ORIGINAL ARTICLES

Renal function in sick very low birthweight infants: 1. Glomerular filtration rate

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Abstract

A total of 135 measurements of polyfructoside clearance as a measure of glomerular filtration rate (GFR) were made in 39 infants of 25·5–33 weeks' gestation, birth weight 720–2000 g, between the ages of 0·5 and 33 days. GFR was related to postconceptional age and increased exponentially from geometric mean 0·59 ml/min at 26 weeks' postconceptional age to 1·40 ml/min at 33 weeks. GFR in the first week and GFR at later ages were the same for a given postconceptional age. GFR was the same in sick infants with severe ventilatory failure as in less ill infants. There was no evidence that GFR was influenced by nitrogen input. GFR increases postnatally in a preprogrammed way irrespective of other postnatal events. When factored by body weight GFR in the first week increased only little from arithmetic mean 0·70 ml/min/kg at 26 weeks to 0·84 ml/min/kg at 33 weeks, but older infants often had a falsely high GFR per kg when they lost weight in the first week or two after birth or failed to gain weight later.

There have been many but conflicting reports concerning the maturation of glomerular filtration rate (GFR) in preterm infants.[1-10] Most emphasise that GFR is low compared with that in older children, and that this limits excretory ability, and that there is a rapid postnatal increase. Measurement of GFR and other aspects of renal function is more difficult in the smallest infants especially in the first week when they may be oedematous and ill and because of inherent difficulties with urine collection, and much of the discrepancy between studies may reflect experimental differences. Careful studies have shown that GFR increases after birth slowly and progressively in a preprogrammed way dependent only on postconceptional age in well preterm infants.[1] [2] Few studies have examined GFR in the sickest and most immature infants.

The purpose of the present study was to refine existing methods of measuring GFR by polyfructoside clearance and to examine postnatal changes in GFR in very low birthweight infants including some with severe respiratory disease. The study had health authority ethical committee approval and informed parental consent was obtained.

Patients and methods

This study was part of a wider study of renal glomerular and tubular function in 42 very low birthweight infants, chosen to be studied in the first postnatal week, and later if possible. Gestation at birth was 25·5–33 weeks, birth weight 720–2000 g. Two infants were over 1500 g. The exact timing of the studies was difficult because so many different events befell the patients that it was impossible to perform clearance studies at the same age and on the same number of occasions in all subjects and clearance studies were only performed when intravenous treatment was being given. The polyfructoside used was Polyfructosan-S (Laevosan-Gesellschaft), an inulin substitute hereafter called PF-S. Many experiments failed and were irretrievable because of interruption of the PF-S infusion or acute clinical deterioration requiring resuscitation or administration of plasma. Some subjects received various drugs occasionally (for example frusemide, aminophylline boluses, indomethacin, digoxin, and vancomycin) or plasma for volume replacement that might interfere with results, so they were not studied for 24–48 hours afterwards. Most did receive aminophylline, which is routinely used as a respiratory stimulant, being commenced between age 2 and 14 days. The author has found no evidence of significant renal effect of chronic aminophylline administration.[11]

All patients were managed clinically by neonatal physicians. Water treatment was started according to the regimen: 60, 90, 120, 150, 150, etc ml/kg/day (days 1, 2, 3, 4, ≥5) for infants >1500 g; 80, 120, 150, 180, 180, etc for 1000–1500 g; and 100, 130, 150, 180, 200, etc for <1000 g. Sodium was started at 3, 4, and 5 mmol/kg/day in these three weight groups from the second day. There was complete freedom to vary these regimens according to individual circumstances. Extra sodium was only given in response to evidence of sodium depletion with hyponatraemia and high urine sodium losses. This was common after the middle of the second week. Potassium was given from the second day at 1–2 mmol/kg/day and was rarely varied. Glucose was started at 6–8 mg/kg/min (as 10% glucose) and changed according to blood glucose concentration. Nitrogen was given as Vamin 9 glucose (KabiVitrum) 40 ml/kg/day (380 mg nitrogen/kg/day) from the third day when tolerated. Actual water, sodium, potassium, and nitrogen inputs are summarised in the table. One baby had prenatal steroid.

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Mean, minimum, and maximum water, sodium, potassium, and nitrogen inputs for all infants in the two age periods 3–10 days and 11–21 days

	3–10 days	11–21 days
Sodium (mmol/kg/day)		
Mean (min, max)	4·7 (1·2, 9·7)	6·2 (1·2, 12·3*)
Potassium(mmol/kg/day)		
Mean (min, max)	1·6 (0, 3·5)	1·9 (0, 4·2)
Water (ml/kg/day)		
Mean (min, max)	152 (77, 233)	154 (84, 222)
Nitrogen (mg/kg/day)		
Mean (min, max)	230 (0, 476)	218 (0, 560)

*One infant who was severely sodium depleted received 18 mmol/kg sodium on day 21.

The infants were evenly distributed about the 50th weight centile according to the growth charts of Keen and Pearse.[12] Four subjects never lost weight after birth, one less than and three greater than 28 weeks' gestation. Three of these developed patent ductus arteriosus (PDA) at 3 to 7 days of age when their weights had increased by 2%, 5%, and 8%. A further two gained weight initially before eventually losing weight. These two also developed PDA at 2 and 6 days with weights equal to and 4% above birth weights. All the other subjects lost weight after birth, reaching a nadir at 3 to 10 days when weight
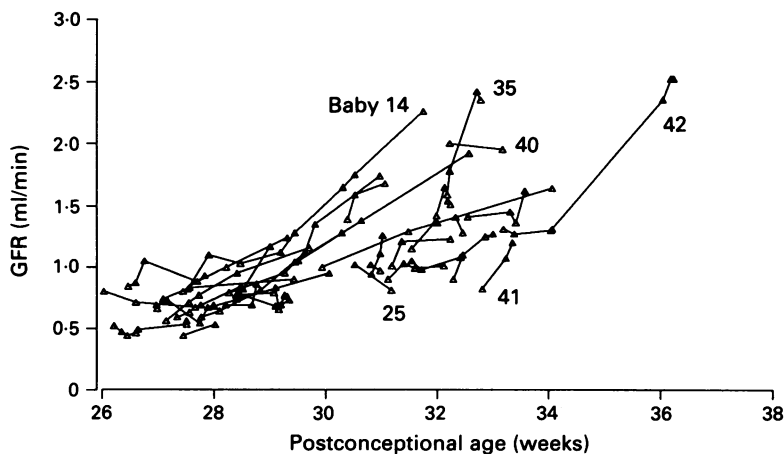

Figure 1   GFR uncorrected for body size as a function of postconceptional age (n=135). Sequential points are joined for individual subjects.
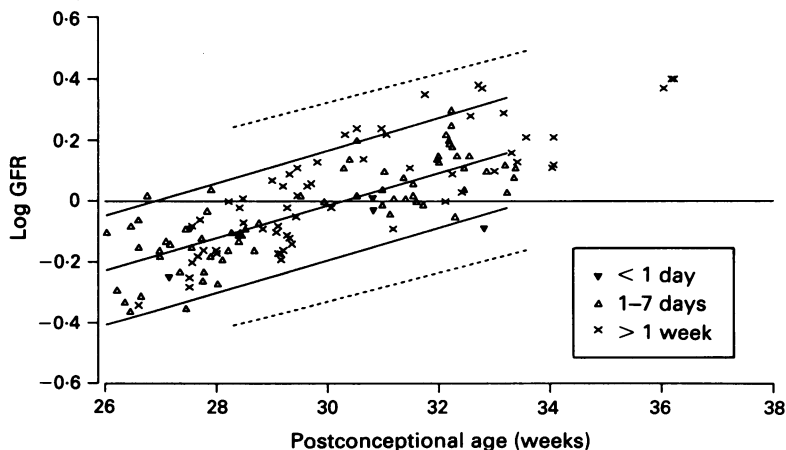

Figure 2   Log₁₀ transformation of fig 1 for three age groups (postnatal age). The diagonal solid lines are the regression line ±2 residual SDs (approximate 95% tolerance limits) for those points which are the first for each baby in the first postnatal week but older than 24 hours (n=36). The regression line is: Log_{10} GFR (ml/min)=−1·615+0·0534× postconceptional age (weeks). The dashed lines show the approximate 95% tolerance limits recalculated from Coulthard (1985)[2] for the first measurement in the first week.

was 3% to 23% below birth weight. Twelve of these developed PDA at 2 to 8 days when weight was up to 23% below birth weight. In eight of these 12 the PDA developed when the weight was more than 10% below birth weight. In the subjects who lost weight, birth weight was regained at age 10 to 31 days (median 17). In those less than 28 weeks' gestation the median was 24 days and in those greater than 28 weeks 13·5 days.

Six subjects did not have respiratory distress syndrome, 16 had severe respiratory distress syndrome with an alveolar-arterial oxygen partial pressure difference $(AaDpo_2)$ greater than 13·3 kPa (100 mm Hg) at any time. Only two did not receive assisted ventilation. Three babies died while being studied and two died later. No patient had anuria, haematuria, or proteinuria or any other evidence of acute tubular necrosis before or during the studies.

A total of 135 measurements of PF-S clearance were made in 39 infants, between the ages of 0·5 and 33 days. On 37 occasions the single injection method was used and in the remainder the constant infusion method. Both methods have been described previously.[13–15] For the single injection method 200 mg/kg PF-S was injected intravenously smoothly over 3–6 minutes. Samples of 0·1 ml arterial blood were taken at 10, 40, 80, 120, 180, 360, and 480 minutes and GFR calculated from the area under the concentration time curve by:

GFR=PF-S injected/area under curve

For the continuous infusion method a 25 mg/ml solution in water was infused intravenously at 0·6 ml/kg/hour through a 0·22 μm filter using a Graseby MS2000 syringe pump accurate to ±1%. For the first eight hours of the infusion, the infusion rate was at exactly double this final infusion rate which was then continued for 24 hours or more before 0·6 ml blood samples and fresh voided urine samples (aspirated from cotton wool balls) obtained. If the infusion ever became extravascular the cannula was replaced within one hour and at least six hours added to the infusion time before sampling. GFR (ml/min) and urine flow rate (urine volume or renal water excretion rate, ml/day) were calculated by:

GFR=PF-S infusion rate/plasma PF-S concentration

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

Urea excretion rate (mmol/day) was calculated by:

Urea excretion=urine flow rate×urine urea concentration

PF-S concentration was measured in duplicate 13 μl samples of plasma, diluted urine, or infusate using a modification by the author of the cysteine/tryptophan/sulphuric acid method with an alkali denaturing step to remove interfering sugars.[14–16] This method is highly sensitive and specific and the coefficient of variation was less than 2% for sample concentrations of 0·1 to 0·5 mg/ml.
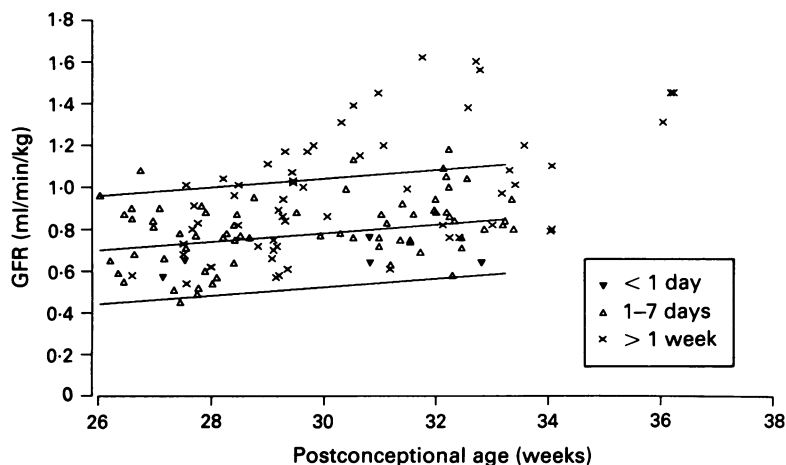
Figure 3   GFR factored by either birth weight or latest weight (whichever is the greater) as a function of postconceptional age (n=135). The diagonal solid lines are the regression line ±2 residual SDs (approximate 95% tolerance limits) for those points which are the first for each baby in the first postnatal week but older than 24 hours (n=36). The regression line has the formula: GFR (ml/min/kg)=0·167+0·0205 × postconceptional age (weeks).
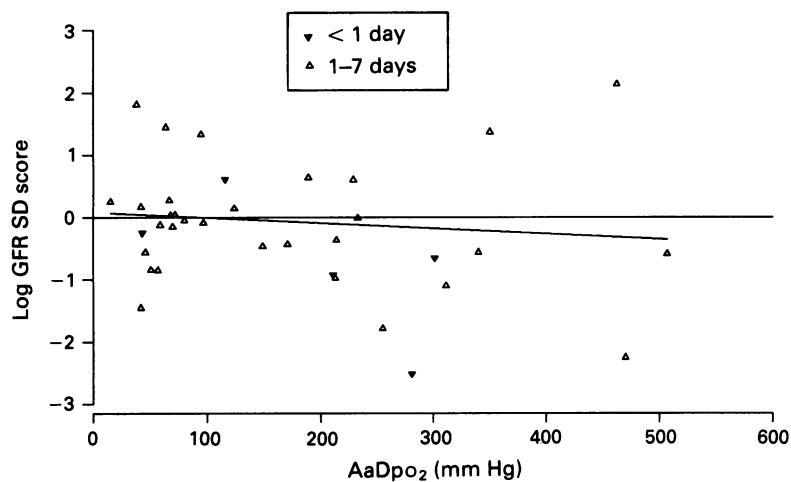

Figure 4   SD score (vertical distance from regression line) for the points in fig 2 for those aged 1–7 days as a function of AaDpo$_2$ (n=31). The regression line has the formula: GFR SD score=0·084–0·00087×AaDpo$_2$ (mm Hg). Five measurements at <1 day are also shown.
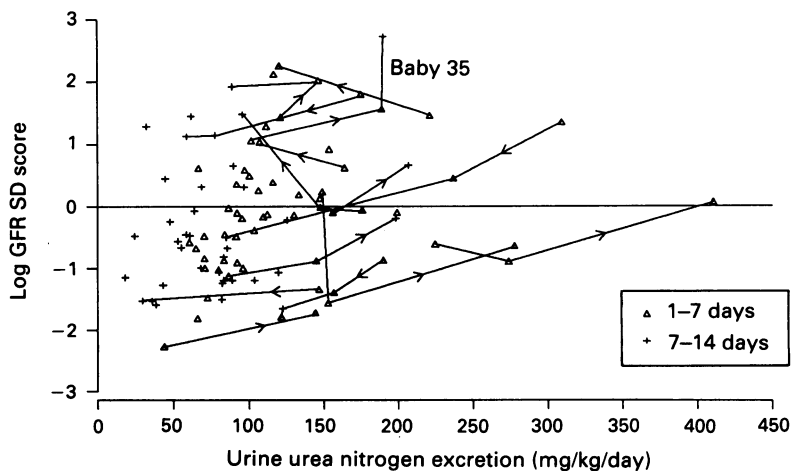

Figure 5   SD score (vertical distance from regression line) for the points in fig 2 for those aged 1–14 days as a function of urine urea excretion (n=98). Points are joined for some individuals with timing indicated by arrows. The regression line is not shown because the data are a mixture of cross sectional and longitudinal.

Results

Figure 1 shows all the results for GFR plotted against postconceptional age. This scattergram and figs 2, 4, and 5 include a mixture of cross sectional and longitudinal data. There is a steepening increase in GFR with increasing postconceptional age between 26 and 34 weeks. The relationship is approximately exponential (fig 2). The range of raw GFR widens with increasing postconceptional age whereas the range of the logarithm of GFR is approximately constant. The geometric mean of GFR is 0·59 ml/min (95% tolerance interval 0·40 to 0·90 ml/min) at 26 weeks' postconceptional age and 1·40 ml/min (0·90 to 2·10) at 33 weeks.

The diagonal continuous lines in fig 2 are the logarithmic least squares regression line and the approximate 95% tolerance limits (mean ±2 residual SDs) for all those points which represent the first measurement made in each of 36 infants at less than 1 week of age but greater than 24 hours. This avoids bias from the inclusion of multiple measurements from individuals. The regression slope, 0·053, is significantly different from zero (95% confidence interval 0·039 to 0·067, p<0·0001).

Figure 3 shows GFR factored by body weight plotted against postconceptional age. Not all babies were weighed every day in which case the most recent weight was used, but if the infant's weight was less than the birth weight then the birth weight was used. This was the case in the majority of points on this graph. The regression line and tolerance limits are shown for the first measurement made on each baby at 1 day to 1 week, as in fig 2. The general relationship is linear for measurements less than 1 week, but these points are as a whole lower than those at greater than 1 week which confirms that in the majority of individuals GFR factored by weight increases more steeply with age. GFR in the first week increased only little from arithmetic mean 0·70 ml/min/kg (95% tolerance interval 0·45 to 0·95) at 26 weeks to 0·84 ml/min/kg (0·59 to 1·09) at 33 weeks. The regression slope, 0·0205, is only just significantly different from zero (95% confidence interval 0·0004 to 0·0406). This slope is reduced to zero if GFR is factored not by weight but by weight raised to the power 1·3 (weight$^{1·3}$).

Five measurements made by single injection PF-S clearance between 12 and 24 hours of age all fall within the tolerance interval for later measurements in the first week, although low in the range, suggesting that the immediate rapid postnatal increase in GFR to its final level occurs in about 24 hours.

For the 36 first week measurements a SD score has been calculated for GFR from fig 2, being the vertical distance in residual SDs from the regression line. This is plotted in fig 4 against simultaneously measured AaDpo$_2$ in 31 cases. The regression slope, –0·00087, is not significantly different from zero (95% confidence interval –0·00355 to +0·00181). Similarly, there was no relationship with arterial:alveolar oxygen partial pres-

sure *ratio*, or with FIO_2, arterial PO_2, PCO_2, pH, or base deficit. There was no trend for the SD score to vary with the age at which the GFR was measured in the first week.

One baby who had a steeper than normal rise in GFR (No 35, fig 1) had a high amino acid input (>300 mg nitrogen/kg/day) and a high urea nitrogen excretion in the four days before the final measurements at the end of the first week. Another, number 41, had a high nitrogen input but low excretion. Baby number 25 had a fall in GFR but a high nitrogen input and low excretion. In order to investigate whether GFR is influenced by intravenous amino acid input, SD scores were calculated for all GFR measurements in the first two weeks from the regression in fig 2. Linear regression analysis was then used to show how these scores varied with nitrogen input in the preceding 24 hours, with urine urea nitrogen excretion, with the difference between nitrogen input and excretion, and with plasma urea concentration. All regressions were non-significant except for that for urea excretion (regression slope 0·0041, 95% confidence interval 0·0008 to 0·0074) where there was a tendency for higher urine urea excretion to be associated with higher GFR in the first week. This suggests that the urea load being excreted may have some effect on GFR, but is clearly not the only cause of variation between individuals. There was no relationship between plasma urea or recent nitrogen input and GFR.

Discussion

The constant infusion method assumes that the plasma inulin concentration is constant with the infusion rate of inulin equal to the urinary excretion rate. This steady state requires at least four hours in adults. The method has been validated in adults and newborns[13 17 18] and carries some advantage over the traditional method in that it avoids the need for timed urine collections which, in the absence of high urine flow rates, are liable to inaccuracy especially in very small subjects. However, it is most important that the assumption that infusion rate is equal to the excretion rate is justified. In the preterm newborn the time required after commencement of such an infusion may be up to 48 hours in some cases before plasma steady state is reached or 24 hours after a priming double rate infusion of eight hours.[14 15] Some studies have assumed that steady state is reached after periods of only a few hours, and their results may thereby by invalidated.[13] The single injection method is also reliable and accurate if sampling is continued for 8–10 hours after the injection and the laboratory inulin assay is very accurate and precise.[14]

MATURATION OF GFR

The present study supports the view that GFR increases in a programmed way,[1 2] at least from 26 weeks' gestation and from the second postnatal day, which is unaffected by the gestation at birth. In the majority of infants studied, GFR matures after birth slowly and progressively, irrespective of changes in body weight and of various pathological events including respiratory disease.

An impression is gained from fig 2 that the crosses and triangles are scattered in approximately the same distribution. This impression is supported in fig 1, where the lines joining successive measurements in individuals follow the general trend of the group as a whole, approximately parallel to the regression line. There are some exceptions where there is a steeper increase (for example babies 35 and 41) or shallower or even a decrease in GFR (for example babies 25 and 40) as postconceptional age increases. These exceptions may be due to genuine differences in the maturation of GFR, or may be partly explained by methodological imprecision.

Apparent rapid increases in GFR after birth are most likely to be due to cessation of growth and the factoring of GFR by a weight or surface area which is falsely low as in fig 3.[2 19] Weight loss is common after birth, particularly in preterm babies, even those who do not have serious illness. It is not surprising that there is an increase in GFR, unfactored by any parameter of body size, with increasing maturity, because in the last trimester of pregnancy there is rapid increase in fetal weight paralleled by an increase in kidney size. Although this maturation of GFR has been described here and by others as 'logarithmic',[1 2] this is in fact an arbitrary label which conveniently describes the steepening increase in GFR within the 25 to 40 weeks' postconceptional age range. There is no implication that the fetal GFR at a given postconceptional age is the same as that of an infant already born. The little information on GFR before birth suggests that GFR is lower and increases after birth rapidly to the level observed within these studies within 24 hours after birth.[20-22] At any given gestational age, therefore, the kidney before birth has matured such that it has the capacity to attain a normal postnatal GFR as soon as the postnatal circulatory changes have been effected after 24 hours. Even at gestations as low as 26 weeks the kidney has the capacity to assume its excretory role long before the fetus is in fact due to be born, and this capacity is achieved by the second postnatal day. Even the five measurements between 12 and 24 hours age fell within the 95% tolerance interval. It is unlikely that the maturation of GFR is caused by volume expansion and/or excessive sodium input because most infants were volume contracted despite moderate sodium supplementation since birth.

The results are very similar to those of Coulthard who measured GFR in 39 relatively healthy infants of gestation 27 to 40 weeks at birth using a 24 hour continuous inulin infusion technique.[2] Linear regression has been reperformed on Coulthard's original raw data.[2] When only samples from infants less than 34 weeks' gestation at birth are included, with no repeated observations, to make comparison with the present study more

meaningful, the number of observations was 23. There is no difference between the regression (slope 0·0508, intercept –1·54) and that of the present study. Coulthard's tolerance interval is somewhat wider, shown by the dashed lines in fig 2. The apparent rapid postnatal increase in GFR/kg was abolished when the weight used to factor GFR was a projected weight (a theoretical weight as if growth continued at a normal intrauterine rate). Therefore the apparent acceleration of GFR/kg in some babies was due to a temporary cessation of body growth whereas the GFR continued to mature at an apparently preprogrammed rate. A similar exercise in the present study yields a similar result but is not illustrated because of the arbitrary nature of projected weight.

Similar results were also obtained by Al-Dahhan *et al* using creatinine clearance.[1] Between 28 and 42 weeks' postconceptional age, creatinine clearance increased in an approximately exponential fashion when uncorrected for body size. Their regression for log GFR against postconceptional age (slope 0·07) was just outside the 95% confidence intervals of the present study. The range was wider at lower gestations, but not as wide as that of Coulthard,[2] 0·35 to 1·1 ml/min at 29–30 weeks and 0·9 to 2·0 at 34 weeks. GFR seemed to increase rapidly from 32 weeks because of its approximately exponential shape. Their regression line for first week measurements was no different from those at more than 26 days, suggesting that GFR after birth depends on postconceptional age, not postnatal age, as in the present study where there are more measurements in infants less than 28 weeks' gestation and more sequential measurements than previously.

WEIGHT AS STANDARD FOR GFR

No attempt has been made in the present study to factor GFR by body surface area or a function of body length[23] because it has been shown that weight is the best standard.[19 24] All previous measurements of GFR in preterm infants emphasise that this quantity is low compared with more mature and older individuals. But what is meant by 'low' GFR in an immature infant? Even when corrected for *projected* weight as in Coulthard's study[2] GFR is lower in the most immature subjects than more mature. This may be accounted for by the lower metabolic rate of the more immature individuals who should be growing fast. Growth has been described as a 'third kidney', because it reduces the need for renal nitrogen excretion.

The relationship between GFR and body size is complex. It is conventionally accepted that GFR is most likely to relate to the basal metabolic rate, since the principal function of glomerular filtration is the excretion of waste products of metabolism. It is useful that in adults and older children metabolic rate correlates well with, and is proportional to, body surface area or weight $^{0·67}$.[25] Small *adult* mammals have higher metabolic rate/kg but this relationship does not extend to infants.[19] Barratt has argued that extracellular volume would be more appropriate because this is the domain which is actually filtered.[26] But this is illogical because the extracellular fluid is only an intermediate vehicle for excretion of metabolic by products. The *volume* of the extracellular fluid does not determine the concentration of metabolic waste products therein, but rather the *production rate* and the GFR (extracellular fluid concentration=production rate/GFR for a substance completely cleared by glomerular filtration). Intracellular fluid volume (if it could easily be measured) might be a better standard because it is likely that metabolic rate will be proportional to cell mass. In the present study GFR must be factored by weight$^{1·3}$ in order to abolish the trend with increasing postconceptional age. This is different from older children but not unexpected because more mature and therefore larger babies have a higher cell mass per kg.[27] It may therefore be inappropriate to refer to GFR as being *low* when in fact it is entirely appropriate for the infant's metabolic needs. It is a different matter when considering the excretion of drugs because the low GFR and the relatively high extracellular fluid volume will demand an increased unit dose and a longer interdose interval.

In practice, expressing GFR as factored by body weight (birth weight or latest weight, whichever is higher) will be the most valuable and easiest, so long as it is realised that this will result in different 'normal ranges' at different gestations, and at different ages, as seen in fig 3.

THE INFLUENCE OF PROTEIN INTAKE ON GFR

A further question is whether the postnatal increase in GFR that occurs despite the illness and weight loss of the infants is promoted by either the catabolic state with endogenous urea production or the exogenous nitrogen that is administered, and secondly whether sodium wastage may be in part caused or worsened by such a forced increased in GFR. High protein intake has been shown to increase GFR in healthy adults and infants,[28] suggesting that there is a renal reserve available to promote the excretion of increased nitrogenous waste. In healthy immature newborns, in the presence of an increased renal urea load there is an obligatory increase in urine osmolality (presumably caused by urea), GFR, and sodium excretion.[28] These findings suggest that high protein intake may not be desirable in sick immature infants who cannot anabolise the administered protein and who have high urea production and high plasma urea. The present study has not convincingly demonstrated an effect in sick very low birth-weight infants. This needs further study but accurate nitrogen balances would be needed and total urine nitrogen should be measured, not just urea. Urea as a marker of renal function is further discussed in part 2.[29]

THE EFFECT OF RESPIRATORY FUNCTION ON GLOMERULAR FUNCTION

Although perinatal asphyxia has often been

associated with acute renal failure in term infants, changes in renal function have also been found in preterm infants with milder degrees of hypoxia or acidosis. The literature on renal function in infants with respiratory distress syndrome is mixed and confusing, some reporting no reduction in GFR, others that such babies have poor renal function.[8] [30-35] The pathophysiological changes associated with hyaline membrane disease, including asphyxia, hypotension, poor tissue perfusion and acidosis, are thought to account for what has been called this functional renal failure in such infants. The apparent decrease in GFR appears to be related to the severity of the respiratory distress syndrome and has been thought to be partly responsible for the impairment of free water excretion. This is a little difficult to interpret because the problem is really confined to the first few days after birth when the methods for measuring GFR may not be reliable. None of the babies in the present study developed any reduction in GFR despite many having birth asphyxia or severe respiratory disease later. Other factors including antidiuretic hormone, atrial natriuretic peptides, adenosine, and prostaglandins are likely to be involved in the genesis of oliguria.[36-38] This will be considered further in part 3.[39]

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