The period of infancy is peculiarly suited to a study of creatine and creatinine metabolism for several reasons. The quantity of musculature present at birth and its rate of growth relative to that of the body as a whole have been determined through anatomical studies (1). The diet of the infant is relatively simple and constant in character over a long period of time; and infancy is a period of rapid growth and development. While the literature abounds with short term studies of creatine-creatinine metabolism in infancy (2), many of the studies are difficult to interpret. Often the subjects were convalescent, rather than well infants; dietary habits of the infants previous to the study are not recorded, and conditions of study differ so much that no complete picture of creatine-creatinine metabolism during the 1st year of life yet exists.

The present report records the urinary creatine and creatinine excretions during infancy as determined from 424 3 day studies of 52 healthy infants from 2 weeks to 1 year of age, and from 73 24 hour studies of twenty-three normal infants during the 1st week of life. The distribution of the data is shown in Table I. The new born infants, with two exceptions, were fed human milk; the infants above 2 weeks of age were given curded whole milk feedings with 6 per cent of added carbohydrate. The diet after the 2nd week of life thus contained much more protein and was of higher caloric value than the diet of the new born infants. The customary vitamin supplements were given. The general health and the rates of growth and development of the infants were excellent.

* This study was aided by a grant from Mead Johnson and Company, Evansville, Indiana.
Creatine-Creatinine Excretion

Urine samples were collected under toluene and each 24 hour specimen was analyzed separately. Folin's micromethod was used for creatinine (3); creatine was converted to creatinine by autoclaving in the presence of picric acid for 30 minutes at 15 pounds pressure (3). Nitrogen was determined in food and excreta by the Kjeldahl-Gunning method (4). The values obtained are shown graphically in Figs. 1 to 4.

**Table I**

<table>
<thead>
<tr>
<th>Age range</th>
<th>No. of infants</th>
<th>No. of periods*</th>
<th>Average weight kg.</th>
<th>Age range</th>
<th>No. of infants</th>
<th>No. of periods*</th>
<th>Average weight kg.</th>
</tr>
</thead>
<tbody>
<tr>
<td>days</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2</td>
<td>23</td>
<td>41</td>
<td>3.4</td>
<td>20-25</td>
<td>37</td>
<td>79</td>
<td>7.2</td>
</tr>
<tr>
<td>3-8</td>
<td>18</td>
<td>32</td>
<td>3.4</td>
<td>25-30</td>
<td>30</td>
<td>58</td>
<td>7.8</td>
</tr>
<tr>
<td>wks.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-5</td>
<td>5</td>
<td>11</td>
<td>3.2</td>
<td>30-35</td>
<td>18</td>
<td>39</td>
<td>8.0</td>
</tr>
<tr>
<td>5-10</td>
<td>18</td>
<td>27</td>
<td>4.7</td>
<td>35-40</td>
<td>14</td>
<td>29</td>
<td>8.9</td>
</tr>
<tr>
<td>10-15</td>
<td>34</td>
<td>60</td>
<td>5.5</td>
<td>40-45</td>
<td>12</td>
<td>23</td>
<td>8.2</td>
</tr>
<tr>
<td>15-20</td>
<td>36</td>
<td>68</td>
<td>6.5</td>
<td>45-50</td>
<td>7</td>
<td>10</td>
<td>9.3</td>
</tr>
</tbody>
</table>

* A period represents a single 24 hour determination for infants under 8 days of age, the average of two or three 24 hour determinations for infants under 5 weeks, and a 3 day average for all other infants.

**Fig. 1.** The relation of daily creatinine excretion to the weight of the infant. The formula for the regression line is given in Table II, A.
Creatinine

In Fig. 1, the creatinine data from the individual periods of study are plotted against the weight of the infants. Fig. 1 shows the consistent increase in creatinine excretion as the child increases in size and also the range of variability of creatinine excretion by infants of a given weight. In general, the values observed agree well with those reported by others studying infants fed similar diets (5-7).

**TABLE II**

*Results of Statistical Analyses of Creatine and Creatinine Excretion of Infants*

<table>
<thead>
<tr>
<th>Y</th>
<th>X</th>
<th>Coefficient of correlation, r</th>
<th>Probable error</th>
<th>Coefficient of alienation</th>
<th>Regression line of Y on X</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine-weight</td>
<td>0.9056 ± 0.0055</td>
<td>0.424</td>
<td>0.0055</td>
<td>Y = 13.555X - 9.334</td>
<td></td>
</tr>
<tr>
<td>Creatinine-length</td>
<td>0.893 ± 0.0065</td>
<td>0.450</td>
<td>0.0065</td>
<td>&quot; = 3.233X - 123.947</td>
<td></td>
</tr>
<tr>
<td>Creatinine-age</td>
<td>0.8333 ± 0.0094</td>
<td>0.553</td>
<td>0.0094</td>
<td>&quot; = 1.716X - 46.774</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine-weight</td>
<td>0.7645 ± 0.0128</td>
<td>0.645</td>
<td>0.0128</td>
<td>Y = 12.648X - 17.788</td>
<td></td>
</tr>
<tr>
<td>Creatinine-age</td>
<td>0.7313 ± 0.0144</td>
<td>0.682</td>
<td>0.0144</td>
<td>&quot; = 1.709X - 31.084</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine + creatine-weight</td>
<td>0.8849 ± 0.0007</td>
<td>0.465</td>
<td>0.0007</td>
<td>Y = 20.776X - 30.2821</td>
<td></td>
</tr>
</tbody>
</table>

* The "probable error" is such a number that the chances are even that the true coefficient of correlation in each case lies in the interval r ± p.e.; or the chances are about 22 to 1 that the true coefficient of correlation lies in the interval r ± 3 p.e.

The data shown in Fig. 1 have been analyzed statistically and the correlation coefficients of creatinine with weight, length, and age of the infants determined. The results are shown in Table II, A. The correlation coefficients of creatinine with both weight and length are excellent and nearly identical, that with age slightly less good. As the daily creatinine excretion increased steadily throughout the period of infancy, it is to be expected that the three coefficients would be somewhat similar.
The creatinine-weight coefficient, 0.9056 + 0.0055, is unusually high for biological data and when one considers the impossibility of obtaining urine collections in exact 24 hour specimens from infants, the coefficient of alienation is surprisingly low. It may therefore be concluded that the factor chiefly responsible for the quantity of creatinine excretion is a function of body weight.

Length was considered by Daniels and Hejinian (6) as preferable to weight as a reference for creatinine comparisons among infants. The correlation between creatinine and length of the infants studied here was almost equal to that between creatinine and weight; the coefficient of alienation was slightly larger. The similarity of coefficients can be explained on an anatomical basis. Length is a function of skeletal growth. The skeleton remains at approximately the same percentage of body weight throughout life; the musculature is a constant proportion of body weight throughout infancy (1). During the period studied, then, both the musculature and the skeleton would remain in the same proportion to each other. Creatinine as a measure of quantity of muscle would thus show almost as good correlation with skeletal weight (measured by length) as with the weight of the body as a whole. The actual coefficients obtained show that this relationship holds, but in view of the probable causes, the creatinine-weight comparison seems preferable as being the more direct relationship.

The lower correlation coefficient of creatinine and age, compared with the others, is considered indicative that the apparent correlation should be ascribed wholly to the increasing weight rather than to any cause affected more directly by age. As a further test, the correlation coefficient of creatinine per kilo and age was determined. For this analysis, the data from the new born infants were excluded. The coefficient obtained, 0.083 ±0.034, within 2.5 times the probable error of zero, shows conclusively that during the 1st year creatinine excretion is not affected by the age of the infant.

The very close correlation between creatinine and weight indicates that the effect of exogeneous factors is either constant or negligible. The exogenous factors of chief interest are the intakes of creatine and creatinine from milk. Human milk and cow’s milk contain approximately equal amounts of creatine and creati-
nine (8). The average daily milk intake of the new born babies was 50 cc. for the first 2 days and 340 cc. for the 6th to 8th days, equivalent to an intake of total creatine-creatinine increasing from 0.6 mg. per kilo to 4 mg. per kilo. The average creatinine excretion increased from 8.6 to 10.5 mg. during this period. The collection error of the first 2 days of life, however, was relatively large, as the average 24 hour urine was less than 25 cc. The average milk intake per kilo of all the infants increased rapidly until a maximum was attained when the infants were about 4.5 kilos in weight. It then decreased throughout the remainder of infancy until at 1 year of age the average per kilo intake was 25 per cent less than the maximal. The maximal creatine-creatinine intake was 6 to 7 mg. per kilo. The amount of creatinine excreted increased from 8.6 mg. per kilo at birth to 12.5 mg. per kilo when the infant weighed about 5 kilos, after which the excretion per kilo remained constant. The quantity of intake of creatine and creatinine, therefore, exerts no consistent effect upon the quantity of creatinine excreted by the infants.

Analytical values of creatine content of muscle in infancy are variable. Rose (9) found the creatine content of the musculature in a new born infant to be 190 mg. per 100 gm. Denis (10) found variable amounts, averaging over 300 mg. per 100 gm. for infants about a year old. It seems probable that the creatine content of tissues increases during later infancy, whereas during this period the creatinine excretion per kilo remains constant.

No relation was observed between muscular activity as measured by achievement and the per kilo creatinine excretion.

It seems clear from the preceding discussion that the chief factor responsible for creatinine excretion is a function related to body weight and presumably more directly to the muscle weight. Scammon (1) found that the musculature is approximately 25 per cent of the body weight at birth and grows at a rate slightly lower than that of the body as a whole throughout the 1st year of life. These data were obtained early in the century and the infants studied were presumably fed human milk or cow's milk, diluted. The new born infants of the present study were fed human milk; those above 2 weeks of age were given cow's milk, undiluted. The nitrogen retentions of the latter group were much higher than those reported for infants fed human milk. Does this increased
retention of nitrogen change the percentage of body weight due to musculature and does it also alter the characteristics of infantile growth; that is, does the percentage of body weight due to musculature increase throughout the period of infancy?

To answer these questions comparison was made of the creatinine excreted per kilo by infants given the two types of feeding. The average creatinine excretion for the 1st week of life was 10 mg. per kilo, and one older infant fed human milk excreted an average of 9.9 mg. per kilo. Values observed by others for healthy infants fed human milk varied from 8 to 12 mg. per kilo (5, 11), with an average of 9.8 mg. per kilo. The value of 10 mg. per kilo therefore may be assumed as an approximate average creatinine per kilo excretion for infants given human milk.

The infants of this study who were fed cow's milk were given this food with its higher protein content at 10 to 14 days of age. Before the 5th week of life, the average excretion of creatinine had increased to 12 mg. per kilo and after the 5th week remained approximately constant at 12.5 mg. per kilo even though the per kilo nitrogen intake decreased slowly thereafter (Fig. 3). One may thus conclude that a marked increase in protein intake in infancy results in a rapid increase in percentage of muscle tissue

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**Fig. 2.** The relation of daily creatine excretion to the weight of the infant. The formula for the regression line is given in Table II, B.
up to a definite point, after which the proportion of muscle to body weight tends to remain constant as long as the dietary regimen is maintained. If one assumes that a creatinine excretion of 10 mg. per kilo represents a musculature 25 per cent of the total body weight, then an average creatinine of 12.5 mg. per kilo would indicate that the musculature of these infants represents about 30 per cent of the total weight. From the appearance of the infants, this increase in percentage of muscle seems to be at the expense of water and fat.

The average creatinine per kilo of the individual infants above 5 weeks of age varied from 10 mg. per kilo for the obese to 14.5 mg. per kilo for the very slender infants.

In conclusion, the data tend to show that the quantity of creatinine excreted by normal infants depends almost solely upon the quantity of musculature. The infant tends to maintain the musculature at a constant proportion of body weight throughout the 1st year of life, but the exact proportion maintained is somewhat higher in infants fed a high protein diet than in those fed human milk.

Creatine

The creatine-weight values are plotted in Fig. 2 in the same manner as the creatinine values of Fig. 1.

Each infant studied always excreted creatine. It is obvious from Fig. 2 that the creatine excretion of infants, like that of creatinine, increases steadily as the infant grows. It is also obvious that the quantities excreted daily are far more variable than those of creatinine. A part of this variability can be ascribed to method, but only a part. Whereas it was always observed that two infants of the same weight and body build excreted approximately the same amounts of creatinine daily, the same was not true for creatine excretion. Most of the infants habitually excreted somewhat less creatine than creatinine, six babies excreted only about half as much creatine as creatinine, and twelve consistently excreted as much or more creatine than creatinine. Four infants excreted more creatine than creatinine in early infancy, but after about the 20th week the creatinine excretion consistently exceeded that of creatine. The above factors, as well as the fact that the period to period variation in creatine excretion
Creatine-Creatinine Excretion

was greater than that observed with creatinine, are responsible for the wide range of creatine values observed.

The data have been analyzed statistically with the results shown in Table II, B. The coefficients of correlation of creatine with

weight and age are fair, but the coefficients of alienation are almost equal to those of correlation. It seems that neither weight nor age alone is a predominating factor in determining the degrees of creatininuria in infancy.

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**Figure 3.** The relation between nitrogen metabolism and creatine excretion. The arithmetic means for nitrogen per kilo and creatine and creatininine per kilo are calculated for 5 week intervals of age.
Certain exogenous factors are known to affect creatine excretion. Of these, the most important for this study are the intakes of protein and creatine. To study these, the arithmetic means of the per kilo nitrogen intake, urinary excretion, and retention, and the excretion of creatine per kilo have been calculated for the new born period and for each succeeding 5 week period of infancy. The resulting curves are shown in Fig. 3. The creatine excretion, which was lowest at birth (4.6 mg. per kilo), remained at this value until the end of the 1st week, after feeding was well established. It then rose steadily to more than double the original value, or 10.5 mg. per kilo, a level which was attained between 15 and 20 weeks of age, and thereafter maintained throughout the remainder of infancy. The nitrogen intake of the infants was increased more than 3-fold upon institution of the feedings of cow's milk at the end of the 2nd week of life. The intake per kilo decreased slowly after the 5th week. The intake of exogenous creatine also reached a maximum before the 5th week and paralleled the nitrogen intake thereafter. Alterations in the creatine intake, like those of creatinine, were not paralleled by changes in creatine excretion. Similarly, no definite relationship could be observed between creatine excretion and any phase of nitrogen metabolism, intake, retention, or catabolized nitrogen, expressed as urinary excretion.

These results are in apparent contradiction to the findings of others (2). Such studies, it may be noted, have been of short duration. The infants of this study had been given the high protein feedings for 10 days to 2 weeks or more before the creatine excretion was studied. Unpublished studies on older children in this laboratory have indicated that a large part of the added creatinuria induced by a sharp increase in protein intake is a temporary phenomenon. It seems highly probable therefore that the excess creatinuria caused by increased protein intake of infants is also largely transitory. Whether all of it is transitory can only be determined through the study of a group of infants fed human milk for a period of several months. It has been possible for us to study only one such infant. His average excretion of creatine was 4.7 mg. per kilo, an amount similar to that of the new born infants and below that of any other older infant studied. He was given cow's milk for a period of 1 week, where-
upon the creatine excretion increased to 7.8 mg. per kilo, an initial increase lower than the average, but within the range, of the creatine excretion of the large group. Unfortunately it was not possible to study this infant further. Other studies bearing on the question include the report of Marples and Levine (7) quoting the creatine excretions of eight infants fed high protein diets. Seven of the babies excreted amounts of creatine comparable to those reported in this study, but the eighth, a month-old infant, excreted habitually less than 2 mg. per kilo daily. Ellinghaus, Müller, and Steudel (12) studied the total creatine-creatinine excretions of three infants given first a cow's milk formula, then human milk. The nitrogen intake was halved during the period when human milk was fed, but the total creatine-creatinine excretion was slightly increased. It seems possible that the creatine excretion of infants given a high protein diet may average somewhat greater than that of infants fed human milk, but certainly protein intake is not a major factor involved in determining the creatine excretion.

A comparison of the creatine and creatinine curves of Fig. 3 is of interest. Age is definitely not a factor in determining creatinine output per kilo, as was shown by the correlation coefficient, zero. The difference in values obtained for the new born and the older infants is explained as a true difference in quantity of musculature, due to differences in protein intake. To find the correct regression curve of creatine per kilo on age, however, one must assume an exponential law. Thus, while it may be concluded that age is not a factor in determining creatinine excretion, the same statement cannot be made for creatine.

The differences in quantity of creatine excreted per kilo by the individual infants of the same age and weight and under the same dietary regimen are further indication that the chief factor controlling creatinuria is endogenous. Of such factors which have been considered as influencing the creatine excretion, those most pertinent to the period under discussion are the creatine content of muscle (9, 10), the relative maturity of muscle (2), the carbohydrate metabolism of muscle (13), and the amount of thyroid hormone (13, 14).

The creatine content of muscle has been discussed under creatinine. Its relationship to creatine excretion seems no more obvious than that with creatinine excretion.
The creatinuria of infancy and childhood has been explained as the result of a low saturation point of the immature musculature for creatine (2). The continuous increase in creatine excreted per kilo during the early part of infancy is evidence against this explanation, as are also the findings (7, 15) that prematurely born infants often excrete no creatine, and that their creatine excretion remains lower for several months after birth than that of infants born at term.

Animal experiments (16) tend to show a definite connection between thyroid activity and carbohydrate metabolism, particularly glycogen content, of muscle. As far as the period of infancy is concerned, little is known definitely about either the glycogen content of muscle or the development of thyroid function (17). Such evidence as we have concerning the latter may be interpreted to indicate that thyroid secretion exerts a controlling influence over creatine metabolism during this period of life. The low creatine excretion of prematurely born infants may be correlated with the finding of Talbot (18) that these infants have a basal heat production definitely lower than that of infants born at term. Even at 4 months of age both the amount of creatinuria and the basal metabolic rate are lower for the prematurely born than for the full term infant. It is known that cretins excrete less creatine than normal children (14) and that creatine excretion is increased on institution of thyroid therapy. Creatinuria is increased also in cases of hyperthyroidism.

It was not possible to determine the basal heat productions of the infants reported in this study. From the data reported by Talbot (18) and the average weights of the babies of the different age groups studied (Table I), the average heat production in calories per kilo has been estimated for each age group. The resulting curve, together with that of creatine excretion per kilo, is shown in Fig. 4. The heat production in calories per kilo and the creatine excretion per kilo both increased during early infancy, and both remained approximately constant during later infancy. Although the relation between the two is not linear, both follow the same type of exponential law. Differences in relative activity of the thyroid might well account for the noticeable differences observed in relative quantities of creatine excreted by the different infants. It does not explain as readily the shift from high to lower creatine excretion observed in four infants at about 20 weeks.
of age, unless one assumes an unusual residual supply of maternal hormone in these infants.

The findings in general tend to exclude exogenous factors from responsibility for the quantity of creatine excreted in infancy. A high protein intake may possibly increase the excretion of creatine, but no direct parallelism is observed between the level of protein intake and creatine excretion. The evidence presented indicates that the factor responsible for creatinuria is endogenous and supports the theory that activity of the thyroid may be directly or indirectly one of the chief factors concerned during infancy.

![Graph](http://www.jbc.org/)

**FIG. 4.** The creatine excretion per kilo and the basal heat production per kilo calculated for infants of the same average weights (data from Talbot (18)).

**Creatine and Creatinine**

Harding and Gaebler (19) from a study of older children concluded that the excretion of creatine plus creatinine per kilo of body weight is a constant when the protein intake is high, and is the same for children as for adults. The sum of the average creatine and creatinine values per kilo for the infants of the present study increased from approximately 15 mg. at birth to 22.5 mg. after about 18 weeks of age. The latter value is similar to those observed in children by Harding and Gaebler. Average values for individual infants above 18 weeks of age, however, varied from 18 to 28 mg. per kilo, a difference of more than 50 per cent. The correlation coefficient of total creatine (as creatinine) and weight
(Table II, C) falls between that of creatinine-weight and creatine-weight, as would be expected of a fortuitous relationship. The creatine and creatinine curves of Fig. 3 also indicate no relationship between the two substances.

The creatine and creatinine excretions may be considered as manifestations of two different phases of muscle metabolism. The amount of creatinine excreted depends solely upon the quantity of muscle tissue, whether the individual is a new born infant or an adult. The creatine excretion, on the other hand, seems to be associated with some other phase of muscle metabolism, not directly related to quantity of muscle tissue, but more closely linked with hormonal control. The two phases of muscle metabolism are neither parallel nor reciprocal during early infancy; therefore probably at no time are they closely interrelated.

SUMMARY

This report summarizes the data from approximately 500 studies of creatine and creatinine excretion of infants from birth to 1 year of age. The quantities of both creatine and creatinine excreted increase throughout the entire period studied. The creatine excretion is far more variable than that of creatinine.

It is concluded that the creatinine excretion of infants is dependent practically in entirety upon the quantity of musculature. Infants fed high protein diets have a somewhat higher percentage of the body weight as muscle than infants fed human milk.

No consistent relationship is observed between the quantity of creatine excretion and creatine intake, or between creatine excretion and any phase of nitrogen metabolism.

Relative immaturity of muscle does not seem to be a factor in determining quantity of creatinuria.

The data have been interpreted as indicating that thyroid activity may be directly or indirectly the principal factor concerned in determining the quantity of creatine excretion of infants.

During early infancy, creatine and creatinine excretions neither parallel each other nor show any reciprocal relationship; this is considered evidence that the two substances represent different phases of muscle metabolism, not closely interrelated.
The authors are indebted to Dr. E. D. Plass of the Department of Obstetrics for permission to study the new born infants, and to Mr. Abraham Oleshen of the Department of Mathematics for the statistical analysis of the data.

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Ruth Catherwood and Genevieve Stearns


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