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Renal Function in Preterm Neonates

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ABSTRACT

The plasma creatinine concentration is elevated at birth and decreases concomitantly with the rapid increase in glomerular filtration rate that occurs in the first postnatal weeks. The velocity of these changes was assessed during the first 3 wk of life of 66 term and preterm infants. The plasma creatinine concentration, creatinine clearance, and sodium fractional excretion were measured serially at weekly intervals, starting 1–4 d after birth [mean = 1.5 ± 0.8 (SD) d]. Premature infants were separated into three groups according to their birth weight: group 1, 1001 to 1500 g; group 2, 1501 to 2000 g; and group 3, 2001 to 2500 g. Group 4 included 28 term infants (mean birth weight = 3165 ± 78 g). Mean gestational ages in the preterm groups were 31.3, 32.8, and 34.4 wk in groups 1, 2, and 3, respectively. The plasma creatinine concentration on d 1.5 was significantly higher in preterm (91 ± 4 μmol/L) compared with term infants (66 ± 3 μmol/L). The differences in plasma creatinine were still present during the second week of life, with values of 64 ± 5, 58 ± 7, 47 ± 8, and 40 ± 4 μmol/L in groups 1, 2, 3, and 4, respectively. The difference vanished by d 22–23. On d 1.5, creatinine clearance correlated positively with gestational age, amounting to 0.65 ± 0.14, 0.92 ± 0.19, 1.42 ± 0.31, and 3.36 ± 0.32 mL/min in groups 1, 2, 3, and 4, respectively. Creatinine clearance increased rapidly with postnatal age, the velocity of the maturation being less marked in the most premature infants. The fractional excretion of sodium was significantly higher in the most premature infants, with values of 2.0 ± 0.3, 2.2 ± 0.5, 1.1 ± 0.2, and 0.3 ± 0.1% in groups 1, 2, 3, and 4, respectively. The differences vanished by the third week of life. The negative correlation between plasma creatinine on d 1.5 and gestational age suggests that the neonate's creatinine plasma concentration does not simply reflect the mother's plasma concentration. (***Pediatr Res* 36: 572–577, 1994**)

Abbreviations
GFR, glomerular filtration rate
BW, birth weight
VLBW, very low birth weight
GA, gestational age

Renal function is low at birth, especially in the most premature infants (1–5). The functional maturation of the GFR after birth has been well documented in term neonates. Studies using inulin (3, 4, 6, 7) or creatinine (1, 2, 8–12) as a glomerular marker have demonstrated a rapid increase in GFR in the neonatal period, with the value of inulin clearance actually doubling in the first 2 wk of life (3, 4).

The pattern of maturation of GFR in premature neonates has been the subject of controversy. Studies using inulin, the gold standard for measuring GFR, have shown a characteristic pattern in the development of GFR during gestation. From the 28th to the 35th wk of gestation, GFR (expressed in mL/min/1.73 m^2) increases rapidly (4). Because kidney size bears a linear relationship to the body surface area (13), this finding indicates that renal function matures more rapidly than renal mass. Thereafter, GFR reaches a plateau until the end of gestation, indicating that renal function and renal mass mature in parallel (4, 14). As in term neonates, birth is followed by a rapid increase in inulin clearance during the first weeks of life (3, 4). The velocity of the postnatal increase in inulin clearance is slightly inferior in premature neonates compared with term neonates, but the difference does not appear to be statistically significant (1, 4, 14).

Observations based on creatinine clearances in low-BW infants have produced conflicting results (2, 9). It has been suggested that creatinine clearance develops very slowly before 34 wk of conceptional age, even though body size and kidney weight increase appreciably during this time. In Arant's study (2), only 34 wk after conception did creatinine clearance appear to increase rapidly, regardless of postnatal age. Thus, in an infant born prematurely at 28 wk of gestation, GFR would not increase rapidly until the infant is 5–6 wk old (2). The reason for the discrepancy in results obtained from inulin or creatinine clearance studies is not clear. It could be due to the physiologic specifics of creatinine handling in

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premature neonates or to differences in the clearance study protocols (8, 11).

Conflicting results have also been published concerning the tubular transport of sodium in premature neonates. Extremely elevated sodium fractional excretion rates have been reported in some studies (15), leading to the conclusion that premature babies present with salt wasting (16). Other authors observed much lower sodium fractional excretion rates, reaching the conclusion that VLBW infants were able to maintain sodium balance during the first week of life (10, 17, 18). Differences in fluid and electrolyte intakes used in the different study protocols could explain the apparently conflicting results.

The present study was planned with the aim of observing the maturation of creatinine clearance and sodium excretion in the first weeks of life of neonates with various GA and BW.

METHODS

Sixty-six physiologically stable newborn infants with GA of 29 to 40 wk and BW of 1009 to 3910 g were studied during the first 3 wk of life. The clinical diagnosis included prematurity, high risk for infection, transient hyperbilirubinemia, and transient mild respiratory distress syndrome. The estimate of GA was made from the menstrual history and the Dubowitz score (19). The 66 infants were divided into four groups, according to their BW: group 1, 11 neonates with BW of 1009 to 1500 g (mean BW = 1332 ± 44 g; mean GA = 31.3 ± 0.5 wk); group 2, 15 neonates with BW of 1520 to 2000 g (mean BW = 1730 ± 45 g; mean GA = 32.8 ± 0.4 wk); group 3, 12 neonates with BW of 2040 to 2420 g (mean BW = 2239 ± 41 g; mean GA 34.5 ± 0.2 wk); and group 4, 28 term infants with BW of 2400 to 3910 g (mean BW = 3165 ± 78 g).

All infants were fed a cow-milk formula (Nan or Alprem, Nestlé, Switzerland). Feeding was initiated after 12 h of life and progressively increased up to the fifth day. The formula supplied 544 kJ/kg/d (130 kcal/kg/d) to premature and small-for-gestational-age infants and 418 kJ/kg/d (100 kcal/kg/d) to full-term infants. As a rule, fluid intake was 80 mL/kg on the first day and then increased by 20 mL/kg/d to reach 150 mL/kg/d. Fluid intake was increased by 20 mL/kg/d whenever a decrease in BW of more than 10% was observed. It was decreased by 20 mL/kg/d whenever the actual weight exceeded BW during the first 4 d of life. The cow-milk formula provided 1–1.2 mmol of sodium per 100 mL of milk (Alprem) or 0.8 mmol of sodium per 100 mL of milk (Nan). Usual therapeutic measures were continued unchanged throughout the clearance studies.

The infants were studied at weekly intervals on three occasions during daytime. The first blood sample and urine collection were obtained on d 1 in 50 infants, on d 2 in seven, on d 3 in seven, and on d 4 in two infants [mean age = 1.5 ± 0.8 (SD) d]. They were thereafter studied on d 8–9, 15–16, and 22–23. Urine was collected by means of an external collecting device. At the end of the 8- to 12-h collection period, manual suprapubic pressure was applied after the last voiding to ensure complete emptying of the bladder. Urine specimens were stored at 4°C before creatinine and sodium analysis. Plasma creatinine concentrations were determined during the urine collection period using 50 μL of blood collected from heel prick, which was performed only when needed for other reasons.

Blood pressure was measured in all neonates on three occasions during the urine collection period with the automatic oscillometer method (Dinamap, model 847 XT, Critikon, Inc., Irvine, CA). A 4-cm cuff was used and applied to the left or right upper arm with the baby lying supine. The protocol was approved by an *ad hoc* ethical committee of the department.

Creatinine in blood and urine was determined by the Jaffé kinetic method, which is available on the Beckman Creatinine Analyzer-II (Beckman Instruments Inc., Fullerton, CA). The endogenous creatinine clearance was taken as an estimate of GFR and calculated from the standard U·V/P formula, where V = urine flow rate, U = urine creatinine concentration, and P = plasma creatinine concentration. It was expressed in mL/min or mL/min/1.73 m^2. The body surface area was estimated from the Du Bois and Du Bois formula (20). Sodium was measured in plasma and urine by flame photometry (Flame Photometer, Il-543, Instrumentation Laboratory, Lexington, MA). The fractional excretion of sodium was assessed by using the standard ratio U/P Na:U/P creatinine, where U and P are the urine and plasma concentrations, respectively, of sodium or creatinine. The fractional excretion of sodium is expressed as a percentage.

Calculations of regression lines and correlation coefficients followed standard statistical methods (21). Mean values are expressed as mean ± SEM.

RESULTS

Plasma creatinine concentration. The plasma concentration of creatinine was elevated on the first measurement in all neonates (Fig. 1); the concentration was significantly more elevated ($p < 0.001$) in the low BW infants, with values of 66 ± 3 μmol/L in the term infants (group 4) compared with 95 ± 5, 90 ± 5, and 83 ± 5 μmol/L in groups 1, 2, and 3, respectively (Table 1). The difference between values observed in term infants (66 ± 3 μmol/L) and mean values observed in groups 1, 2, and 3 (91 ± 4 μmol/L) were statistically different ($p < 0.001$). The concentration decreased in all groups during the subsequent 3 wk to reach 27 ± 7 μmol/L in the term infants and 35 ± 3, 30 ± 2, and 30 ± 10 μmol/L in groups 1, 2, and 3, respectively. Creatinine plasma concentration did not differ significantly between the four groups on the last measurement, with a mean value of 31 ± 5 μmol/L. Plasma creatinine correlated significantly with postnatal age in all groups ($r = -0.738$ to -0.795; $p < 0.001$).

Plasma sodium concentration. The plasma sodium concentration at birth was similar in all groups, with values

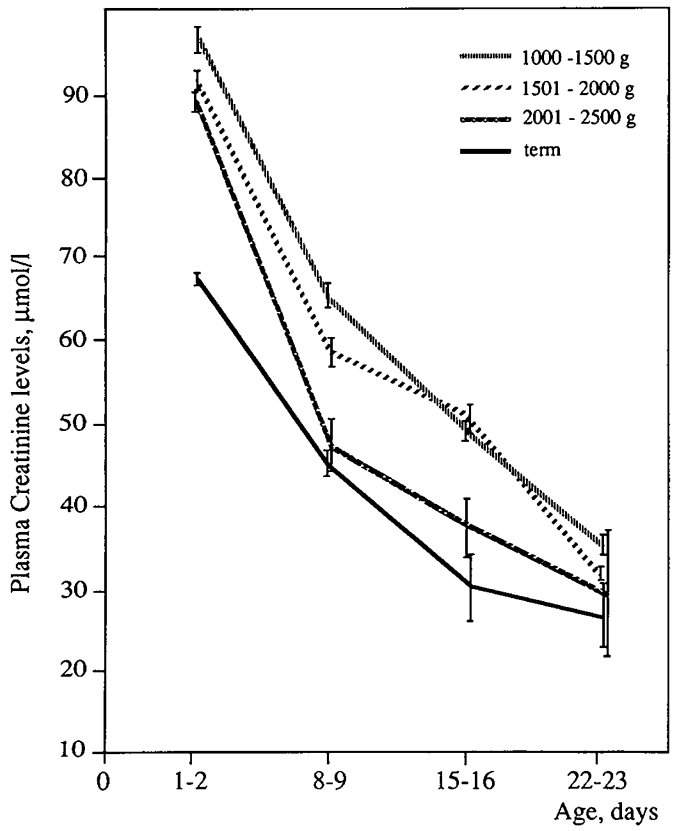

Figure 1. Plasma creatinine concentrations (µmol/L) during the first weeks of life.

ranging from 134 ± 2 to 137 ± 1 mmol/L (Table 1). Except for in infants in group 1, the plasma concentration did not change significantly throughout the observation period. In group 1, the plasma sodium concentration was transiently depressed after 2 wk of life; a nadir of 132 ± 2 mmol/L ($p < 0.05$) was recorded on d 15–16.

Creatinine clearance. Clearance values were low during the first week of life; the lowest values were observed in infants with the lowest BW. This statement was true both for absolute values of creatinine clearance and for values expressed in relation to the body surface area (Table 2, Fig. 2). Creatinine clearance increased in the following weeks in all infants. This increase correlated significantly with postnatal age. The velocity of the postnatal maturation of creatinine clearance was higher in term neonates ($p < 0.01$) both when creatinine clearance was expressed in absolute terms and when it was factored by the body surface area.

Fractional excretion of sodium. On d 1–2, the fractional excretion of sodium was 0.3 ± 0.1% in term infants (Fig. 3) and 2.0 ± 3, 2.2 ± 0.5, and 1.1 ± 0.2% in groups 1, 2, and 3, respectively. The difference between term neonates and the other three groups was statistically significant ($p < 0.001$). All values decreased during the subsequent weeks and were below 0.8% on d 15–16 (Fig. 3).

Table 1. *Plasma creatinine and sodium concentrations during the first weeks of life**

Group	Postnatal days 1–2	8–9	15–16	22–23
I (1001–1500 g)				
Creatinine (µmol/L)	95 ± 5	64 ± 5	49 ± 4	35 ± 3
Sodium (mmol/L)	137 ± 1	135 ± 1	132 ± 2†	136 ± 2
n	11	10	8	8
II (1501–2000 g)				
Creatinine (µmol/L)	90 ± 5	58 ± 7	50 ± 8	30 ± 2
Sodium (mmol/L)	136 ± 2	139 ± 1	139 ± 2	139 ± 1
n	15	11	11	9
III (2001–2500 g)				
Creatinine (µmol/L)	83 ± 5	47 ± 8	38 ± 8	30 ± 10
Sodium (mmol/L)	134 ± 2	138 ± 1	135 ± 2	136 ± 3
n	12	7	4	2
IV (full-term)				
Creatinine (µmol/L)	66 ± 3	40 ± 4	30 ± 8	27 ± 7
Sodium (mmol/L)	136 ± 1	139 ± 1	137 ± 1	135 ± 3
n	28	14	4	3

* Mean values ± SEM.
† $p < 0.05$ compared with values on d 1-2.

Table 2. *Creatinine clearance (mL/min) during the first weeks of life**

Group	Postnatal days 1–2	8–9	15–16
I (1001–1500 g)	0.65 ± 0.14	1.31 ± 0.24	1.73 ± 0.29
	n = 11	*n* = 10	*n* = 8
II (1501–2000 g)	0.92 ± 0.19	1.91 ± 0.24	2.86 ± 0.56
	n = 15	*n* = 11	*n* = 11
III (2001–2500 g)	1.42 ± 0.31	3.1 ± 0.6	3.84 ± 1.3
	n = 12	*n* = 7	*n* = 4
IV (full-term)	3.36 ± 0.32	5.17 ± 0.93	7.52 ± 1.9
	n = 28	*n* = 14	*n* = 4

* Mean values ± SEM.

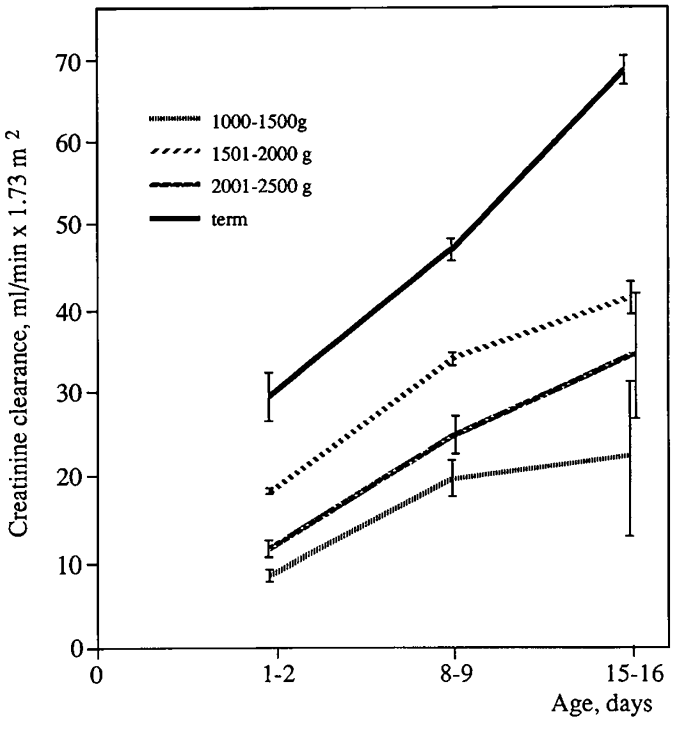

Figure 2. Creatinine clearance (mL/min/1.73 m^2) during the first weeks of life.

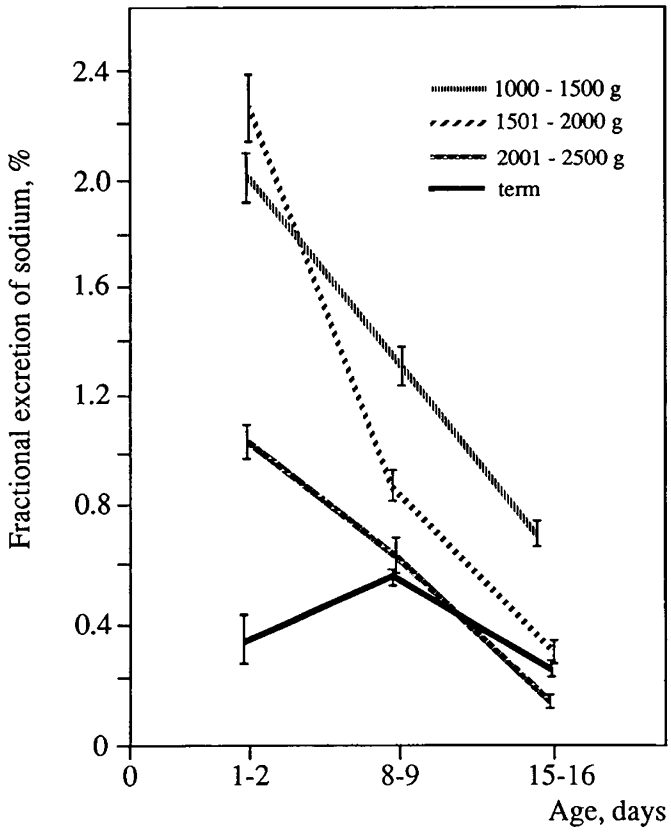

Figure 3. Fractional excretion of sodium during the first weeks of life.

None of the infants developed significant hyponatremia during the study period.

Blood pressure. Blood pressure measured during the urine collection period was lowest in the most premature infants. Mean blood pressure increased linearly with postnatal age ($r = 0.92$, $p < 0.001$) (Table 3). Creatinine clearance correlated significantly with mean blood pressure ($p < 0.001$).

DISCUSSION

The maturation of both creatinine clearance and sodium tubular transport was followed in 66 newborn babies hospitalized in the neonatal unit. None of these neonates was truly normal, but all were physiologically stable when they were included in the study. Many had conditions that could have transiently impaired GFR, *e.g.* respiratory distress syndrome (22), artificial ventilation, or the administration of aminoglucosides. Although all these conditions have been shown to possibly impair GFR, they have been observed to do so in severe conditions. Normal renal function has indeed been demonstrated in neonates with compensated respiratory distress syndrome (23). Depression of GFR by artificial positive pressure ventilation has been observed, usually in infants whose intravascular volume was depleted, a situation that was certainly not present in our neonates. Finally, the nephrotoxicity of gentamicin has been difficult to demonstrate in neonates, especially in the most premature ones. For all these reasons, the factors mentioned above are unlikely to have impaired GFR in our groups of newborn infants. The data collected thus appear clinically relevant.

Plasma creatinine. Our data confirm results observed previously (8, 24) demonstrating that *1*) the plasma creatinine of newborn infants is elevated at birth and *2*) it decreases rapidly to reach stable levels within 3 wk. Interestingly enough, the plasma creatinine is significantly higher in VLBW infants and appears to be inversely related to GA. The same trend was reported, without comment, by Rudd *et al.* (25). The neonate's plasma creatinine at birth has been claimed to reflect the mother's plasma concentration (26). This hypothesis does not fit in well, however, with the observation that the plasma creatinine concentration is highest in the most premature infants. If the mother's and the infant's plasma creatinine concentrations were equilibrating through a freely permeable placenta, the premature neonates should have had lower concentrations. The maternal plasma creatinine is indeed lowest at the beginning of the last trimester (27). This corresponds to the peak elevation of GFR during the course of pregnancy (28). The elevated levels of plasma creatinine in the VLBW infants probably reflect the difficulty these infants have eliminating the excess creatinine transferred from the mother: their GFR is still too low during the first postnatal days to effectively eliminate this excess. Also, it cannot be excluded that the level of noncreatinine chromogens increases in the mother during pregnancy and is highest around the 26th

Table 3. *Blood pressure (mm Hg) during the first weeks of life**

	Postnatal days					
	1–2		8–9		15–16	
Group	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
I (1001–1500 g)	42 ± 3	18 ±2	51 ± 4	18 ± 3	57 ± 4	30 ± 5
	$n = 11$		$n = 10$		$n = 8$	
II (1501–2000 g)	54 ± 3	25 ±3	56 ± 3	18 ± 3	60 ± 3	23 ± 5
	$n = 15$		$n = 11$		$n = 11$	
III (2001–2500 g)	53 ± 3	29 ±3	61 ± 5	25 ± 6	74 ± 12	29 ± 9
	$n = 12$		$n = 7$		$n = 4$	
IV (full term)	63 ± 2	32 ±2	73 ± 4	41 ± 6	80 ± 4	53 ± 4
	$n = 28$		$n = 14$		$n = 4$	

* Mean values ± SEM.

to 35th wk of gestation. Finally, the possibility that creatinine back-diffuses across the immature tubular cells, resulting in net reabsorption, must be considered. If such a reabsorption, as is present in immature animals (29), is present in VLBW infants, it could account for the elevated levels of plasma creatinine at birth and also for the slow decrease in levels of plasma creatinine in the most premature infants.

The present results confirm the claim that plasma creatinine concentration should be interpreted with caution during the first postnatal weeks of neonates. During this period, sequential determinations rather than single values of plasma creatinine must be obtained to give valuable information on GFR.

Creatinine clearance. Creatinine clearance was low at birth, the lowest values being observed in the most premature infants. This observation confirms data obtained from creatinine clearance studies (1, 2, 8–11) or, in a more accurate way, from inulin clearance studies (3, 4, 6, 7). Although inulin remains the best glomerular marker, its measurement is not easy. Consequently, GFR has often been assessed by the clearance of creatinine, which has been shown to correlate reasonably well with inulin clearance. A correlation coefficient of 0.738 was observed by Stonestreet and Oh (30) when the value of creatinine clearance was assessed in VLBW infants and compared with inulin clearance. The scatter of individual values was, however, substantial. Various factors could account for the variability of creatinine clearance in the VLBW infants, related either to *1*) technical difficulties in the measurement of plasma creatinine in neonates *2*) unsteady values of plasma creatinine occurring during the first weeks of life (8, 23, 25, 30), or *3*) the possible tubular net reabsorption by back-diffusion of creatinine during the neonatal period. Experimental evidence in piglets (29) and newborn rabbits (unpublished observations) indeed suggests that creatinine is not only filtered but also significantly reabsorbed by the immature kidney. Whether the same characteristics apply to immature infants is not known. These observations, however, clearly point to a possible drawback in the use of creatinine as a glomerular marker in VLBW infants.

With these limitations in mind, creatinine clearance can still be used as an index of GFR. In the present study, the maturation of creatinine followed a characteristic pattern similar to that observed by Svenningsen (14) and Fawer *et al.* (4) in their studies on the maturation of inulin clearance in newborn infants. Immediately after birth, a progressive increase in creatinine clearance was observed in all infants. This is in contrast with Arant's claim (2) that creatinine clearance does not rise postnatally until the 34th conceptional wk is attained. Although creatinine clearance increased in all groups in the first 3 wk of life, the velocity was significantly different among newborn infants. The slope of maturation was steeper in the most mature infants. This is in agreement with the findings of Aperia *et al.* (1) but is in contrast with Svenningsen's studies (14) as well as our own previous study (4). It should be noted that the two latter studies were based on inulin clearance, whereas the former was based on creatinine clearance. Whether the drawbacks associated with creatinine, as described above, account for the discrepancy remains to be demonstrated.

In our studies, creatinine clearance correlated well with mean blood pressure. This is in agreement with our previous finding (4) and has also been observed by others in experimental studies in animals (31). The increase in systemic blood pressure that occurs during postnatal maturation could well result in an increase in glomerular flow and transglomerular pressure in premature neonates whose renal autoregulation may still not be totally efficient.

The present results confirm the concept that birth is a potent stimulus to the development of GFR. From a clinical point of view, the rapid maturation of GFR indicates that the filtration rate must be kept in mind when prescribing drugs or fluids. To avoid the accumulation of drugs excreted mainly by glomerular filtration (aminoglucosides, digoxin, vancomycin), drug dosage has to be adapted to the anticipated level of GFR. When necessary, creatinine clearance is a clinical useful measurement.

Sodium handling. It has been claimed that premature neonates have difficulties in maintaining sodium balance on a standard sodium intake of 1–2 mmol/kg/d. This phenomenon has been ascribed to urinary losses of sodium by very premature neonates and to a lesser extent to poor intestinal absorption of sodium (32). These losses decrease with increasing gestational and postnatal age. Inability of the preterm kidney to retain sodium has been attributed to deficient proximal reabsorption and to the incapacity of the distal tubule to cope with the delivery of an increased fractional load of sodium despite high serum aldosterone levels (33). In tiny premature infants, fractional sodium excretion has been shown to attain 5 to 15%. Larger preterm infants have somewhat lower fractional excretion rates, amounting to 1–5% (18).

Our results clearly show that term neonates are able to maintain sodium balance when administered 1–2 mmol/kg/d of sodium during the first weeks of life. In preterm neonates, the fractional excretion of sodium that we recorded was not higher than 2.2%, demonstrating that these infants were already able to maintain sodium balance when given sodium intakes of 1–2 mmol/kg/d. Only in the group of neonates with BW below 1500 g did the sodium plasma concentration transiently decrease during the second postnatal week. Our findings suggest that the high fractional excretion rates reported previously (15) are not due to tubular immaturity but most probably are iatrogenic in nature. Administering quantities of fluid or sodium that are too large could result in high fractional excretion rates.

The present data confirm those of Shaffer *et al.* (34) and indicate that sodium balance can be well maintained even in the most premature infants (16) provided that a minimum of 1–2 mmol/kg/d of sodium is given for the first 2–3

wk of life. This corresponds to the time when the premature infant must get rid of a large volume of extracellular fluid. After the third week of life, when the excess extracellular fluid has been excreted, sodium intake must be increased to provide enough salt for growth. Sodium intakes of 2–3 mmol/kg/d may then be needed.

Our finding that sodium balance is well maintained in premature infants given relatively low sodium intakes of 1–2 mmol/kg/d is important. Indeed, the wrong concept that premature babies are always salt losers has led to the inappropriate prescription of large amounts of salt supplements, sometimes reaching 5 mmol/kg/d. Inappropriate expansion of extracellular volume by elevated intakes of salt and water in premature babies may have severe consequences that include a patent ductus arteriosus, cardiac failure, necrotizing enterocolitis, intracranial hemorrhage, and bronchopulmonary dysplasia (35).

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