THE CREATININE COEFFICIENT IN THE INFANT.

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The urinary excretion of creatinine in the adult both in health and disease has been extensively studied. In infants, however, data concerning the urinary output of this important endogenous catabolite are still incomplete. Investigations on this line therefore are called for, since they might prove of value for a better understanding of both the physiology and the pathology of the infant.

Until Folin developed his method for quantitative determination of creatinine there was much difference of opinion whether creatinine did exist in the urine of the infant or not. In 1905, however, von Hoogenhuyze and Vorploegh⁽¹⁾ were able to show that creatinine was constantly present. In a few infants they made quantitative estimations and found the values to vary between 0.41 and 1.7 mg. per 10 c.cs. of urine, the lower figure being in a weak artificially-fed baby. Lesné and Binet⁽²⁾, on the basis of a study of 13 cases, state that the total creatinine output in infancy increases with age, varying between 1.4 and 19.0 mg. per kg. of body-weight in 24 hours. Their results are expressed as per volume of urine and are rather inconstant. In a recent publication⁽³⁾, studying the day and night creatinine excretion, I have shown that in infants the creatinine output is quite independent of the volume of urine voided and consequently the above results cannot be accepted as a basis for any quantitative estimations.

Funaro⁽⁴⁾, in a study of a few subjects, finds that the urinary creatinine in infants varies between 4.6 and 10.8 mg. per kg. of body-weight in 24 hours. He does not think however that excretion is affected by the nutritional condition of the infant. Amberg and Morrill⁽⁵⁾, in a study based on 24-hourly urine collections, find in five new-born infants that the creatinine output ranges between 6.71 and 9.94 mg. per kg. of body-weight in 24 hours. Utheim⁽⁶⁾ in 1921 studied 19 infants, two of whom were normal, the others suffering from various morbid conditions and most of them athreptic. Her figures for creatinine output expressed in terms of body-weight show wide variations and are somewhat lower for underweight infants. However, the two normal infants she observed yielded 9.1 and 10.5 mg. of creatinine per kg. of body-weight in 24 hours.

In a previous paper⁽⁷⁾, and concurrently with the question of uric acid excretion in the infant, I have dealt with the rate at which creatinine is eliminated in the urine. The cases studied comprised both normal and undernourished infants. It was found that in both groups, *i.e.*, the normal and underweight infants, the creatinine elimination showed itself to be closely related to the body-weight and independent of the age, except in so far as weight and age are connected. When expressed in terms of body-weight the creatinine output ranged between 10.2 and 15.9 mg. per kg. in 24 hours. Although the values obtained did not show a very wide variation it was observed nevertheless that the higher values were generally found in the infants in a poor nutritional condition.

It will be seen from the above review of the previous work that the data concerning this subject are scanty and that there prevails considerable difference of opinion and findings. It was on this account that the present work was undertaken in an effort to estimate more accurately the relationship of the creatinine output to the weight of the infant and to evaluate, if possible, the creatinine coefficient as defined by Schaffer as a measure of the state of muscular development.

The cases reported in the present study were selected from the wards of the Royal Hospital for Sick Children, Glasgow. The infants were in varying state of nutrition, but none of them showed evidence of any acute gastro-intestinal disturbance or of the so-called specific diseases (syphilis or tuberculosis) or of fever⁽⁸⁾. To secure similarity of conditions the infants selected were all in the first year of life, so that there was agreement in diet, habits and physiology in general. Their nutritional condition is expressed in percentages of expected weight (normal weight for age) using Holt's⁽⁹⁾ figures of weight for age. All the subjects had the usual and similar nursing care and in nearly all instances the diet was whole cow's milk, which is the standard feeding of the clinic; in a few cases milk modifications were employed. The caloric intake was regulated according to individual requirements and the feeding was unchanged for several days before and during the experiments. The infants were weighed before and after the period of study and the weights recorded are an average of these two estimations. For urine collections Findlay's method⁽¹⁰⁾ was used. Urine samples were collected for two 24-hourly periods in order to serve as a check for quantitative collections and also to lessen the possible error due to any differences in the amounts of urine evacuated from the bladder and actually excreted by the kidneys. This made possible the exclusion of cases of inaccurate collections. Urine was preserved on ice and by adding toluol. Creatinine estimations were done on the day following collections, using Folin's⁽¹¹⁾ colorimetric method. The details of the findings are shown in the following table:—

TABLE I.
All urinary specimens were collected for two consecutive 24-hour periods.

Case:	Age (weeks)	Body-weight	% of expected weight	Urine c.c.s. in 24 hours.	Creatinine in Mgs.			Case:	Age (weeks)	Body-weight	% of expected weight	Urine c.c.s. in 24 hours	Creatinine in Mgs.			Coefficient
					Total in 24 hours.	Per kg of body-weight	Coefficient						Total in 24 hours	Per kg of body-weight	Coefficient	
1	32	8.75	110	472 414	80.4 82.8	9.2 9.4	3.5	15	48	6.90	72	794 723	83.6 80.6	12.1 11.7	4.5	
2	16	5.80	93	235 305	72.0 67.8	12.5 11.6	4.6	16	33	5.90	72	498 645	71.3 73.5	12.1 12.4	4.7	
3	27	6.92	91	572 385	76.5 81.1	11.0 11.7	4.2	17	9	3.40	70	306 357	46.4 46.2	13.7 13.6	5.2	
4	22	6.37	90	990 1116	67.3 72.8	10.5 11.4	4.1	18	12	3.90	68	420 455	45.9 49.2	11.8 12.6	4.6	
5	52	8.62	89	630 703	108.3 110.6	12.5 12.9	4.8	19	49	6.40	67	124 172	77.4 75.5	12.1 11.8	4.5	
6	35	7.05	84	690 738	90.4 96.4	12.7 13.7	5.0	20	21	4.54	66	232 202	48.5 48.4	10.7 10.7	4.1	
7	34	6.85	83	559 512	72.7 74.1	10.6 10.8	4.1	21	20	4.15	61	380 423	52.7 56.1	13.0 13.5	5.1	
8	25	6.01	82	540 586	67.1 70.2	11.1 11.6	4.3	22	20	4.03	59	245 384	49.9 53.7	12.4 13.4	4.9	
9	6	3.50	81	351 322	38.5 36.1	11.0 10.3	4.1	23	49	5.50	57	330 555	72.6 68.7	13.2 12.5	4.9	
10	37	6.90	80	897 785	89.6 92.4	13.0 13.4	5.0	24	13	3.40	55	291 268	33.6 35.7	10.1 10.6	3.9	
11	33	6.35	79	523 552	96.0 91.3	15.1 14.4	5.6	25	11	2.78	51	332 268	36.8 39.8	13.2 14.3	5.2	
12	8	3.52	77	490 380	44.3 46.1	12.3 13.1	4.8	26	14	3.03	50	152 204	42.6 39.1	14.0 12.9	5.1	
13	6	3.25	75	327 351	38.3 42.5	11.8 13.0	4.7	27	21	3.40	49	244 267	41.6 39.3	12.2 11.6	4.5	
14	48	7.10	74	655 642	99.6 96.9	14.0 13.6	5.2	28	18	2.50	38	105 196	28.6 30.0	11.4 12.0	4.5	

All the subjects of these investigations were fed on cow's milk, *i.e.*, a diet practically creatinine-free, consequently we are dealing with creatinine of endogenous origin. Again, they form a group which is homogeneous as regards feeding, habits, routine life and physiology in general, but whose main differences are those of age and nutritional state. This condition obviously directs our investigation to the finding out whether, and if so to what extent these two differentiating factors, age and nutritional condition as expressed in terms of body-weight, are related to creatinine output.

Infancy is the period of life in which age plays the most important rôle. There is no age during which not only morphological and anatomical but physiological changes occur with such rapidity as during infancy and early childhood. The infants studied ranging in age from 6 to 52 weeks thus provide a group in which these changes are most marked.

A review of the values as shown in the Table No. I. for total 24-hourly creatinine output as compared with age will show that age *per se* is not the determining factor. Variations are observed in the total creatinine elimination, but they would seem to be due to some factor other than age. For example, Cases 2, 7 and 19 are respectively 16, 34 and 49 weeks old, yet the total daily creatinine output on two successive days is found to be respectively, 72.0 and 67.8 mg.; 72.7 and 74.1 mg.; and 77.4 and 75.5 mg. That infants of such varying age should excrete amounts of creatinine which are approximately so equal is one of the most striking features of all our work on this question.

Having thus ruled out any connection between the age of the infant and the creatinine elimination there remains for consideration the question of body-weight. But before proceeding to the analysis of the results from this point of view it seems useful to review the literature concerning the origin and significance of the urinary creatinine and to state the prevailing opinions.

Folin⁽¹²⁾ first established the fact that the rate of creatinine excretion is an index of the level of endogenous nitrogen metabolism. This conception is generally accepted although some authors still believe that a small portion may be converted into urea⁽¹³⁾. Schaffer⁽¹⁴⁾, on a basis of extensive studies, finds that the creatinine output is directly proportionate to the muscular development and the power of an individual. He advances the opinion that creatinine is derived by some special process of catabolism taking place largely, if not entirely, within the muscle. This view finds confirmation in further studies of Folin and his co-worker, Denis⁽¹⁵⁾. Benedict and Mayers⁽¹⁶⁾, on the other hand, while observing the creatinine excretion to be related to the body-weight, find no constant ratio between the creatinine output and the muscular development of the subject. It is to be noted that all these studies were done in the adult.

A survey of the cases included in the present study as shown in Table No. I. gives ample evidence that there is a close relationship between the body-weight of the infant and the daily creatinine output. The values obtained in practically all the cases of the group vary within very narrow limits—10.1 and 13.7 mg., though 9.2 and 15.1 mg. are the extremes. It is of interest to note that the lowest value was obtained in the case of an overweight infant, which observation is in accord with Folin's statement that fat persons yield less creatinine per unit of body-weight than do lean persons.

According to Cathcart⁽¹⁷⁾ a normal adult yields as much as 30 to 40 mg. of creatinine per kg. of body-weight in 24 hours. Infants thus show a marked difference as it is seen that their excretion amounts to decidedly less than half (10-13 mg.) of that amount. How can this apparent difference in creatinine metabolism be explained? Sufficient evidence has been accumulated to show that creatinine is produced entirely within the muscle and in this connection it is important to bear in mind that the proportions of the various body-tissues are different in the infant and in the adult. While the infant's body is relatively rich in water and fat and poor in muscle, the proportion of muscle in the adult is high. It is computed that muscle forms 47 per cent. of the body-weight of the adult but only 23 per cent. of that of the infant. Thus weight for weight the infant has just one half of the creatinine yielding tissue (muscle) possessed by the adult. Schaffer, assuming that urinary creatinine is formed wholly in the muscle and that the muscular tissue constitutes about half of the body-weight in the adult, estimates that on the average 50 mg. of creatinine are formed by one kilogram of muscle per day. Applying this computation of Schaffer, which is based on lower values for creatinine output than these given by Cathcart, to two cases of our series, one of them 93 per cent. and the other 38 per cent. of expected weight, and thus representing the two extremes in nutritional state, the theoretical creatinine output as compared with the observed output is as shown in the following table:—

Case	Body-weight	Percentage of expected weight	Amount of Muscle = 23 % of body-weight	Creatinine output in 24 hours	
				Observed average of two days	Theoretical = 50 mg. per kilo of muscle
2	5.80	93	1,334 grms.	69.9	66.7
28	2.50	38	575 grms.	29.3	28.75

This striking agreement between the actual and the theoretical findings surely points clearly to the fact that in wasting in infancy the loss of muscle is in direct proportion to that of the other tissues, and thus opposed to the conclusions drawn from the study of basal metabolism. This hypothesis

is further substantiated by a prolonged study of a recovering underweight infant:—

A.L. Male. Aged 10 weeks. Admitted June 26, 1926. Weight on admission 2·70 kg. The history was the usual one of a non-thriving infant. Healthy at birth, weighing 3·40 kg.; never breast-fed; vomiting often expulsive in character since first week of life, latterly diarrhoea. On admission, stools normal, but vomiting severe.

The clinical findings were negative, except that the case was that of a small wasted infant, and the diagnosis was improper and irregular feeding. In the first 24 hours peptonised milk was given, then whole cow's milk which was continued during the whole period of study. Vomiting stopped within two days and the infant rapidly improved and increased steadily in weight. Creatinine estimations were done weekly.

The full data are seen in the accompanying table:—

TABLE II.

On the first and last occasions for purposes of control urine was collected for two successive 24-hour periods.

Age (weeks)	Feeding— whole cow's milk—calories	Body- weight kg.	% of expected weight	Urinary output c.cs.	Creatinine	
					Total in 24 hours	Per kg. of body-weight
11	192	2·78	50	332	38·8	13·9
—	456			268	39·8	14·3
12	456	3·00	53	381	41·3	13·7
13	456	3·23	56	377	45·6	14·1
14	504	3·52	58	460	46·9	13·3
15	504	3·74	60	409	49·2	13·1
16	504	3·90	62	357	54·7	14·0
17	558	4·19	65	492	57·1	13·6
18	558	4·45	68	503	63·3	14·2
19	558	4·70	70	430	66·2	14·1
20	558	4·80	71	230	69·0	14·4
				184	67·1	14·0

The striking feature of the results obtained in the case is that parallel with the remarkable gain in weight there is a rise of total 24-hourly creatinine output and that quite irrespective of the volume of urine voided. Also, even if the age factor had not been ruled out as a factor determining the daily creatinine output, the short period of time within which parallel changes in body-weight and creatinine output occurred is impressive, although characteristic of the age of infancy. The constant ratio between

the body-weight and the rate of creatinine elimination shown by the subject is to our mind strong confirmation of our view of the question. The chart given below shows the facts graphically.

CHART I.—BABY A.L.

Much study has been given to the problem of the wasting infant and the question has often been raised of the relative parts that the disappearance of the different tissues play in the loss of body-weight. Presumably, and especially in the condition of acute dehydration, there is first of all a relatively greater loss of water; adipose tissue is probably the next affected. Fleming⁽¹⁸⁾ in his study of basal metabolism in the athreptic infant advances the opinion that in the first or slighter degrees of wasting, in fact till the infant has lost 35% of his weight, the reduction of body-weight occurs at the expense of metabolically inactive tissue—water and fat—and that it

is only when the fall in weight increases beyond this level that active metabolic tissue or muscle is lost. It would seem to us that in the present study there is a good opportunity of testing this hypothesis if one assumes that urinary creatinine is a measure of the amount of muscular tissue.

It will be seen from the table that the nutritional state of the infants studied has been indicated by percentages of expected weight. It will also be observed, as already stated, that the figures for creatinine output per kilogram of body-weight in 24 hours remain practically constant in all the infants in the group, except that perhaps in the series of cases, which are between 60% and 80% of expected weight, the variations are somewhat greater. On the basis of these results we feel justified in concluding that at any stage of wasting in an infant the reduction of muscle tissue as indicated by creatinine output is apparently parallel with the loss of total body-weight. In moderate degrees, however, there may be relatively a slightly greater loss of "dead" tissue, as is evidenced by the greater varying values obtained for creatinine excretion in these cases. It is, of course, just in these degrees of nutrition that there may be a greater variation in the relative amounts of water and fat, which would explain the wider variations in the figures obtained.

Arguing from the premise that there is a close relationship between the muscular development of an individual and the amount of creatinine excreted Schaffer⁽¹⁹⁾ established his "Creatinine Coefficient," which represents the number of milligrams of creatinine nitrogen eliminated per kilogram of body-weight in 24 hours. This coefficient is considered to be the index of muscular development and power of a subject, and is estimated (Schaffer) to vary for an adult man between 8 and 11. Tracy and Clark⁽²⁰⁾ in agreement with this conception find this coefficient in adult women to be lower, on an average 5.8. We have computed in our cases that the coefficient in infancy ranges between 3.5 and 5.6, the lower value being obtained for an overweight infant. The average creatinine coefficient in the infant is found to be 4.6, *i.e.*, half of that in the adult, but as we have already remarked that relatively the muscular tissue in the infant is also only one-half of that of the adult, the low ratio in the infant is easily understood.

RÉSUMÉ.

The rate of creatinine excretion in 28 male infants between the ages of 6 and 52 weeks and in varying nutritional condition ranging in percentage of expected weight between 38 and 110 was studied. The main findings were as follows:—

1. The daily creatinine elimination being constant is entirely independent of the age of infant.
2. The daily creatinine output in all the infants is found to be closely related to the body-weight and practically independent of the nutritional condition.

3. Using the evidence regarding the origin and significance of the urinary creatinine it was found that in wasting the reduction of active (muscular) tissue is parallel with the degree of wasting or total loss of body-weight.

4. A case of an undernourished infant studied for a longer period of time beginning with a nutritional state of 50% of expected weight until the infant through a remarkable and rapid improvement reached 71% of expected weight gives full confirmation to the above expressed statement.

5. The creatinine coefficient as an index of muscular development of the infant was determined and was found to be on an average 4.6, as compared with that in adult (male:—8.11, and female:—5.8) thus indicating the relatively poor development of the muscular system in infancy.

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