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Sodium homeostasis in term and preterm neonates

I Renal aspects

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SUMMARY Eighty five 24 hour sodium balance studies and creatinine clearance measurements were performed in 70 infants of gestational age 27–40 weeks and postnatal age 3–68 days. The kidney's capacity to regulate sodium excretion was a function of conceptional age (the sum of gestational age and postnatal age) and an independent effect of postnatal age was also observed—extrauterine existence increased the maturation of this function. The sodium balance was negative in 100% of infants of <30 weeks' gestation, in 70% at 30–32 weeks, in 46% at 33–35 weeks, and in 0% of >36 weeks, and the incidence of hyponatraemia closely paralleled that of negative sodium balance. Despite a low glomerular filtration rate (GFR) urinary sodium losses were highest in the most immature babies but fractional sodium excretion (FENa) was exponentially related to gestational age. An independent effect of postnatal age could be identified on FENa but not in GFR. These findings indicate that in infants of >33 weeks' gestation sodium conservation is possible because of a favourable balance between the GFR and tubular sodium reabsorption, but that below this age GFR exceeds the limited tubular sodium reabsorption capacity. The rapid increase in sodium reabsorption in the first few postnatal days seems to be due to maturation of distal tubular function, probably mediated by aldosterone. We suggest that the glomerulotubular imbalance for sodium is a consequence of the immaturity of the tubuloglomerular feedback mechanism, and we estimate that the minimum sodium requirement during the first 2 weeks of extrauterine life is 5 mmol (mEq)/kg/day for infants of <30 weeks' gestation and 4 mmol (mEq)/kg/day for those born between 30 and 35 weeks.

The improved survival rate of very low birthweight (VLBW) infants achieved in recent years has led to the recognition that the requirements for care of such babies differ from those appropriate for term infants. It has been reported[1–3] that VLBW infants frequently become hyponatraemic when fed on human milk or conventional 'humanised' infant formulae, while mature newborns have no difficulty maintaining normal electrolyte values on the same diet. The importance of 'late hyponatraemia'[1] in relation to somatic and central nervous system growth and development is unknown but it is unlikely to be beneficial and its cause and consequences are therefore important subjects for further investigation. We undertook the present study to clarify the physiological mechanisms underlying sodium homeostasis in the immature human newborn, and to relate these to other aspects of neonatal renal physiology; and to determine the optimum dietary sodium requirement for premature babies in relation to gestational and postnatal age.

Patients

Seventy healthy newborn infants were studied in the nurseries and special care baby unit of this hospital. Their gestational ages ranged from 27 to 42 weeks, and birthweights from 800 to 4200 g. Gestational age was estimated from the mother's menstrual history and on physical assessment of the infant using the criteria of Dubowitz *et al.*[4] All the infants were in good condition at the time of the study and none required mechanical ventilation or other major procedures. Preterm infants, kept in their incubators throughout, were fed by nasogastric tube, and term babies were breast or bottle fed by their mothers on the obstetric wards and in the nurseries. Water and electrolyte administration followed the unit's routine feeding policy (Table).

Table *Routine fluid regimen given to babies during the study*

Day	*Preterm*	*Term*	*Small for dates*
1	65	65	100
2	80	80	110
3	90	90	120
4	100	105	140
5	120	120	150
6	140	130	160
7	175	145	170
8	200	150	200

The investigation was approved by the ethical committee of the hospital and informed consent was obtained from parents. A total of 100 studies was performed on or after the third postnatal day.

Methods

Balance studies. Each study lasted for 24 hours. The volume of all feeds was recorded and a sample of milk from the same batch was stored for subsequent analysis. The sodium and potassium content of any drugs or intravenous fluids given during the study was included. Twenty four hour urine collections were made by spontaneous voiding into Abbott urine bags, using the method of Tarlow.[5] A plastic tube was attached to the bag and continuous gentle suction was applied using a Robert's pump. Stools were collected on plastic sheets on which the babies rested and which were replaced immediately after each stool was passed: stools were frozen and stored for analysis. A heparinised blood sample (0·8 ml) was collected by heelprick at the middle of the 24 hour period.

Laboratory methods. Creatinine was estimated in urine and plasma by a kinetic modification of the alkaline picrate method[6] using a modified LKB automatic analyser. Sodium and potassium concentrations in plasma and urine were measured on an IL flame photometer. Stools were pooled for each 24 hour study period and transferred to a weighed dry container in which they were homogenised using a Volter mixer. 1 g of homogenate was placed in a glass tube to which 1 ml concentrated nitric acid was added. After thorough mixing the tubes were heated at 100°C and stirred intermittently until the solution was completely clear. The samples were then diluted and flame photometry performed. Duplicate 1 ml milk samples were cleared in the same way before flame photometry.

Statistical methods. Data were analysed using Student's *t* test and linear and exponential correlation and regression.

Results

The term conceptional age is used throughout to mean the sum of gestational age and postnatal age at the time of each study. Twenty-four hour creatinine clearance increased exponentially with conceptional age, expressed both in absolute terms and after correction for body surface area (Fig. 1). The relation between conceptional age and fractional sodium excretion (FENa) is shown plotted semi-logarithmically in Fig. 2.

We tried to distinguish between the effects of conceptional age and postnatal age on the maturation of glomerular filtration rate and tubular sodium reabsorption by dividing the observations into 5 groups according to postnatal age: the conceptional ages did not differ appreciably between any 2 of the groups (Fig. 3). The relation between GFR and conceptional age in babies aged 5–6 days and 26–28 days is shown in more detail in Fig. 4. The maturation of GFR and sodium reabsorption were compared directly by plotting them on linear axes against conceptional age (Fig. 5).

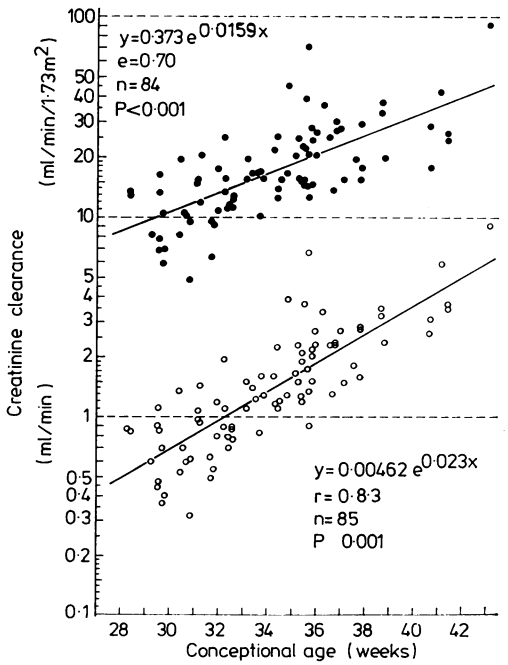

Fig. 1 *Creatinine clearance, corrected (closed circles) and uncorrected (open circles) for body surface area, plotted against conceptional age. In this and subsequent figures the regression statistics were calculated from x (conceptional age) expressed in days, although the axis is marked in weeks for convenience.*

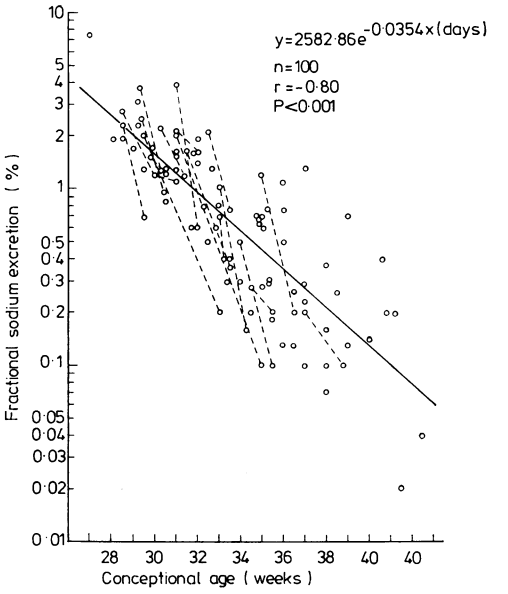

Fig. 2 *Fractional sodium excretion, expressed as percentage of filtered load, against conceptional age. The solid line is the calculated regression line; broken lines connect studies performed on the same infants on different days.*

The results of the sodium and potassium balance studies, in which net balance is plotted against postnatal age for 4 groups born at different gestational ages, are presented in Figs. 6 and 7. Plasma sodium concentrations below 130 mmol (mEq)/l were recorded on at least 1 occasion in 43% of babies born at 27–29 weeks, 13% of those born at 30–32 weeks, but in no infant born after 32 weeks: the lowest recorded value was 107 mmol (mEq)/l on the twelfth postnatal day in an infant born at 29 weeks. The urinary potassium:sodium (K^+:Na^+) ratio is shown plotted against conceptional age in Fig. 8. As in Fig. 2 the broken lines connect sequential studies performed on the same infants.

Discussion

The studies were performed after the first 3 days of extrauterine life, since during the first 1 or 2 days after the birth the GFR may reflect a transitional state of circulatory adaptation rather than the functional state of the kidney once this adaptation has taken place.[7] The data were not analysed according to birthweight because the functional maturation of the kidney has been shown to be age dependent rather than weight dependent.[8] Endogenous creatinine clearance was chosen over other

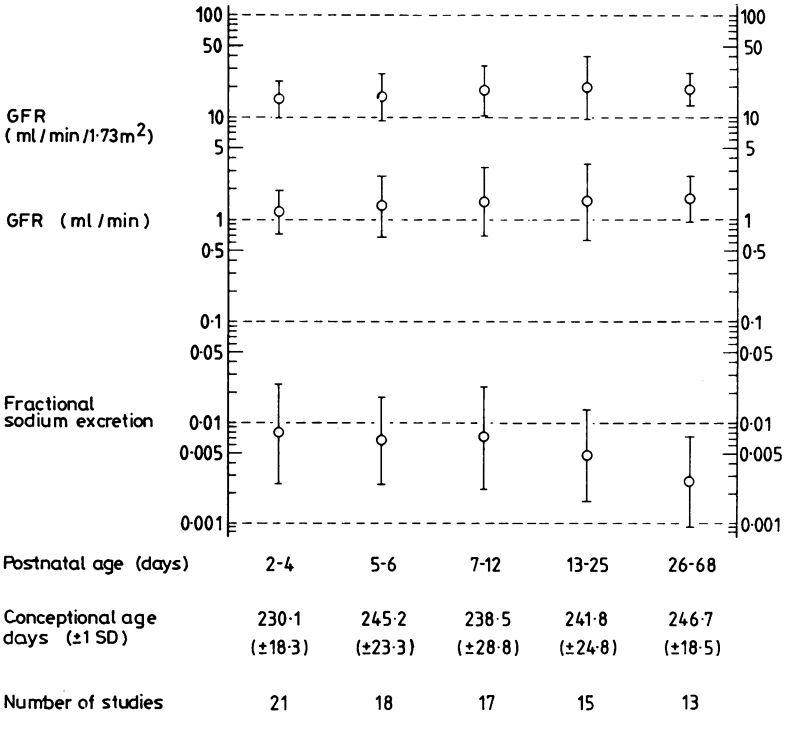

Fig. 3 *Glomerular filtration rate (GFR) (creatinine clearance), corrected and uncorrected for surface area, and fractional sodium excretion grouped by postnatal age at the time of study. The bars indicate ±1 logarithmic standard deviation. No 2 groups differed significantly with respect to conceptual age. Glomerular filtration rate is essentially identical in all groups; fractional sodium excretion (FENa) is significantly lower in infants of >25 days than in those of 2–12 days (P<0·001).*

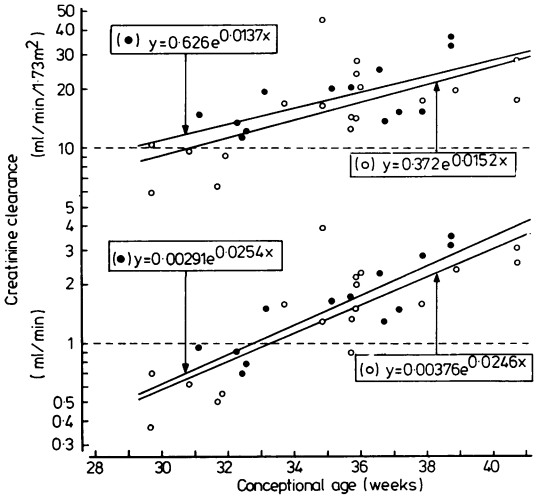

Fig. 4 *The relation between conceptional age and glomerular filtration rate in infants of 5–6 days' (open circles) and 26–68 days' (closed circles) postnatal age, corrected (top half) and uncorrected (bottom half) for body surface area. The regression lines do not differ significantly either in slope ($P > 0{\cdot}4$) or in vertical separation ($P > 0{\cdot}2$). Similar analyses performed on the other postnatal age groups (see Fig 3) showed that none of the groups differs from any other or from the overall regression line for the whole study group (Fig 1).*

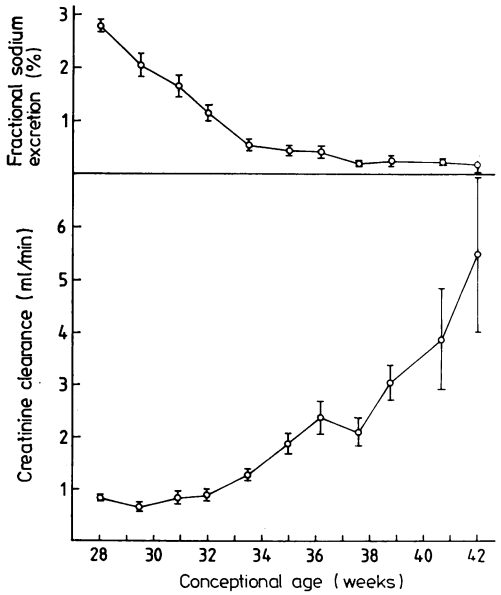

Fig. 5 *Fractional sodium excretion and glomerular filtration rate (mean ± 1 SEM) against conceptional age. Note the different relation between the 2 variables before and after 33 weeks' conceptional age.*

theoretically more accurate measures of GFR because of convenience and because it is a sufficiently reliable method in this age group.[9–11] The GFR, both absolute and corrected for surface area, rose with conceptional age and the relation was exponential rather than linear,[9] which indicates increasingly rapid glomerular functional maturation with age.[8 12–14] The failure of Guignard *et al.*[15] to show such a relation was probably due to lack of data from babies of <35 weeks' gestation. Our finding that GFR is the same in babies of similar conceptional ages but different postnatal ages (Figs. 3 and 4) agrees with the results of Fawer *et al.*[16] and indicates that after the first few days postnatal age per se has little or no influence on GFR, which increases in a 'programmed' fashion according to absolute developmental age. Aperia *et al.*[9] showed that GFR increased between 1 and 5 weeks of age at approximately the same rate in term and preterm infants, but that during the first week it rose more rapidly in term babies. Svenningsen[14] reported similar findings, although the effect of postnatal age was not examined in detail beyond the first week. It seems likely that these very early differences between preterm and term infants reflect differences in the rapidity with which the circulatory alterations are made at delivery. After this period each infant finds its own predetermined 'track'—a function of conceptional age, along which subsequent development proceeds. This implies further that intrauterine and extrauterine maturation of glomerular function proceeds at the same pace.[17]

The non-linearity of the increase in GFR supports the impression that several mechanisms contribute to the developmental changes in GFR. Although glomerulogenesis continues until 34 weeks' gestation,[18] the number of glomeruli is unlikely to be a limiting factor since most are not functioning at birth even in term infants. The major factor is probably increasing renal blood flow and glomerular perfusion[19 20] secondary to rising renal arterial pressure and falling renal vascular resistance, but changes in glomerular permeability to water[21] and glomerular surface area[22] may also contribute.

Our finding of high urinary sodium excretion rates in preterm infants agrees with reports from many centres.[3 8 23–28] Since GFR is lower in preterm than in term infants the higher sodium excretion rates seen in the former must be attributed to lower tubular reabsorption of the ion.[28] If GFR and FENa, representing glomerular and tubular function respectively, are plotted against conceptional age on the same time axis (Fig. 4) it is apparent that above 33 weeks salt reabsorption is efficient despite the

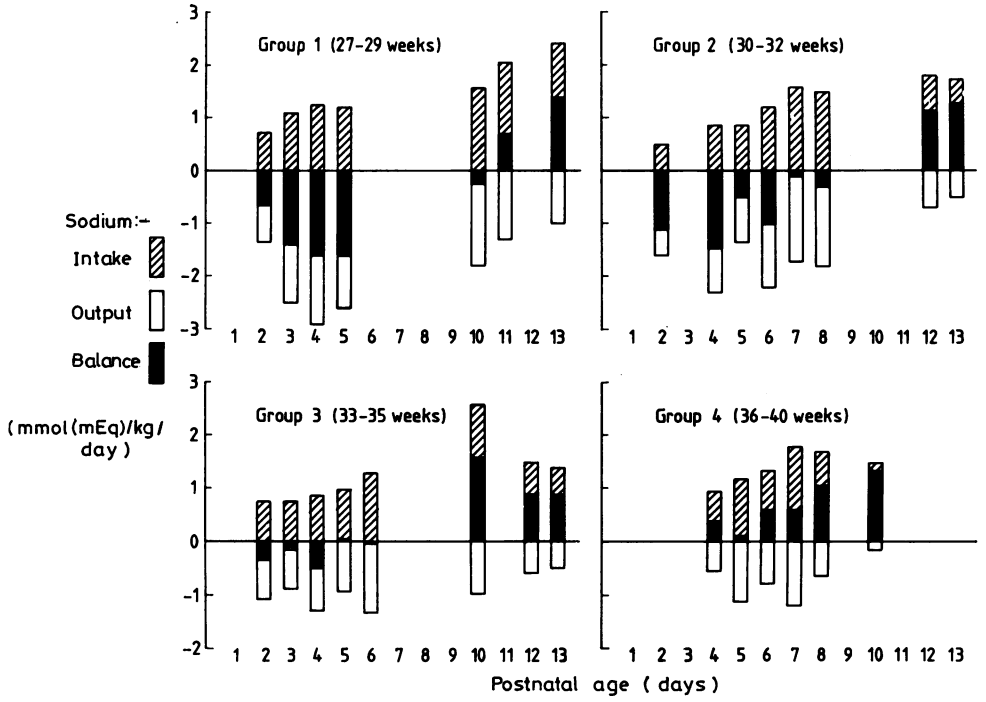

Fig. 6 *The relation between postnatal age and sodium balance in infants born at 27–29 weeks', 30–32 weeks', 33–35 weeks', and 36–40 weeks' gestation.*

rapidly increasing GFR. Before this age salt wasting occurs, implying that in the more mature infants there is effective coupling between glomerular and tubular function. The fact that proximal tubular reabsorptive capacity in very premature infants lags behind filtration rate[8] suggests that the mechanism that will later ensure glomerulotubular balance is not yet functionally mature. We agree with Aperia *et al.*[9] that this is likely to be due to failure of tubuloglomerular feedback at the macula densa.

Our findings give no insight into the specific site of inadequate sodium reabsorption in immature babies. Sulyok *et al.*[29] suggested that distal tubular function increases rapidly in this respect during the first 2 postnatal weeks, but since these results were not obtained during maximal water diuresis there is doubt about the reliability of this conclusion. We have shown an accelerating effect of extrauterine existence (postnatal age) on sodium reabsorption but not on GFR (Fig. 3). This conclusion is further supported by examination of Fig. 2, in which the average slope of the broken lines connecting sequential studies on the same infants is clearly steeper than that of the overall relation. It is tempting to suggest that this is related to the increase in activity of the renin-angiotensin-aldosterone system that has been shown to occur shortly after birth and correlates well with urinary sodium excretion in 1 week old infants.[30]

We did not estimate plasma aldosterone concentrations, but plasma and urinary aldosterone values are high in both premature and term babies.[24 28 31] The action of aldosterone on the mature distal tubule causes an increase in sodium reabsorption and potassium secretion and thus the urinary potassium:sodium ratio is an index of aldosterone dependent distal tubular activity.[32] This ratio was low in the most immature infants, rising steadily with increasing conceptional age (Fig. 8). This confirms the results of Aperia *et al.*,[28] who also found that the ratio showed no correlation with aldosterone excretion rate in very immature babies. The most likely explanation of these findings is that the responsiveness of the tubule to aldosterone, at first very low, rises progressively with maturation, and that this maturation is accelerated after birth. The positive balance for potassium (Fig. 5) seen even in the most immature infants with marked sodium wasting is further evidence of resistance to the action of the hormone.

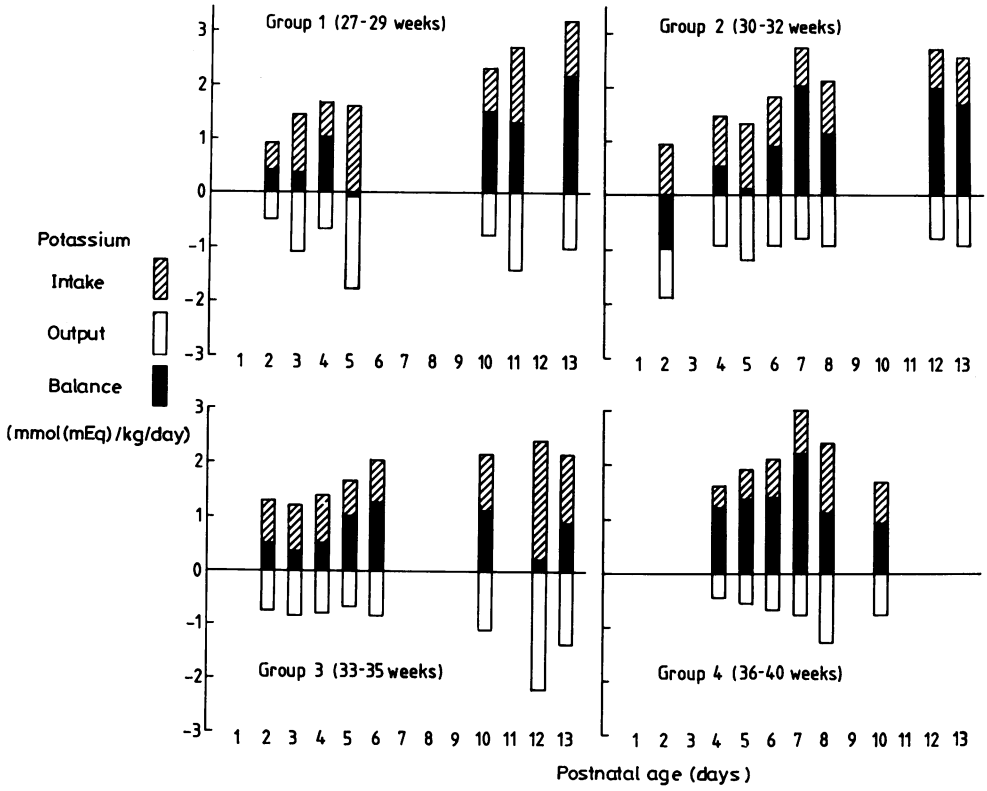

Fig. 7 *The relation between postnatal age and potassium balance; groups as in Fig 6.*

Unresponsiveness to aldosterone might be explained in several ways. The immature tubule may lack receptors for the hormone, an antagonist to its action may be present, or the transporting enzyme system (Na^+–K^+ ATPase) may be deficient. The first 2 explanations are conjectural, but there may be evidence to support the third. Schmidt and Horster[33] showed activity of the enzyme to be low in all segments of the newborn rabbit tubule. In rats there is increased enzyme activity throughout fetal life, although an appreciable postnatal rise has also been shown.[34 35]

Sodium balance was most strongly negative in the least mature infants but with increasing maturity changed to positive as a result of declining output (input changed little). These results are qualitatively and quantitatively similar to those reported by Sulyok,[30] but the larger negative sodium balance described by Engelke *et al.*[27] probably reflects the inclusion of some very sick babies in their study. Positive balance was achieved in the least mature infants (27–29 weeks' gestation) by the end of the second postnatal week, in those of 33–35 weeks by the middle of the first postnatal week, and in those of 36 weeks and over before the third day of age (when our study began). Thus although the most prematurely born babies achieve positive balance at a lower conceptual age than the more mature ones, they require a longer postnatal period to adjust. Here again our results are in general agreement with those of Sulyok[23] and Honour *et al.*[24]

Preterm infants fed on conventional artificial formulas or pooled human milk receive insufficient sodium to compensate for high urinary losses, leading to a high incidence of hyponatraemia. Indeed the sodium intake provided (1–2 mmol (mEq)/kg/day) is even less than the calculated intrauterine sodium accretion rate required for normal fetal growth.[36] A sufficient intake to prevent hyponatraemia should be provided and this may be achieved by giving a salt supplement or special high sodium formulas in the early postnatal period. An estimate of the minimum dietary requirement for sodium may be calculated by

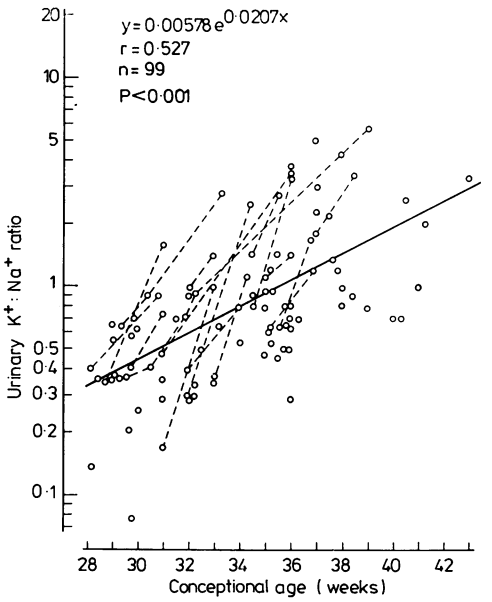

Fig. 8 *The relation between urinary sodium:potassium (Na^+:K^+) ratio and conceptional age. The solid line is the calculated regression line: broken lines connect studies performed on the same infants on different days.*

adding measured urinary and faecal losses to the intrauterine sodium accretion rate. Thus we suggest that infants born before 30 weeks' gestation should receive at least 5 mmol (mEq)/kg/day, and those of 30–35 weeks 4 mmol (mEq)/kg/day, during the first 2 postnatal weeks. Since all the infants studied achieved positive external sodium balance by the end of the second postnatal week on human milk or SMA, there appears to be no need to extend supplements beyond this.

We thank Sister Barbara Nichol and the nursing staff of the special care baby unit, Guy's Hospital, for invaluable assistance and support; Miss Ann Chapman for typing the manuscript.

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Fifty years ago

Ketogenic diet in the treatment of pyuria in childhood

J BASIL RENNIE (*Glasgow*)

In October 1931, Helmholz published the results of the treatment of pyuria in children by means of the ketogenic diet. This form of treatment was suggested by the observation that the urine of a patient being treated for epilepsy by ketogenic diet remained free of bacterial cloudiness after being kept for a week.

Summary: (1) Six cases of chronic pyogenic infection of the urinary tract were treated with ketogenic diet. (2) At the end of treatment the urine was sterile in 4 cases and growth on culture scanty in a 5th, but 3 relapsed in three weeks. The 6th case showed no change in the condition. (3) In the 2 cases who were permanently cured the duration of the disease was short and no abnormality of the urinary tract was observed. In each of the 4 cases in which treatment failed abnormality of the urinary tract was demonstrated by pyelography. (4) It would appear that ketogenic diet is of little value as a curative agent in pyuria associated with abnormality of the urinary tract.

Archives of Disease in Childhood 1933; **8:** 47–50.

(Brilliantly simple observation and action by Helmholz, overtaken 5 years later by the advent of sulphanilamide. Rennie continued his interest in renal disorders and was one of the first to differentiate idiopathic nephrotic syndrome of childhood from other more serious variants: he became a physician in Glasgow. PRE).