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Fractional excretion of uric acid in infancy and childhood

Index of tubular maturation

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Passwell, J. H., Modan, M., Brish, M., Orda, S., and Boichis, H. (1974). *Archives of Disease in Childhood*, **49**, 878. **Fractional excretion of uric acid in infancy and childhood: index of tubular maturation.** Normal newborns had a low glomerular filtration rate measured by creatinine clearance which progressively increased to reach adult levels by one year of age when corrected for surface area. There was also an increased fractional excretion of uric acid (34·6% ±11·2 SD). Progressive maturation of this tubular function was observed within the first year of life. Thereafter, stable levels approaching adult levels of excretion were maintained. Linear regression functions of log-transformed values of fractional excretion of uric acid by weight were fitted separately to the newborns, infants <1 year, and children aged 1 to 7 years. The 3 groups were found to constitute three distinct populations with regard to both the slope of the regression lines and the scatter of values about the line, which decreased significantly from the youngest to the oldest group. In low birthweight infants both glomerular and tubular maturation, as evidenced by these parameters, were related to age rather than to weight.

It is suggested that the large urinary uric acid load excreted in the first days of life is facilitated by the concomitant deficiency of acidification and concentration of urine.

Pink stained diapers due to urate deposition is a common occurrence in the newborn nursery. The presence of large amounts of urates in the renal tissue of neonates as 'urate infarcts' is also a well known incidental finding at necropsy. These two facts were impressed upon us by a routine survey in newborns, where large amounts of uric acid crystals were found in the urinary sediment. Accordingly, we undertook this study to investigate the excretion of uric acid by the kidney of the normal newborn and the progressive maturation of this function during the first year of life.

Material and methods

Five groups of children were studied. (1) An unselected group of 16 normal newborns; (2) 24 normal infants up to the age of one year; (3) 15 children aged 1–7 years; (4) 4 low birthweight newborns aged <8 days; (5) 4 low birthweight infants aged 16–74 days.

Male infants predominated because of the difficulty of collecting urinary specimens in the females. No sex differences were found in the various tests of renal function. All the newborn infants were products of normal pregnancies and were born with Apgar scores of 10. Informed consent was obtained for all the studies.

Renal studies. Disposable urine collectors were used. The infants were under constant supervision throughout by a special nurse in order to assure complete urine collections. Collections were started 72 hours after birth and the first urine was discarded. Collection thereafter proceeded for 24 hours in newborns. The end point was taken as the last time urine was passed as noted by the special nurse. This last fresh specimen was used for *p*H examination (*p*H meter 29 Radiometer) and routine urine analysis. In older infants and in children, at least 3 complete timed specimens were collected for clearance calculations. Venous blood for blood chemistry was withdrawn at the end of the collections.

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TABLE I

Range of renal function parameters in 5 groups of newborns

Study group	Age	No. studied	Creatinine clearance (ml/min)	Corrected creatinine clearance (ml/min per 1·73 m²)	Serum uric acid (mg/100 ml)	Urinary uric acid/urinary creatinine	Fractional excretion of uric acid (%)
Normal newborns	3–4 dy	16	1·4–5·5 (3·6±1·8)	12·6–43·0 (28·0±12·3)	1·7–5·2 (3·7±1·1)	0·8–2·9	20–59 (34·6±11·2)
Normal infants	4 dy–1 yr	24	7·4–29	52–100	2·6–5·0	0·7–3·2	13–26
Normal children	1–7 yr	15	20–60	70–122	3·1–5·0	0·9–1·9	11–17
Low birthweight newborns	<8 dy	4	1·8–2·8	13·5–31	1·2–2·8	0·9–1·3	43–57
Low birthweight infants	16–74 dy	4	3·8–7·6	40–50	1·5–3·8	1·3–1·6	28–34

Figures in parentheses are mean ± SD.

Osmolarity of the complete urine collection, and blood and urine creatinine levels were determined by standard laboratory procedures. The blood and urinary uric acid levels were determined by the method of Caraway (1955). The fractional excretion of uric acid is the percentage of the filtered uric acid not reabsorbed by the tubules. As uric acid is freely filtered by the glomerulus, this parameter was calculated from endogenous creatinine and uric acid clearance results.

Results

Routine urine analysis was normal in all the subjects. In Table I the parameters of renal function in the 5 groups are presented. The mean creatinine clearance of the newborn infants in the first week of life was 3·6 ml/min (±1·8 SD). After correction for surface area, the mean was 28·0 ml/min per 1·73 m² (±12·3 SD). Fig. 1 shows the creatinine clearance of the subjects by weight. When corrected for surface area, normal adult values were generally attained by one year of age. The mean serum uric acid level of the newborn of 3·7 mg/100 ml (±1·1 SD) was lower than that of the normal adult (4·5–6 mg/100 ml). Similar values were obtained during the first year of life.

Fig. 2 shows the distribution of fractional excretion of uric acid by weight and group; a negative correlation of the fractional excretion with weight is apparent. Also, as the weight increases there is a striking decrease in the weight specific SD, i.e. the SD at any point on the weight scale. A large scatter of the fractional excretion is noted among the newborns, a medium scatter in infants weighing up to 11 kg (approximately coinciding with the age of one year), and an extremely small scatter in the older children.

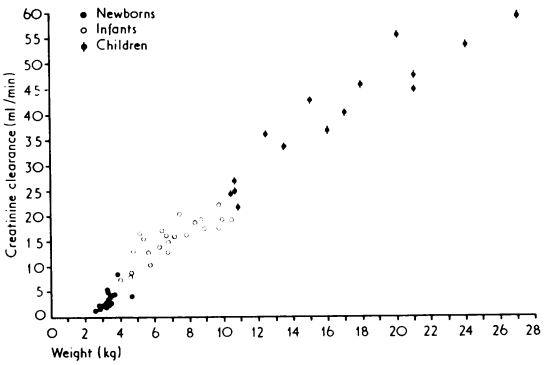

FIG. 1.—*Creatinine clearance (ml/min) of study subjects (excluding the 8 low birthweight subjects) by weight.*

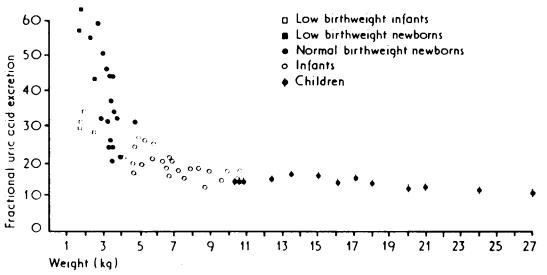

FIG. 2.—*Fractional excretion of uric acid of all study subjects by weight.*

Since the correlation with weight was curvilinear, these trends were analysed by log transformation of the fractional excretion values. The results are presented in Table II and Fig. 3. The analysis shows that the newborns, the infants, and the children aged 1–7 years constitute three distinct populations with regard to the correlation of these variables. When a linear equation is fitted to the data these populations differ significantly by two parameters: (1) the slope of the line b, as shown by the fact that the 95% confidence intervals of the

TABLE II

Parameters of the regression functions of fractional excretion of uric acid on weight*

Parameters of regression function	Newborn†	4 dy–1 yr	1–7 yr
b (slope)	−0·332	−0·0684	−0·0174
95% confidence limits for b			
Lower limit	−0·167	−0·0369	−0·0089
Upper limit	−0·497	−0·0999	−0·0259
a (intercept)	4·62	3·39	2·94
Sy.x (residual SD about regression line of log-transformed data)	0·257	0·139	0·078
Sw (weight specific SD of nontransformed fractional excretion of uric acid)	11·3	2·8	1·2

*$\text{Log}_e\, y = a + bx$ or $y = e^{(a + bx)}$, where y = fractional excretion of uric acid; x = weight (kg).

†Since the values of the 4 low birthweight newborns fell close to the line fitted to the normal newborns (Fig. 4), data for all newborns were pooled for the calculation of parameters of regression function given here.

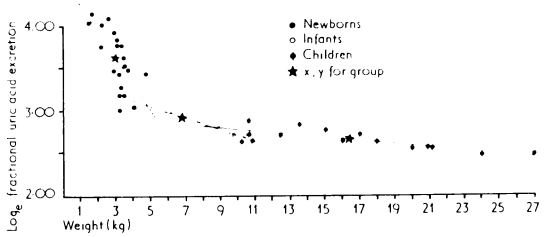

FIG. 3.—*Linear regression lines fitted to log transformed fractional excretion of uric acid by weight, of newborns (includes the 4 low birthweight newborns), infants, and children aged 1–7 years.*

three slopes do not overlap; (2) the residual SD about the regression lines (Sy.x.), i.e. the weight specific SD of the fractional excretion.

The fractional excretion of uric acid of 4 premature newborn babies fell close to the line fitted to the newborns of normal birthweight, and results for low birthweight infants, who were older, fell close to the line fitted to the data of infants, even though their weight was still under 2·50 kg (Fig. 4). This correspondence with age rather than weight was observed in other aspects of renal function in infants of low birthweight (Table I).

The uric acid creatinine ratio showed no meaningful pattern during the first year of life (Table I). The *p*H of the urine of the newborns ranged from 5·7–6·2, while older infants were capable of normal acidification of their urine (*p*H 5·5). The mean osmolarity of urine of the newborn was low, 310 mOsm/kg.

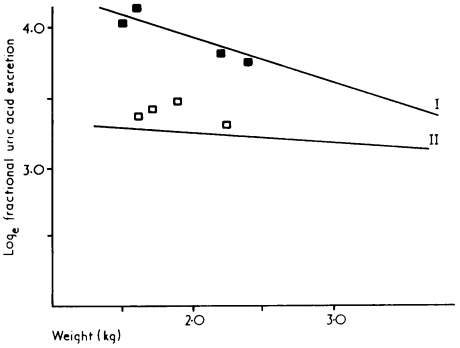

FIG. 4.—*Correspondence of values of low birthweight newborns and low birthweight infants, to extrapolated regression lines of fractional excretion of uric acid by weight, of the respective groups of normal birthweight study subjects. I, Extrapolated regression line of normal birthweight newborn* (■). *II, Extrapolated regression line of low birthweight infants* (□).

Discussion

Studies of the various renal functions in infants have enabled paediatricians to understand their limited capacity to maintain homoeostasis. The neonatal glomerular filtration rate is 20% of the normal adult value when corrected for surface area, and the data of our study confirm those in published reports. From the limited data in our low birthweight infants, this function was related more to their age than to their weight (Table I) (Barnett *et al.*, 1948; Barnett, 1950). Tubular function in infancy is at an even lower level than that of the glomerulus (Edelmann and Spitzer, 1969). This is manifest by a lowered renal threshold of bicarbonate (Edelmann *et al.*, 1967), and amino acids (Brodehl and Gellissen, 1968), a decreased maximal tubular excretory capacity of glucose (Tudvad, 1949), and a decreased tubular reabsorption of phosphate (McCrory *et al.*, 1952).

Several morphological changes are thought to be responsible for this (Edelmann and Spitzer, 1969). Fetterman *et al.* (1965) showed that the infant's tubules have marked heterogeneity of length and width. Thus, there are many tubules which are not only comparatively shorter, but also wider than the mature tubules. The small surface area of these short and wide tubules relative to their volume results in an overall poor reabsorption. Also, the ratio of glomerular to tubular surface area is large in infancy, and it decreases with age due to the proximal tubules growing faster than the glomeruli. In addition, the ratio of renal size to body surface

area, which is relatively small in infancy, becomes constant from about the age of two years onwards.

Uric acid is the end product of purine metabolism and, as far as is known in man, is a pure waste product. In body fluids at *p*H 7·4 uric acid exists predominantly as sodium monourate, which is readily converted to uric acid at lower *p*H levels. While uric acid is freely filtered through the glomeruli, only about 10% of the filtered uric acid is excreted in the urine of the normal adult. This is due to the reabsorption of the filtered uric acid, mainly by the proximal portion of the nephron (Seegmiller, Laster, and Howell, 1963).

The serum uric acid of the newborn may be increased in the first day of life, especially after a prolonged labour or perinatal complications, and then decreases to reach stable levels by the third day of life (Marks *et al.*, 1968). The serum uric acid levels in our newborn infants were not raised, since they were taken at 72 hours after birth. However, the increased fractional urinary uric acid excretion at this age indicates that the newborn has a far larger uric acid load to cope with than older children. The source of this uric acid load is probably to be found in the physiological fall of the leucocyte count seen at this age (Wharton *et al.*, 1971). The increased fractional excretion of uric acid in infancy is a further example of immature function of the proximal tubules, and is probably due to lack of reabsorption, rather than to an increased secretion.

As a result of the increased uric acid load and the decreased reabsorption of uric acid in the first days of life, the urine uric acid/creatinine ratio is increased. Subsequently, as the serum uric acid falls, there is a concomitant decrease in the urinary uric acid/creatinine ratio (Kaufmann, Greene, and Seegmiller, 1968). It seems that this ratio would decrease further as the percentage of reabsorption of uric acid increased due to tubular maturation. However, we did not find any significant change in this ratio with age or weight in our study groups. Thus, while the urinary uric acid/creatinine ratio is of use for early detection of the Lesch-Nyhan syndrome (Kaufmann *et al.*, 1968), it is not sufficiently sensitive to detect the normal maturational changes in the reabsorption of uric acid.

We have shown that the fractional excretion of uric acid is inversely correlated with the weight of the infant. However, the varying slopes of the regression lines which were observed in our three groups of newborns, infants, and children over the age of one year, suggest that the fractional excretion of uric acid is a function of age as well as of weight. The fact that this parameter virtually reached adult values at the age of one year is in accord with the other manifestations of the morphological and functional maturation of the kidney.

While the data on our low birthweight infants are limited, they support the contention that the age of the infant is also an important factor in determining the tubular maturation. This is indicated by the fact that the correlation with weight of the low birthweight newborn resembles the correlation in the normal newborn, while in the older low birthweight infants it resembles the correlation in older normal infants (Fig. 4). Several additional factors including fluid intake and diet are probably important in determining the rate of maturation of tubular function.

The low reabsorption of the filtered solute by the proximal tubules is partly explained by the different morphology of the nephron in infancy. In addition, functional inter-relations of the reabsorption of various solutes are important. The reabsorption of uric acid, sodium, and glucose are inter-related (Steele, 1971). Studies in puppies have shown that when a stimulus for sodium reabsorption is produced, the bicarbonate threshold increases (Moore *et al.*, 1972). It is likely that these functional inter-relations of the reabsorption of the various solutes are affected by the maturational process of the kidney in infancy.

The paradoxical reabsorption of uric acid, a waste product, provides a mechanism which probably protects the kidney from the harmful effects of an increased uric acid load. Firstly, the formation of uric acid crystals within the tubules where the *p*H becomes progressively more acid is prevented. Secondly, in the medulla, where sodium concentration is high, precipitation of sodium urate with the resultant inflammatory response it elicits is avoided (Epstein and Pigeon, 1964). An example where this mechanism breaks down may be the instances of uric acid nephropathy which occur in lymphoproliferative disorders when the kidney has to cope with a large uric acid load (Passwell, Boichis, and Cohen, 1970).

Particularly in the first 2 weeks of life, the infant's capacity to concentrate urine and his ability to lower the urinary *p*H and to excrete hydrogen ion as titratable acid and ammonia is also limited (Edelmann and Spitzer, 1969). The relatively alkaline *p*H and low urine osmolarity of our newborn infants reflect these deficiencies and are consistent with the findings of other authors. Thus, it seems that the excretion of the uric acid in the newborn is facilitated by the concomitant limited ability to concentrate and acidify the urine at this age.

References

Barnett, H. L. (1950). Kidney function in young infants. *Pediatrics*, **5**, 171.

Barnett, H. L., Hare, K., McNamara, H., and Hare, R. S. (1948). Measurement of glomerulər filtration rate in premature infants. *Journal of Clinical Investigation*, **27**, 691.

Brodehl, J., and Gellissen, K. (1968). Endogenous renal transport of free amino acids in infancy and childhood. *Pediatrics*, **42**, 395.

Caraway, W. T. (1955). Determination of uric acid in serum by a carbonate method. *American Journal of Clinical Pathology*, **25**, 840.

Edelmann, C. M., Jr., Rodriguez-Soriano, J., Boichis, H., Gruskin, A. B., and Acosta, M. I. (1967). Renal bicarbonate reabsorption and hydrogen ion excretion in normal infants. *Journal of Clinical Investigation*, **46**, 1309.

Edelmann, C. M., Jr., and Spitzer, A. (1969). The maturing kidney. A modern view of well-balanced infants with imbalanced nephrons. *Journal of Pediatrics*, **75**, 509.

Epstein, F. H., and Pigeon, G. (1964). Experimental urate nephropathy: studies of the distribution of urate in renal tissue. *Nephron*, **1**, 144.

Fetterman, G. H., Shuplock, N. A., Phillipp, F. J., and Gregg, H. S. (1965). The growth and maturation of human glomeruli and proximal convolutions from term to adulthood: studies by microdissection. *Pediatrics*, **35**, 601.

Kaufmann, J. M., Greene, M. L., and Seegmiller, J. E. (1968). Urine uric acid to creatinine ratio—a screening test for inherited disorders of purine metabolism. *Journal of Pediatrics*, **73**, 583.

McCrory, W. W., Forman, C. W., McNamara, H., and Barnett, H. L. (1952). Renal excretion of inorganic phosphate in newborn infants. *Journal of Clinical Investigation*, **31**, 357.

Marks, J. F., Kay, J., Baum, J., and Curry, L. (1968). Uric acid levels in full-term and low-birth-weight infants. *Journal of Pediatrics*, **73**, 609.

Moore, E. S., Fine, B. P., Satrasook, S. S., Vergel, Z. M., and Edelmann, C. M., Jr. (1972). Renal reabsorption of bicarbonate in puppies: effect of extracellular volume contraction on the renal threshold for bicarbonate. *Pediatric Research*, **6**, 859.

Passwell, J., Boichis, H., and Cohen, B. E. (1970). Hyperuricemic nephropathy: report of a case of lymphoblastic lymphosarcoma. *American Journal of Diseases of Children*, **120**, 154.

Seegmiller, J. E., Laster, L., and Howell, R. R. (1963). Biochemistry of uric acid and its relation to gout. *New England Journal of Medicine*, **268**, 712.

Steele, T. H. (1971). Control of uric acid excretion. *New England Journal of Medicine*, **284**, 1193.

Tudvad, F. (1949). Sugar reabsorption in prematures and full term babies. *Scandinavian Journal of Clinical and Laboratory Investigation*, **1**, 281.

Wharton, B. A., Bassi, U., Gough, G., and Williams, A. (1971). Clinical value of plasma creatine kinase and uric acid levels during first week of life. *Archives of Disease in Childhood*, **46**, 356.

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