THE DAY-AND-NIGHT CREATININE AND CREATINE IN THE URINE OF INFANTS.

BY

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The difficulties which are encountered in collecting infants' urine quantitatively for satisfactory metabolic periods are well known, and therefore many studies of the urinary constituents in infants have been made on isolated samples collected during short periods. But, as it is possible that the output of these substances may vary from one hour to another, it seemed advisable to make a study of the urine of infants collected in short successive periods throughout the day and night. In this way there would be obtained not only information on the value of results based on fractional collections, but also additions to our knowledge of infant physiology.

In a previous paper(1) I have reported the results of a study of the creatinine excretion in infants. The chief conclusion was that a healthy well-nourished infant excretes, on an average, 10 mg. of creatinine per kilogram of body weight in 24 hours, and thus as an end-product of endogenous protein metabolism creatinine is a constant factor. As a preliminary to any further investigation of creatinine, and for the reasons stated above, it seemed expedient that the day and night elimination of creatinine in infants should be determined in three-hourly periods. And further, in view of the observation that creatine is a normal constituent of the urine of infants (Folin(2) and others) it was also considered important to determine the rate at which this urinary product is excreted.

Owing to the active water exchange the daily urinary output of a healthy infant is normally high, and because of the slight control of the muscles regulating bladder evacuation, micturition in infancy occurs at very frequent intervals. These intervals, however, may not be regular, and the question may be asked if the amount of urine voided during a given short period corresponds to the amount actually excreted by the kidneys. For obvious reasons we did not feel justified in deciding this point by additional catheterisations of the infant at the beginning and end of each period, and our study is based on the samples voided spontaneously. But the high urinary output and the size of the bladder in the infant do not seem to support the idea of long or even appreciable urine retention; and further we hoped by careful selection of the subjects (infants in good nutritional condition and health, of similar habits, feeding and age), and by securing a liberal intake of water, that the results would be satisfactory.
Six healthy male infants between the ages of 5 and 11 months were selected. They all had similar and usual nursing care and were all of the standard feeding of the clinic (whole cow’s milk), with the exception of Case 1 which was partially breast-fed. The feeding was uniform for several days before and during the study, and the caloric intake was regulated according to individual requirements.

The experiments were carried out as follows: For the collection of urine infants were immobilised in a comfortable metabolism bed in use in this hospital(5). Urine samples were collected in three-hourly periods during the day and night, starting at 10 a.m. Following the first day of fractional collections, one total 24 hour collection was employed as a check, comparing the figures obtained for the total daily creatinine output. Urine samples were preserved on ice and by adding toluol. Creatinine measurements were made within 24 hours of the collections of urine, using Folin's(6) colorimetric method. Creatine was converted into creatinine by autoclaving. The results in detail are given in Table I.

The most striking feature of the results shown in Table I. is the remarkable constancy of the findings in all the subjects studied. This justifies the discussion of all the cases together.

Creatinine.—Considering the experimental conditions previously described the three-hourly elimination of creatinine is notably constant in Cases 1, 3 and 5, while it is less so in the other cases. However, even in these instances the variations are much less wide than would be expected from the varying urinary output. Thus in Case 2 the amount of creatinine excreted during the period 10 a.m.-1 p.m. was 8.8 mg. in 58 cc. of urine, while during the following three-hourly period 10-0 mg. of creatinine were found in 304 cc. of urine. Again, in the examples where the variation is more marked the rise or fall in creatinine tends to occur in successive periods. This suggests an overlapping due to imperfect evacuation of the bladder in the periods concerned.

Schaffer(6) has found that the creatinine excretion in adults on a creatinine-free diet is remarkably constant, not only from day to day, but from hour to hour. As our subjects were on a creatinine-free diet a similar result might have been expected as there is no evidence of the presence of any disturbing factor. In this connection it is of interest to mention that in a study of endogenous uric acid excretion in the infant(6) I found it more regular than in the adult. These facts would seem to indicate a remarkable regularity in the endogenous reactions of infant life.

It is evident that the longer the periods of collection of the urine the more closely will the amount evacuated from the bladder correspond to that excreted by the kidneys. Applying this to our results it will be seen that the amounts of creatinine excreted during the day and during the night are equal in Cases 1, 2 and 5; while the other cases fail to show this equality by only 3—4 mg.

<table>
<thead>
<tr>
<th>Case. Age, Weight — Day—Month</th>
<th>Analysis</th>
<th>Total in 24 hours</th>
<th>Total, Three-hourly periods</th>
<th>Second Day, Total in 24 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total (mg.)</td>
<td>Day</td>
<td>Night</td>
</tr>
<tr>
<td>1. 28 weeks</td>
<td></td>
<td>Total Creatinine</td>
<td>15.7</td>
<td>5</td>
</tr>
<tr>
<td>6/5 kg.</td>
<td></td>
<td>Preformed Creatinine</td>
<td>81.1</td>
<td>30</td>
</tr>
<tr>
<td>29/30-5</td>
<td></td>
<td>Creatine as Creatinine</td>
<td>74.8</td>
<td>30</td>
</tr>
<tr>
<td>30/31-5</td>
<td></td>
<td>Urine cc.</td>
<td>572</td>
<td>270</td>
</tr>
<tr>
<td>2. 21 weeks</td>
<td></td>
<td>Total Creatinine</td>
<td>168.5</td>
<td>84.9</td>
</tr>
<tr>
<td>6/3 kg.</td>
<td></td>
<td>Preformed Creatinine</td>
<td>72.8</td>
<td>30</td>
</tr>
<tr>
<td>5/6-6</td>
<td></td>
<td>Creatine as Creatinine</td>
<td>85.7</td>
<td>48</td>
</tr>
<tr>
<td>6/7-6</td>
<td></td>
<td>Urine cc.</td>
<td>990</td>
<td>676</td>
</tr>
<tr>
<td>3. 35 weeks</td>
<td></td>
<td>Total Creatinine</td>
<td>230.9</td>
<td>112.2</td>
</tr>
<tr>
<td>7/5 kg.</td>
<td></td>
<td>Preformed Creatinine</td>
<td>90.4</td>
<td>43</td>
</tr>
<tr>
<td>12/6-6</td>
<td></td>
<td>Creatine as Creatinine</td>
<td>140.5</td>
<td>59</td>
</tr>
<tr>
<td>22-6</td>
<td></td>
<td>Urine cc.</td>
<td>738</td>
<td>333</td>
</tr>
<tr>
<td>4. 24 weeks</td>
<td></td>
<td>Total Creatinine</td>
<td>172.8</td>
<td>91.1</td>
</tr>
<tr>
<td>6/4 kg.</td>
<td></td>
<td>Preformed Creatinine</td>
<td>87.1</td>
<td>35.5</td>
</tr>
<tr>
<td>9/10-6</td>
<td></td>
<td>Creatine as Creatinine</td>
<td>105.7</td>
<td>55</td>
</tr>
<tr>
<td>10/11-6</td>
<td></td>
<td>Urine cc.</td>
<td>540</td>
<td>254</td>
</tr>
<tr>
<td>5. 37 weeks</td>
<td></td>
<td>Total Creatinine</td>
<td>191.6</td>
<td>91.9</td>
</tr>
<tr>
<td>6/5 kg.</td>
<td></td>
<td>Preformed Creatinine</td>
<td>89.6</td>
<td>44.4</td>
</tr>
<tr>
<td>24/23-6</td>
<td></td>
<td>Creatine as Creatinine</td>
<td>102.0</td>
<td>47</td>
</tr>
<tr>
<td>25/26-6</td>
<td></td>
<td>Urine cc.</td>
<td>897</td>
<td>346</td>
</tr>
<tr>
<td>6. 48 weeks</td>
<td></td>
<td>Total Creatinine</td>
<td>213.8</td>
<td>109.9</td>
</tr>
<tr>
<td>7/9 kg.</td>
<td></td>
<td>Preformed Creatinine</td>
<td>83.6</td>
<td>43</td>
</tr>
<tr>
<td>20/21-6</td>
<td></td>
<td>Creatine as Creatinine</td>
<td>130.2</td>
<td>66</td>
</tr>
<tr>
<td>21/22-6</td>
<td></td>
<td>Urine cc.</td>
<td>794</td>
<td>413</td>
</tr>
</tbody>
</table>
It is well known that adults normally excrete more creatinine during the day than during the night, a fact which has been attributed by different observers to varying muscular tonus. The above findings in the infant might lend some support to this theory, since in them the mode of life as regards sleep and muscular tonus is the same by day and by night. It is possible, of course, on the assumption that creatinine is purely a waste product and has no value in synthetic processes, as suggested to me by Professor Cathcart, that there may be in the adult during the day time increased anabolic changes, leading to a more rapid throwing out of effete tissue. If this be the explanation then the results would point to a greater uniformity in the diurnal and nocturnal metabolic processes in the case of the infant.

Creatine.—In all our cases the curve showing the three-hourly creatine elimination is markedly irregular and almost invariably parallel to the urinary output, which would appear to be at least the chief determining factor.

**Chart I.**

Showing excretion of Creatinine, Creatine (in mgs.) and Urine (in ccs.) in three-hourly periods during the day and night.
In this connection it is interesting to record that Fowler and Howk(8)
studying water-drinking in a male adult found that creatine, which is
normally absent from the urine of male adults, appeared after the ingestion
of large amounts of water. They explained this phenomenon by the
increased catabolism of protein induced by the increased intake of water,
the subsequent “flushing-out process” removing end-products from the
body tissues. The variations of creatine output are best illustrated by the
following chart, which represents graphically the findings in Case 1.

The origin of creatinuria in infancy and childhood is a question of great
interest and no little difficulty. In the normal adult creatinuria depends
wholly on the diet and is thus considered exogenous in origin, whereas in
the infant, owing to the general belief that milk is creatine-free, the
creatinuria during this period of life has been usually assumed to be
endogenous in origin. It has been shown by Gamble and Goldschmidt(9),
however, that a higher creatine output resulted when the infant’s diet
consisted of whole milk, than when the diet consisted of milk from which
the whey was removed, and they concluded that creatine of exogenous
origin was thus an important factor in the creatinuria of infants. Folin(10)
has demonstrated that large amounts of creatine may be ingested by a
normal adult man without any appearing in the urine, and Gamble and
his co-worker(11) have shown that creatine ingested by infants may be
excreted quantitatively. It would thus appear that not only the presence
of creatine in milk but also the varying ability of the infant to metabolise
creatine are concerned in both the appearance of creatine in the urine of
the infant and its irregular excretion as shown in our results. It is worthy
of note that the total output of creatine during 24 hours in our cases
approaches the total creatinine output, and that the amounts of creatine
excreted by day and by night are roughly equal.

Conclusions.

(1) In the healthy infant the rate at which creatine is excreted as
judged by three-hourly periods is fairly constant; this constancy becomes
more marked when expressed in day and night ratios. The amount of
creatine excreted is independent of the volume of urine voided.

Two explanations, both hypothetical, are offered for the above stated
facts, viz.:-Uniformity of muscular tonus and uniformity of anabolic
processes in the infant during the day and night.

(2) Creatine output is irregular and is closely related to the volume of
urine passed.

Three factors are suggested in explanation of this phenomenon:
(a) the “flushing-out process” due to the high water intake of the infant;
(b) the presence of exogenous creatine in cow’s milk; and (c) the inability
of the infant to metabolise creatine.
(3) On the basis of the findings in this study it would appear that creatinine estimations for clinical purposes may be done on the basis of collections over short periods, but in the case of creatine studies over longer periods are essential.

I desire to express my gratitude to Professor Leonard Findlay and to Professor E. P. Catheart for their kind help and suggestions.

REFERENCES.