THE UREA CLEARANCE OF YOUNG PREMATURE AND FULL TERM INFANTS [1,2]

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In a previous study (1) of the nitrogen metabolism of premature infants, it was noted that edema developed in some infants when they were changed from diets of human milk to diets of cow's milk containing equivalent amounts of protein, fat, carbohydrate, and fluid. In subsequent studies of water and electrolyte exchange under similar dietary conditions (2), a lag in renal excretion of the extra sodium and chloride ingested in the cow's milk was found to accompany the large gain in weight. These observations suggested the present study to determine whether premature infants have a defect in kidney function. This seemed particularly desirable since the adequacy of renal function (3) presumably acts as a major determinant of minimal fluid requirements.

As a first approach to this problem, measurements were made of the 24-hour plasma urea clearance in a group of young prematurely born and full term infants. The results reported in this paper indicate that the urea clearance of premature infants is lower than that of full term infants of comparable postnatal age, and that in both groups the clearance is lower than that reported for older infants and adults. Moreover, the urea clearance of individual infants rose strikingly with increasing age. No relation was found to exist between urea clearance and urine flow for the group as a whole, and in each of 4 infants, augmentation of the urine flow from 25 to 100 per cent by increasing the fluid intake did not improve the urea clearance.

METHODS

Subjects

Fifteen healthy, male premature infants, ranging in age from 8 to 65 days and in weight from 1.6 to 3.4 kgm., were studied in 35 observations. Twelve observations were made in 9 male full term infants whose ages and weights ranged from 7 to 73 days, and from 2.8 to 4.9 kgm., respectively. All the infants were thriving at the time of study.

Diets

In all but one observation, the diets consisted of cow's milk [3] diluted with water and fortified in most instances with either cane sugar or dextrimaltose to provide an adequate caloric intake. In all but 4 observations (Tables II and III), the daily protein intake was high, *i.e.* from 4 to 6 grams per kgm. The daily fluid intake was within the customary range of 130 to 185 cc. per kgm. in all but 3 observations. All the infants received 10 or 20 drops daily of a vitamin A and D concentrate (percomorph oil); approximately half received daily supplements of 25 mgm. of ascorbic acid.

Urine and blood

Urine was collected (4), using toluol as a preservative, for carefully timed periods of approximately 24 hours. One-half to 1 cc. of venous or occasionally capillary blood was drawn into short tubes, containing either oxalate or heparin, at the beginning and end of the 24-hour period. Blood urea nitrogen was determined gasometrically, using the method of Van Slyke and Kugel (5). Urine urea and ammonia nitrogen were similarly determined and calculations of urea excretion made on the assumption that the ammonia appearing in the urine had been filtered through the glomeruli as urea. This was considered a fairer estimate of urea excretion (6) than the determination of urea alone since, in addition to the variable formation of ammonia from urea by the renal tubules, bacterial formation of ammonia in voided urine was not consistently prevented.[4]

The 24-hour clearance method used by Landis and his co-workers (7) is particularly suited to young infants for two reasons. Catheterization and washing out the bladder

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[2] Presented in part before the meeting of the Society for Pediatric Research, Atlantic City, N. J., May 7, 1941. (Am. J. Dis. Child., 1941, 62, 894.)

[3] The following preparations of cow's milk were used: evaporated or powdered whole milk, powdered half-skimmed milk (alacta), a powdered skimmed milk—olive oil preparation (olac), and a half-skimmed olac. The latter product was prepared specially by the Mead Johnson Co.

[4] Urinary ammonia averaged 14 per cent of the total urinary urea plus ammonia and was less than 20 per cent in 34 of 40 observations in which the partition was determined (Tables II and III).

to insure complete emptying may be omitted without introducing a large error, since the amount of urine retained by spontaneous incomplete voidings comprises only a relatively small fraction of the 24-hour urine flow (volume 75 to 400 cc. per 24 hours in these observations). Secondly, the feeding to these infants of their daily diets in 6 or 8 aliquots at 4 or 3 hour intervals tends to minimize fluctuations in blood urea (Table I).

TABLE I

Hourly variations in blood urea nitrogen

Hours* after feeding	Blood urea nitrogen							Average	Maximum deviation
	1	1½	2	2½	3	3½	4		
Premature	*mgm. per 100 cc.*								*per cent average*
T. R.......		23.7		27.1		23.8		24.9	9
J. S........	33.4		30.9		31.8		30.4	31.6	6
C. M.......		17.0		17.5				17.3	2
C. T.......	27.3		29.6	27.4				28.1	5
I. A........	25.9		26.1		24.0			25.3	8
Full term									
A. A........	20.4			20.9			20.1	20.5	2
F. M.......	19.1			17.9		18.4		18.5	3
W. C.......			20.1		20.7	20.8		20.5	2
T. T.......					27.4 31.2		29.8	29.5	7
J. R.......					26.9 28.3		27.8	27.7	3
K. K.......	17.5		22.0		16.1		17.5	18.3	20
C. A.......			17.9	19.3	19.8	19.9	19.9 18.5	19.2	7

* Infants were fed every 3 or 4 hours throughout the 24 hours, and blood was drawn at the stated intervals following meals.

For each of 5 premature and 7 full term infants, urea nitrogen was determined in 3 or 4 samples of blood taken from 1 to 4 hours following the same or a similar feeding at different times of the day. The maximum deviation in any one specimen was, for 11 of the 12 infants, between 2 and 9 per cent of the average. In 1 infant (K. K.) the maximum deviation in a single specimen was 20 per cent of the average, but omission of this determination would have changed the average blood urea by only 8 per cent. It is of interest that the blood urea nitrogen of this group of thriving infants fed high protein diets (see also Tables II and III) is considerably higher than the customary levels found in adults.

RESULTS

The detailed results of the observations on premature and full term infants are presented in Tables II and III, respectively, and a summary of the results in Table IV.

TABLE II

Urea clearance of prematurely born infants

Subject	Age	Weight	Surface area(a)	Urine		Blood urea nitrogen	Urea clearance cc. per minute	
				Volume	Urea and ammonia nitrogen(b)			
	days	*grams*	*sq. meter*	*cc. per minute*	*mgm. per 100 cc.*	*mgm. per 100 cc.*	*UV/B*	*per sq. meter*
F. L.	17	1600	0.131	0.112	54	5.4(c)	1.1	8.5
	65	3205	0.221	0.259	64	6.5(c)	2.5	11.5
R. K.	27	1800	0.143	0.052	859	26.4	1.7	11.8
	30	1915	0.150	0.096	464	23.2	1.8	11.9
H. A.	10	1890	0.149	0.131	314	23.9	1.7	11.4
	29	2520	0.184	0.183	464	22.5	3.8	20.7
	50	3630	0.243	0.254	371	19.8	4.8	19.8
W. B.	19	1930	0.151	0.132	350	23.5	2.0	13.2
	23	1990	0.155	0.139	286	22.1	1.8	11.6
	24	2010	0.156	0.133	342	20.8	2.2	14.1
	40	2710	0.195	0.110	437	17.6	2.7	13.8
	47	2970	0.209	0.174	461	20.2	4.0	19.1
E. D.	31	1953	0.152	0.064	830	21.9	2.4	15.8
A. G.	23	1970	0.153	0.106	346	19.9	1.8	11.8
	24	2040	0.158	0.127	283	21.1	1.7	10.8
	35	2445	0.180	0.135	370	19.0	2.6	14.4
B. G.	18	1985	0.154	0.126	200	31.0	1.6	10.5
	23	2170	0.165	0.140	392	25.7	2.1	12.7
	31	2510	0.184	0.173	334	19.3	3.0	16.3
P. A.	10	2125	0.162	0.116	429	26.1	1.9	11.7
	29	2750	0.197	0.195	547	32.7	3.3	16.8
	31	2800	0.200	0.249	449	31.2	3.6	17.9
	45	3410	0.232	0.242	523	27.1	4.7	20.3
J. S.	19	2160	0.164	0.106	434	23.2	2.0	12.2
J. C.	8	2200	0.167	0.133	347	22.4	2.1	12.6
	14	2360	0.176	0.141	99	5.2(c)	2.7	15.3
	43	3260	0.224	0.248	436	21.3	5.1	22.8
T. R.	21	2209	0.167	0.080	724	26.6	2.2	13.2
	49	3035	0.212	0.302	391	23.1	5.1	24.1
	58	3340	0.228	0.208	656	24.9	5.5	24.1
V. C.	8	2393	0.178	0.144	612	32.4	2.7	15.3
	10	2385	0.177	0.230	322	27.4	2.7	15.3
R. L.	27	2420	0.179	0.183	447	27.5	3.0	16.8
R. DeL.	32	2555	0.186	0.226	157	13.4	2.6	14.2
A. H.	23	2965	0.208	0.139	674	21.2	4.4	21.3

(a) Surface area for both premature and full term infants was calculated using the formula $5.188 \times wt.^{.75}$ (8).
(b) Urea plus ammonia nitrogen was approximately 90 per cent of the total urinary nitrogen.
(c) These infants received a low protein diet.

In Table IV, the observations have been divided into two groups according to postnatal age. For both groups, under and over 30 days of age, the clearance was lower in premature than in full term infants. The mean clearance for the whole group of premature infants was 15.3 cc. per sq. meter per minute, as compared with 21.0 cc. for the full term infants. Although the ranges overlap, the difference of 5.7 cc. between the mean clearances is almost five times the probable error

TABLE III

Urea clearance of full term infants

Subject	Age	Weight	Surface area	Urine: Volume	Urine: Urea and ammonia nitrogen	Blood urea nitrogen	Urea clearance cc. per minute	
	days	*grams*	*sq. meter*	*cc. per minute*	*mgm. per 100 cc.*	*mgm. per 100 cc.*	*UV/B*	*per sq. meter*
R. J.	30	2790	0.199	0.220	398	23.8	3.7	18.5
W. C.	7	3255	0.224	0.125	246	10.0*	3.1	13.8
	27	3700	0.246	0.146	648	20.5	4.6	18.7
J. R.	39	3730	0.248	0.229	660	27.8	5.4	21.7
W. D.	14	4163	0.269	0.136	741	17.0	5.9	22.0
K. K.	71	4200	0.271	0.136	1049	18.3	7.8	28.8
	73	4275	0.274	0.270	515	16.2	8.6	31.3
D. S.	59	4280	0.275	0.256	507	19.3	6.7	24.5
T. T.	27	4360	0.278	0.191	748	30.5	4.7	16.8
	41	4860	0.302	0.188	691	25.7	5.1	16.7
G. M.	54	4530	0.286	0.156	689	15.2	7.1	24.7
V. F.	23	4600	0.290	0.099	662	16.1	4.1	14.1

* This infant received a relatively low protein intake (3 grams per kgm.).

TABLE IV

Urea clearance of premature and full term infants. Summary of results

Postnatal age	Premature infants: Number of observations	Premature infants: Urea clearance Mean	Premature infants: Urea clearance Range	Full term infants: Number of observations	Full term infants: Urea clearance Mean	Full term infants: Urea clearance Range
		cc. per sq. meter per minute			*cc. per sq. meter per minute*	
Less than 30 days..	21	13.7	8.5–21.3	6	17.3	13.8–22.0
30 days and over...	14	17.6	11.5–24.1	6	24.6	16.7–31.3
Total...........	35	15.3* ± P.E. 0.47	8.5–24.1	12	21.0* ± P.E. 1.08	13.8–31.3

* Difference between means is 5.7 ± 1.18.

of the difference. The mean clearances for both groups of young infants (15 and 21 cc.) are considerably lower than the average clearance of 38 cc. per sq. meter per minute (range 23 to 55 cc.) found in older infants by Schoenthal (9), and the "standard" and "maximum" clearances of adults, 30 and 40 cc. per sq. meter per minute (10). Since, as will be shown later, the clearances in these young infants were "maximum" at the time of observation, *i.e.*, increasing the urine flow did not increase the clearance, there can be no doubt that young infants, both premature and full term, have a defect in urea clearance when compared with older infants and adults. Evidence confirming the existence of this defect in young infants has recently been published (11).

Effect of increasing size and postnatal age on urea clearance

The effect of increasing maturation as measured by increasing size and age on urea clearance is indicated in Figure 1, in which repeated observations on 8 premature and 2 full term infants are presented. The ages at the initial and final observations for each infant are also indicated. It is seen that a rise in clearance took place in each of the 8 premature and in 1 of the 2 full term infants as they grew larger and older. The figure also gives some measure of the variability in clearance between infants of similar size as well as age.

Infant F. L. (premature), who showed a low clearance at both 17 and 65 days of age, was the only infant on a low protein diet at the time of both observations. It has been reported (12) that under certain conditions low protein diets depress the urea clearance and this may have contributed to the persistently low findings for this infant. Further work is needed to elucidate this point.

TABLE V

Effect of increased urine flow on 24-hour urea clearance

Subject	Age	Weight	Fluid intake	Urine: Volume		Urine: Urea and ammonia nitrogen	Blood urea nitrogen	Urea clearance
	days	*grams*	*cc. per kgm.*	*cc. per minute*	*cc. per sq. meter per minute*	*mgm. per cent*	*mgm. per cent*	*cc. per sq. meter per minute*
R. K.	27	1800	111	0.05	0.36	859	26.4	11.8
	30	1915	146	0.10	0.64	464	23.2	11.9
V. C.	8	2393	133	0.14	0.81	612	32.4	15.3
	10	2385	218	0.23	1.30	323	27.4	15.3
P. A.	29	2750	145	0.20	0.99	547	32.7	16.6
	31	2800	186	0.25	1.25	449	31.2	17.9
K. K.	71	4200	136	0.14	0.50	1084	18.3	29.8
	73	4275	182	0.27	0.98	515	16.2	31.3

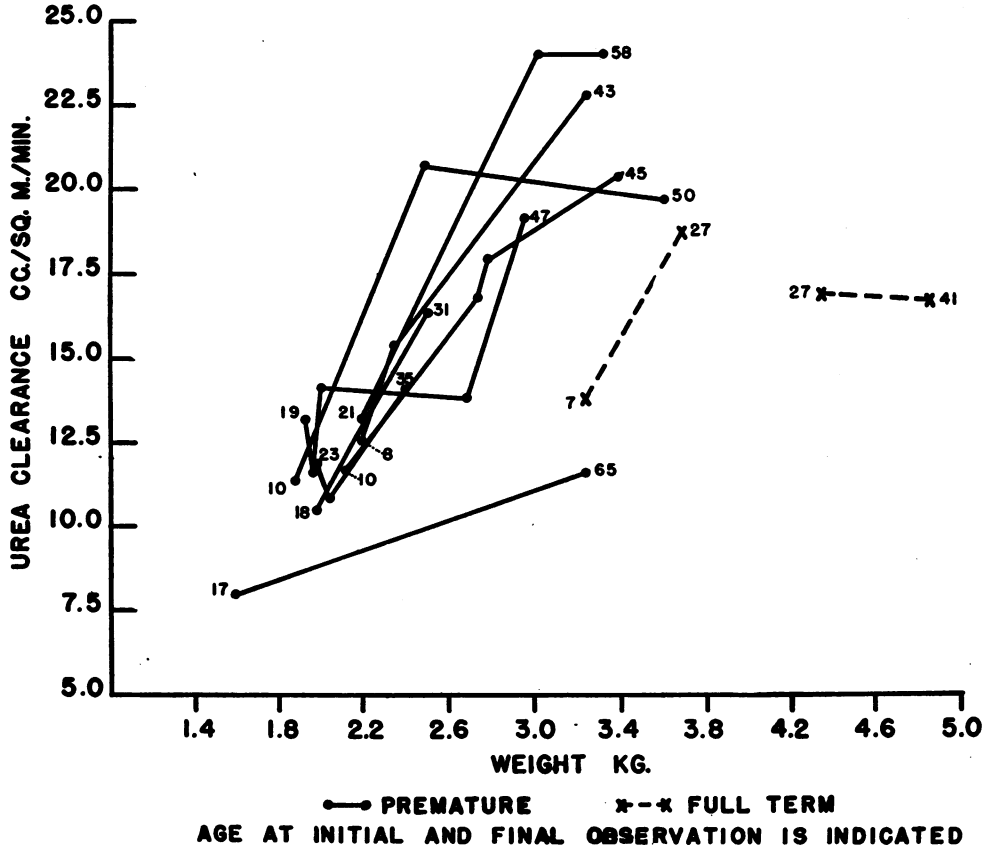

FIG. 1. THE RELATION OF INCREASING SIZE AND DAYS OF AGE TO UREA CLEARANCE IN INDIVIDUAL INFANTS

Effect of variations in urine flow on urea clearance

Because the urine flows for most of the infants were below the arbitrary "augmentation" limit for adults of approximately 0.9 to 1.2 cc. per sq. meter per minute (*i.e.* 1.5 to 2.0 cc. per minute), the effect of increasing the urine flow on the urea clearance was studied in 4 infants. In each of these infants, the urea clearance was determined at two levels of fluid intake, at least 24 hours of the altered intake elapsing before the second observation began. Increasing the fluid intake increased the initial urine flows of 0.4 to 1.0 cc. per sq. meter per minute by from 25 to 100 per cent, but this was accompanied by a proportional decrease in urinary concentration of urea. Since the blood urea did not change greatly, the clearances remained constant. This lack of relation of urine flow, within the ranges studied, to urea clearance is confirmed by the low coefficient of correlation (0.17 ± 0.09) between urea clearance and urine flow computed for the whole group of observations (Tables II and III).

These results are not in accord with the conclusions of McCance and his coworkers (11), who using uncatheterized specimens collected over probably short periods, reported a direct relationship between the urea clearance and the minute volume of urine. They considered this relationship as affording added evidence for instability of renal function in young infants. The discrepancy may be explained in part by the fact that most of the infants studied by McCance and his coworkers were less than 14 days of age, and it may be that in very young infants under conditions of low fluid intakes and very low urine flows (*e.g.*, 0.2 cc. per sq. meter per minute) (11) there is a direct relation between urea clearance and urine flow. The reported results, however, show a large scatter. Furthermore, estimations of urea clearance from spontaneously voided specimens over short periods permit the introduction of a significant systematic error which would show low urea clearances for low urine volumes and large clearances for large volumes. Either catheterized specimens for short periods of time or long periods of collections such as were used in the present study are necessary to minimize this source of error. Suffice it to say that using the 24-hour method, no relation was found in the present study between urine flow and urea clearance, this lack of correlation being evident in an 8-day-old premature infant and in a full term infant of 70 days, over a range of clearances of from 12 to 30 cc. per sq. meter per minute, and over a range of initial urine flows of from 0.4 to 1.0 cc. per sq. meter per minute.

DISCUSSION

The low urea clearance of young infants may be caused by diminished glomerular filtration or increased tubular reabsorption of urea. Shannon (13) has demonstrated that with low urine flows there is an increased reabsorption of urea, possibly due to prolonged contact of urine with the cells of the reabsorbing tubules. The lack of correlation in the whole group of observations between urine flow and urea clearance, and the lack of effect in 4 infants of sharp rises in urine flow on urea clearance, suggest that increased tubular reabsorption of urea due to low urine flow is not the cause for the low urea clearances observed in this study.

The other explanation for diminished urea clearances is a decreased glomerular filtration. We have not yet had the opportunity to measure simultaneous inulin and urea clearances in young infants, but Barnett (14) has reported that the rate of removal of inulin from the blood is slower in full term infants of 5 to 9 days than in infants of 2 to 7 weeks, and that in both groups the rate is slower than in children of 6 to 10 years. Although, as has been pointed out (15), these data are inadequate for quantitative interpretation of the blood inulin curves in terms of clearance, Barnett's explanation would account for the higher urea clearances in older infants noted by McCance and Young (11a) and those reported in the present study.

Histological studies (16) of the glomeruli of the fetus and newborn infant supply anatomical support for the supposition of defective glomerular filtration. The earlier the stage of development of the kidney, the fewer the rows of glomeruli in the cortex, and the less convoluted the capillaries. The actual amount of blood coursing through the glomeruli and the size of the filtering surface may thus be limited by the state of development of the glomeruli. Another factor limiting filtration is the extent of the layer of cuboidal cells lining the glomerulus. The shedding of this layer may be wholly developmental or it may be partly dependent on postnatal circulatory changes. Finally, glomerular dynamics in these young infants may be conditioned by postnatal physiologic adjustments of a systemic rather than solely renal character.

Studies of inulin and diodrast clearance may throw light on the mechanisms involved. Definition of the relation of defective renal function in young infants to peculiarities in water and acid-base metabolism (17) and to such clinical states as dehydration fever, acidosis and tetany in the newborn period must await completion of studies of tubular function.

SUMMARY

The 24-hour plasma clearance of urea was determined in 35 observations on 15 premature infants and in 12 observations on 9 full term infants, ranging in age from 8 to 65 and from 7 to 73 days, respectively. The urea clearance is lower in premature than in full term infants, and in both groups of young infants it is lower than that reported for older subjects. No relation was found to exist between urine flow and urea clearance.

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