5 \mu\text{mol/kg/day}$, shown as horizontal dashed lines in fig 2. The maximum change in any baby, $32 \mu\text{mol/kg/day}$, is less than the 95% tolerance interval, suggesting that each individual kept the creatinine excretion rate within narrower boundaries than the group as a whole.

Figure 3 (A) Upper panel: urine volume (flow rate) calculated from 123 PF-S infusion experiments plotted against estimated urine volume calculated from $90.5/\text{urine creatinine}$ concentration. The points are plotted as the logarithmic transformation for clarity. The diagonal lines are the line of identity and the linear regression line, $y=0.27+0.87x$. (B) Lower panel: the ordinate is the ratio between urine volume measured in PF-S experiments and estimated urine volume calculated from the urine creatinine. The ordinate is near to a normal distribution with the mean (1.0) and mean ± 2 SDs shown as dotted lines.

ESTIMATING URINE VOLUME FROM URINE CREATININE AND GFR FROM PLASMA CREATININE

Figure 3A shows urine flow rate (urine volume or water excretion rate) measured in PF-S infusion experiments plotted on the ordinate against urine flow rate estimated simultaneously from urine creatinine. Estimated urine flow rate (ml/kg/day) is calculated from the formula $90.5/\text{urine creatinine}$ ($\mu\text{mol/l}$), where 90.5 is the overall mean creatinine excretion rate in $\mu\text{mol/kg/day}$. The difference between the two values is because the actual creatinine excretion rate is not equal to the mean value of $90.5 \mu\text{mol/kg/day}$. The data are plotted logarithmically for clarity, not for any statistical reason. A more complicated formula could have been used, based on the regression line, but not with any useful increase in precision. The precision of this formula for estimated urine flow ($90.5/\text{urine creatinine}$) is tested by examining the ratio between measured and estimated urine flow rate, shown in fig 3B plotted on the ordinate. The untransformed ratio is plotted rather than its logarithm (the vertical distance of the points in fig 3A from the line of identity) because the untransformed value has the most nearly normal distribution. The 95% confidence limits (mean ± 2 SDs) for urine flow rates are the estimated value $\pm 39\%$, shown as the horizontal dashed lines in fig 3B.

GFR (ml/kg/min) can similarly be estimated from mean creatinine excretion and plasma creatinine ($\mu\text{mol/l}$) from the formula $90.5 \times 1.101 / 1.44 / \text{plasma creatinine}$ ($69.2 / \text{plasma creatinine}$), where 1.101 is the mean ratio, in the present study, between GFR and creatinine clearance.¹⁶ The confidence limits are somewhat wider, $\pm 46\%$, because of the introduction of this extra variable factor and also greater imprecision in measuring plasma creatinine.

An estimate of urine flow rate is useful in clinical practice in order to estimate renal excretion of urine constituents such as sodium ($E_{\text{Na}} = U_{\text{Na}} \times \text{urine flow rate}$). Urine sodium concentration (U_{Na}) alone is an unreliable indicator of sodium excretion, because it also depends on urine flow rate. Figure 4 shows a more than 5-fold variation in sodium excre-

Figure 4 Urine sodium concentration as a function of sodium excretion rate in 471 urine samples. The latter was either measured in PF-S experiments ($n=124$) or calculated from urine creatinine concentration ($n=347$).

Figure 5 U/P ratios for urea and creatinine compared. Both axes are logarithmic for clarity and so that the distribution is suitable for regression analysis ($n=324$). The diagonal lines are the line of identity and the linear regression line, $U/P \text{ urea} = 0.20 + 0.70 \times U/P \text{ creatinine}$.

Figure 6 Plasma urea concentration as a function of age on 467 occasions.

tion rate, 3 to 20 mmol/kg/day, on occasions when urine sodium concentration is high, around 150 mmol/l, and more than 10-fold, 0.5 to 7 mmol/l, when urine sodium is low, 10 mmol/l. Similarly, urine osmolality is not a useful inverse indicator of urine flow rate compared with urine creatinine concentration. High osmolality urine (>500 mosmol/kg) was observed with high as well as low urine flow rates and in the former case was associated with high excretion of other solute such as sodium.

UREA AND CREATININE CLEARANCES COMPARED

Figure 5 shows urea and creatinine clearances compared. Urine/plasma (U/P) ratios are plotted rather than clearance (UV/P) in order to eliminated the common variable V (urine volume). In the majority of samples U/P urea ratio is lower than that for creatinine, and there is wide scatter. Urea clearance varies from 0.18 to 1.5 times creatinine clearance. The logarithmic transformation is plotted to produce a distribution suitable for linear regression which shows that there is a tendency for urea clearance to be lower at low urine flow rates (regression slope 0.70, 95% confidence interval 0.64 to 0.75, $p<0.0001$). Urea is presumably reabsorbed by the renal tubule in a very variable manner, more in oliguric infants.

UREA EXCRETION AND PLASMA UREA

Plasma urea (fig 6) varied widely, from 0.3 to 18 mmol/l and values tended to be high throughout the whole of the first two weeks. Urea excretion follows a similar pattern with levels 0.6 to 17 mmol/kg/day. Individual sequential graphs show a pattern of a post-natal rise and fall over 1–3 weeks (fig 7). The peak excretion rate (range 2.5 to 17 mmol/kg/day) and peak plasma urea concentration (range 3.6 to 18 mmol/l) for each baby and the age at which they occurred were chosen as summary measures.¹⁷ The peak occurred between the first and 10th day at all gestations but was higher in the most immature. There was a significant negative relationship between peak urea excretion rate and gestational age (regression slope -0.59 , 95% confidence interval -0.97 to -0.21 , $p<0.05$) and between peak plasma urea and gestational age (regression slope -0.62 , 95% confidence interval -1.06 to -0.18 , $p<0.01$). Although there was no relationship between the time of the peak and gestational age, the time of the urea excretion and plasma urea peaks in individuals correlated highly significantly (Pearson's $r=0.58$, 95% confidence interval 0.32 to 0.76, $n=39$, $p=0.0002$). Similarly the magnitude of the peaks correlated significantly in individuals ($r=0.66$, 95% confidence interval 0.44 to 0.81, $n=39$, $p<0.00005$).

Nitrogen input (as Vamin, KabiVitrum) was low until the fourth day in most infants. There was no relationship between nitrogen input and urea nitrogen excretion, with input ranging from 0 to 400 mg/kg/day at all urea

Figure 7 Plasma urea concentration and urea excretion as a function of age for seven infants <28 weeks' gestation.

excretion rates, and similarly none between nitrogen input and plasma urea. The presence of high urea excretion with zero or low nitrogen input on many occasions suggests that many of these infants particularly in the first one or two weeks postnatally are catabolic with respect to protein. In the absence of a high nitrogen input it is likely that the high plasma urea concentrations are caused by the high urea production. Urea production rate by cells was not calculated (from nitrogen excretion and change in plasma urea). In some infants urea nitrogen excretion exceeded input in the second and even third weeks.

Discussion

CREATININE EXCRETION

Creatinine excretion in preterm neonates in the present study is similar to previous estimates of mean 71,^{3 4} 60–80,⁶ 85,² 95,¹ and 100 $\mu\text{mol/kg/day}$.⁵ Only two have emphasised the small but significant increase through the last trimester.^{3 6 18} In all these studies the range is wider than in the present study; in one the range was about 18 to 180 $\mu\text{mol/kg/day}$,³ in others 45 to 180,¹ 57 to 143,⁵ and approximately 30 to 230.² The narrower range in the present study may be due in part to the clinical and laboratory methods used.^{5 16} The differences in the means may be due to different creatinine

methods or methods of estimating or measuring urine flow rate or different postconceptional age of the infants. Creatinine methods should not be inaccurate for urine creatinine because there is no non-creatinine chromogen; however the author has found that some routine laboratory methods measure aqueous standards with inaccuracy up to 20% (B H Wilkins, unpublished observations). One of the above studies used polyfructoside as marker of urine flow⁵; the others measured timed urine collections with the inherent difficulties with that technique. The higher mean of 95–100 $\mu\text{mol/kg/day}$ in two studies^{1 5} may be accounted for partly by the higher mean gestational age (31 and 33 weeks compared with 29 weeks here). Three^{1 3 5 18} found no significant relationship between creatinine excretion and postconceptional age but at least two of these^{1 3 18} considered correlation coefficient instead of regression slope. The variables correlated did not have normal distributions. Correlation is for comparing two independent variables; here we are examining how one variable depends on another. They also apparently ignored bias from multiple measurements in individuals.

Creatinine excretion rate is lower when expressed in terms of body weight than older babies^{2 3 19} and children (B H Wilkins, unpublished observations), even more so when expressed in terms of height or surface area. Weight is chosen as reference because creatinine output is related to muscle cell mass,^{1 19 20} which intuitively relates best to weight. Cell mass, or intracellular fluid volume, and basal metabolic rate are lower in preterm infants than term and older infants,^{21 22} and this may account for the lower values in the more immature.

Creatinine *production* rate could be estimated from *excretion* rate and rate of change of plasma creatinine, but requires also knowledge of creatinine distribution volume (total body water). Although non-renal elimination is probably minimal, the wider range of creatinine excretion in isolated urine samples in the first week may be because plasma creatinine concentration is rising or falling. No attempt has been made to estimate production rate. The present concern is to derive useful and simple formulas based on urine creatinine.

ESTIMATING URINE VOLUME AND GFR

Although there is a significant increase in creatinine excretion with postconceptional age, formulas have been derived for estimating GFR (based on plasma creatinine) and urine volume (based on spot urine creatinine) which are common to all sick preterm infants in the first 2–3 weeks in whom these quantities might be useful. The numerator in these formulas contains 90.5, the overall mean creatinine excretion ($\mu\text{mol/kg/day}$). Improved accuracy and precision would be obtained by applying a variable creatinine excretion from 81 at 26 weeks postconceptional age to 102 at 33 weeks but this would make the calculation more complicated for little useful gain. These

formulas will apply so long as the laboratory creatinine method measures aqueous creatinine standards accurately. Neonatal units should check this. The imprecision of the urine flow rate estimate, $\pm 39\%$, is much lower than the overall variation in urine flow which is >10 -fold; urine creatinine concentration ranges from 300 to 4000 $\mu\text{mol/l}$. The only reliable way of measuring urine flow is to weigh nappies meticulously, but even this does not preclude escape of urine.

Coulthard *et al* have derived similar formulas but calculated an asymmetric 95% confidence interval (-35% to $+53\%$) from the scatter around the regression of logarithmically transformed urine volume on log estimated urine volume, but did not show that the data were normally distributed about the regression line.⁵ It is unlikely that they were, as in the present study. Plotting the logarithmic transformed data does render the distribution of urine volume nearer to normal and standardises variances, but this is only useful when calculating correlation coefficients which is not an appropriate statistical approach to comparing two measures of the same variable.²³

The estimate of urine flow and sodium excretion on spot urines does not measure 24 hour excretion, and does not solve the whole problem of prescribing fluids, but gives a guide to the situation at the time. It is a quick and easy addition to daily weight change and plasma sodium to help make sensible decisions about water and sodium requirements.

The GFR estimate is more imprecise and less useful. Plasma creatinine concentration is a more direct indicator of glomerular function and normal ranges are available from the present study and others.²⁴⁻²⁶

Formulas based on height and plasma creatinine estimate GFR factored by surface area.^{2 27} This may be useful in older children but has been shown to be inappropriate in infants.^{7 8 12} The validity of these formulas was based on a significant correlation coefficient between the formula derived estimate of GFR and a 24 hour creatinine clearance. It is not surprising that the two quantities are correlated but inspection of the data shows wide individual differences between the estimated GFR and creatinine clearance.^{2 27} Inspection of their graphs shows that the estimate of GFR/m^2 was 35% to 280%²⁷ and approximately 50% to 300%² of the measured creatinine clearance which hardly inspires confidence in such a formula.

PLASMA CREATININE

Plasma creatinine in the present study is similar to published normal ranges.²⁴⁻²⁶ Rudd *et al* found little difference between infants less than 28 weeks and those 28 to 32 weeks' gestation.²⁴ Their median was 104 $\mu\text{mol/l}$ at 2 days for <32 week gestation infants, 84 at 7 days, 72 at 14 days, and 60 at 21 days. Their range is wider at all ages, for example 95% tolerance limits of ± 50 to $\pm 60 \mu\text{mol/l}$ at 7 days compared with no more than $\pm 30 \mu\text{mol/l}$ in

this study. This may be because of a more precise and accurate assay with less interference from positively and negatively interfering substances. Any 'normal range' is clearly method dependent. The sick patients in the present study did not have higher creatinines than the more healthy individuals of previous studies, even those with severe respiratory disease. This accords with the finding of no reduction in GFR in patients with severe respiratory disease.⁷ Further, the decline with increasing age is not complete until 1 month.

Plasma creatinine is influenced by the following: (1) the increase in glomerular filtration rate with age^{7 13}; GFR increases postnatally despite the lack of body growth whereas creatinine excretion is related to cell mass which is itself static after birth until weight gain begins. The postnatal weight loss is caused largely by loss of extracellular volume, not loss of cell mass. (2) The increase in cell mass as a proportion of body size as babies grow. (3) The fact that in the early neonatal period plasma creatinine reflects maternal plasma creatinine,^{14 15} accounting for a rise or fall in the immediate postnatal period. (4) Variable transfer of creatinine across the renal tubule.^{2 5 8 16 28-30} (5) Differences in and the imprecision of laboratory methods. It is not surprising, therefore, that plasma creatinine changes in ways which cannot be fully understood.

The lack of any results greater than 130 $\mu\text{mol/l}$ suggests that this may be used as an upper limit of normal (using this laboratory method) in the first few postnatal days for the diagnosis of neonatal renal failure, and there is no need to quote a different figure for different gestations, at least in infants born at less than 33 weeks. However, plasma creatinine will increase slowly after the onset of acute renal failure. Creatinine is distributed in total body water, so when there is an abrupt change in GFR it may take several days for plasma creatinine to reach a new steady state level. The half time of these changes is approximately proportional to volume of distribution divided by GFR. For a volume of distribution of 80% of body weight and a GFR of 0.5 $\text{ml}/\text{min}/\text{kg}$ this half time will be about 18 hours.

Most routine laboratory methods for creatinine use one of many kinetic Jaffé methods which reduce but do not eliminate the over estimation caused by non-creatinine chromogen.⁵ A further problem in newborns is negative interference caused by bilirubin.³¹ It should be borne in mind that day to day changes in apparent plasma creatinine might in part be due to changes in plasma bilirubin. This is not the case here where a resin adsorption end-point Jaffé method has been used but individual units should check their method.

PLASMA UREA AND UREA EXCRETION

Urea excretion rates are very much higher than in older children and adults where it is less than 1 $\text{mmol}/\text{kg}/\text{day}$. The presence of high urea excretion in the absence of any

nitrogen input suggests that many of these infants particularly in the first one or two weeks postnatally are catabolic with respect to protein. This is likely to reflect their general state of ill health⁶ and it is notable that it is accompanied by a high plasma urea concentration. The levels found here are greater than found previously in more mature infants, even those ill with birth asphyxia or respiratory distress.^{32 33}

A high plasma urea concentration may in part be explained by a low urea clearance as in dehydrated, oliguric older subjects where there is increased urea reabsorption in the collecting duct. However, the positive correlation between plasma urea, urea excretion, and negative nitrogen balance suggests that plasma urea closely reflects the urea excretion rate which itself represents the urea production rate by intracellular metabolism. Urea production rate, taking into account change in total body urea, has not been calculated here because body weight was not measured every day in all babies and because urea distribution volume can only be assumed. It is likely that peak urea production is greater than peak excretion because plasma urea is usually rising as excretion is rising. Others have estimated urea production up to 8 mmol/kg/day, declining after the age of 2 days.⁶ It might be argued that the high urea excretion could cause an osmotic diuresis. However, the low urea clearance with tubular urea reabsorption may protect against this. This 'economy of water' is a specific feature of urea that has been known for a long time.^{34 35} No evidence was seen of increased water excretion in infants with high urea excretion in the present study.

Urea clearance was compared with creatinine rather than PF-S clearance because there were many more occasions when both were measured and because it has been shown previously that creatinine clearance is a reasonable estimate of GFR.^{2 5 7 16} Urea clearance tends to greatly underestimate GFR as found by others.^{5 36 37} We agree with Coulthard *et al* that the measurement of urine urea is of little use in clinical practice.⁵ Plasma urea concentration is of no use as a marker of glomerular function. It may, however, be useful in sick immature infants as an index of metabolic derangement or to demonstrate its contribution to hyperosmolality. No influence has been found of nitrogen input on urea excretion, but the possibility that a lower nitrogen input in those with high excretions might have lowered the plasma urea has not been tested. Others have shown that nitrogen is incorporated into tissue in sick preterm infants from the first day³⁸ but this does not conflict with the present study where formal nitrogen balances have not been performed. Plasma urea and urea excretion were not reported in that study. Urea production and plasma urea are high in the fetus.³⁹ Further investigations are needed to determine whether high rates of urea production are caused directly by postnatal illness or whether it is due to high urea production before birth

and cessation of placental function at birth, and whether postnatal nitrogen and energy input influences plasma urea and nitrogen excretion.

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