ON THE CONSTANCY OF THE CREATINE-CREATININE EXCRETION IN CHILDREN ON A HIGH PROTEIN DIET.*

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In a general way it is usually agreed that the appearance of creatine in the urine is concomitant with a lowered creatinine excretion, and such a generalized idea has been adduced as a reason for the biochemical interrelationship of the two substances. So diverse, however, have been the conditions under which creatinuria has been observed to appear and disappear, that such a generalized expression has never been accorded the validity of a biochemical law.

The clearest example of the reciprocal relationship of creatine and creatinine, and the consequent constancy of the excretion of the sum of both in an individual, is perhaps to be found in the work of Benedict and Diefendorf (1) on starvation in a woman. Goldschmidt, Pepper, and Pearce (2) point out the constancy of the total creatinine (creatine + creatinine) in a child of 5½ years, observed before and after splenectomy. Cameron and Gibson (3), from a study of the creatine-creatinine excretion in various cases of muscular dystrophy, and in amputations, argue strongly for the interrelationship of the two.

The clear-cut character of results such as these, however, has not always been attained, and it is such failures which have militated against the placing of the relationship of creatine and creatinine upon a quantitative basis. Thus, to cite only one recent example, we may mention the work of M. S. Rose (4) upon creatinuria in women, where after noticing that “very often when

* The authors wish to acknowledge the assistance of a grant from the Research Committee of the Medical Faculty of the University of Toronto.
the creatine was high the creatinine was low, and vice versa," she observes, "but in plotted curves the sum of the two did not make a straighter line than either one alone."

So many factors, however, have been found to influence the excretion of creatine (acidosis, dietary protein, water drinking), that such failures are not surprising, and it is only when such factors are brought under rigid control or are compensated by observations over longer periods of time and the taking of averages, that the reciprocal relationship of creatine and creatinine is shown to be quantitative.

In the present paper, we wish to show that normal children of the same age and under the same environment, excrete the same quantity of total creatine (creatine + creatinine in terms of creatine). And that, if the total creatine in milligrams be expressed as a coefficient of the body weight in kilos, the figure obtained is a constant, independent of the age of the child, and of the same magnitude as the creatinine coefficient of an adult man. This figure we have called the "total creatine coefficient."

The experiments upon which these conclusions are based were commenced with the object of repeating the observations of Denis and Kramer (5) upon the creatinuria of children, and we may say that our experiments are corroborative of the findings both of these workers and of Powis and Raper (6). We wish, however, in this communication, to report the results obtained on as high a protein diet as the child could conveniently consume. At the outset we wish to emphasize the normal character of our children. They were children living at an Institute1 on the outskirts of the city, and who had been sent there as mild cases of malnutrition with a history of possible exposure to tuberculosis. In none of them, however, had there been any active infection, and all were at normal weight and actively engaged in play in the grounds of the Institution. They were thus during the experiment, and for some time previous had been, under the same environmental conditions of diet and exercise. Twelve children were selected and divided

1 The authors wish to express their thanks to the Governors of the Daughters of the Empire Preventorium for permission to use their laboratories, and the facilities for work which they afforded. Thanks are also due to Professor Alan Brown, of the Department of Pediatrics, for the keen interest he has taken in the work.
into three groups according to age, and each group consisted of
two children of each sex. They were fed at a separate table, and
the diet and urine collections were made the special care of one
nurse. Each group was studied separately. The diet consisted
of cereals, eggs, bread, butter, milk, \(^2\) potato, vegetables, sugar,
and oranges. The amount taken at each meal was charted, and
the nitrogen intake calculated. Except that the children were
deprived of meat and soups made from meat stock, the diet did
not differ markedly from that to which they were accustomed,
and as meat was in the ordinary routine, only supplied once a
day, the experimental period represented no sharp break from
their customary diet. In Table I are presented the average figures
for a 3 day period for each child when on the high protein diet.
The constancy of the nitrogen excretion of each group upon the
same diet will be noted.

Group A, the youngest children, shows a remarkable constancy
in the total creatine excretion, each child varying but a few milli-
grams from the average of the whole group (344 mg.). Group B
also shows a good agreement in the excretion of total creatine by
each child, and it is Group C which shows the greatest discrepan-
cies. In this last group, it would almost appear that the boys
were separating from the girls. If, however, we compare the total
creatine coefficients with the creatinine coefficients, the reciprocal
nature of creatine and creatinine in children comes clearly to light.
The creatinine coefficients range from 10.1 to 18.2, whereas the
total creatine coefficients vary from 21.3 to 27.6, and this last
figure stands alone in this series, a much better high limit being
24.7. The averages for each group too are instructive. The
average creatinine coefficient for each group rises definitely with
increasing age and weight, accompanied as it is by an increasing
percentage of musculature. The total creatine coefficient, how-
ever, is remarkably steady around the total average of 23.1.
 Particularly interesting too, is the case of L. G. in Group C. This
girl was a big, heavy girl, overweight according to her age, and
whose creatinine coefficient was distinctly under the average of
her group. Yet, she excreted nearly half as much creatine again,

\(^2\) The ingested creatine coming from the milk amounted to 20 to 30 mg.
per day. This amount is of insignificance compared with the total
excretion.
Creatine-Creatinine Excretion

as her companion girl in the same group, and her total creatine coefficient becomes almost exactly the same as the total average.

These findings, like those of Folin and Denis (7) and Denis and Kramer (5), receive their simplest interpretation by assuming that

TABLE 1.*

<table>
<thead>
<tr>
<th>Child</th>
<th>Sex</th>
<th>Weight</th>
<th>Nitrogen intake</th>
<th>Total urine nitrogen</th>
<th>Average creatine</th>
<th>Average creatinine excretion</th>
<th>Total creatine</th>
<th>Total creatine coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>H.C.</td>
<td>&quot;</td>
<td>14.0</td>
<td>12.1</td>
<td>6.78</td>
<td>141</td>
<td>10.1</td>
<td>145</td>
<td>308.56</td>
</tr>
<tr>
<td>G.L.</td>
<td>M</td>
<td>14.5</td>
<td>12.1</td>
<td>6.21</td>
<td>180</td>
<td>12.5</td>
<td>121</td>
<td>329.80</td>
</tr>
<tr>
<td>V.D.</td>
<td>&quot;</td>
<td>15.0</td>
<td>12.1</td>
<td>6.85</td>
<td>200</td>
<td>13.6</td>
<td>125</td>
<td>357.00</td>
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<tr>
<td>Group average</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Group A. Ages 2½ to 3½ yrs.

Group B. Ages 4 to 4½ yrs.

<table>
<thead>
<tr>
<th>Child</th>
<th>Sex</th>
<th>Weight</th>
<th>Nitrogen intake</th>
<th>Total urine nitrogen</th>
<th>Average creatine</th>
<th>Average creatinine excretion</th>
<th>Total creatine</th>
<th>Total creatine coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.M.C.</td>
<td>F</td>
<td>16.5</td>
<td>11.4</td>
<td>6.25</td>
<td>223</td>
<td>13.7</td>
<td>100</td>
<td>358.68</td>
</tr>
<tr>
<td>D.F.</td>
<td>&quot;</td>
<td>19.1</td>
<td>11.4</td>
<td>7.34</td>
<td>276</td>
<td>14.2</td>
<td>109</td>
<td>429.16</td>
</tr>
<tr>
<td>W.R.</td>
<td>M</td>
<td>19.0</td>
<td>11.4</td>
<td>8.43</td>
<td>281</td>
<td>15.0</td>
<td>90</td>
<td>415.96</td>
</tr>
<tr>
<td>A.L.</td>
<td>&quot;</td>
<td>17.0</td>
<td>11.4</td>
<td>7.00</td>
<td>261</td>
<td>16.6</td>
<td>77</td>
<td>379.76</td>
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</tr>
<tr>
<td>Group average</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

Group C. Ages 9 to 9½ yrs.

<table>
<thead>
<tr>
<th>Child</th>
<th>Sex</th>
<th>Weight</th>
<th>Nitrogen intake</th>
<th>Total urine nitrogen</th>
<th>Average creatine</th>
<th>Average creatinine excretion</th>
<th>Total creatine</th>
<th>Total creatine coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>C.A.</td>
<td>F</td>
<td>28.8</td>
<td>15.6</td>
<td>10.94</td>
<td>524</td>
<td>18.2</td>
<td>187</td>
<td>794.84</td>
</tr>
<tr>
<td>L.G.</td>
<td>&quot;</td>
<td>33.5</td>
<td>15.6</td>
<td>10.06</td>
<td>430</td>
<td>14.1†</td>
<td>259</td>
<td>769.24</td>
</tr>
<tr>
<td>R.A.</td>
<td>M</td>
<td>25.0</td>
<td>15.6</td>
<td>10.61</td>
<td>454</td>
<td>18.0</td>
<td>90</td>
<td>616.64</td>
</tr>
<tr>
<td>S.G.</td>
<td>&quot;</td>
<td>27.6</td>
<td>14.3</td>
<td>9.13</td>
<td>476</td>
<td>17.6</td>
<td>36</td>
<td>588.16</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group average</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Analytical Methods.—Total nitrogen, micro method of Gulick. Creatine and creatinine, micro method of Folin using creatinine-zinc chloride as standard, pH, method of Palmer and Henderson; these never showed any significant variations.

†Excluded from average.

creatine is produced from protein either in toto or from a special fraction of it, is stored in the muscles, and is converted into creatinine. With the saturation of the muscles with creatine, any excess production will find its way into the urine, and provided the
dietary protein is not reduced to such a low level that a condition of protein starvation occurs, the urinary creatine will appear as a waste product of exogenous origin. If, however, the constancy of the total creatine coefficient, when upon a high protein diet, is admitted, it would involve the conclusion that creatine production reaches a maximum, and that once that maximum is reached no amount of further feeding of protein, however excessive, will result in an augmented creatinuria. Similarly, moderate decreases in protein intake may fail to lower or abolish an existing creatinuria. That such a maximum probably exists can be shown experimentally in dogs, and these results will be reported later.

The acceptance of these conclusions also involves a further corollary that the muscular system does not control the production of creatine. It is certainly remarkable that a child of 3 years should produce per kilo body weight as much total creatine as an adult man. The muscular system of the child has not reached its maximum percentage of the total body weight, and the relative creatinine production is low. It would thus appear that creatine disappears from the urine of the adult man when the creatinine coefficient has attained its average maximum value, and the muscular system has also reached its average adult percentage of the total body weight. This being so, one can only agree in part with Mellanby (8) that the production of creatine is not controlled by the muscular system, which is in harmony with its phylogenetic and ontogenetic history. Cameron and Gibson (3) in a recent article, have expressed a similar conclusion from a study of the creatine-creatinine excretion in muscular dystrophies and amputations.

Influence of Age and Sex upon Creatinuria.

In view of the figures given in Table I and the conclusions which have just been expressed, it is evident that some of the current conceptions on the effect of age and sex upon the creatine excretion of children, require revision. These conceptions are based upon the work of Rose (9) and Krause (10). The former drew the conclusion that creatine was present in the urine of children up to the age of puberty; the latter that creatinuria was present in boys up to the age of 5 to 6 years, but that in girls, it continued up to the age of 10. Undoubtedly, in drawing this conclusion
Krause was influenced by his previous observations that creatinuria could occasionally be found in normal adult women. It is very evident that boys of ages higher than 5 or 6 years excrete creatine, if sufficient protein is supplied in the diet, and judging from the amounts of creatine excreted by the two girls in Group C, that they would continue excreting creatine long after the age of 10.

The relation of the creatinine coefficient to the total creatine coefficient, however, shows that on the average creatine will disappear from the urine of both boys and girls at about the age of 16 years, if each sex develops the muscular system to the same degree. This figure has been attained by plotting the group creatinine coefficients against the group age and extrapolating the curve obtained until it reaches the figure equivalent to the average total creatine coefficient. It is interesting to note that at this age the muscular system has attained its maximum development in relation to body weight forming about 44 per cent of the total (11). In thus setting 16 years as the age at which creatinuria will disappear even upon a high protein diet, it is only intended to convey that that is an average figure. Undoubtedly, cases will be found in which creatinuria persists beyond this age. Thus, Folin and Denis (7) report the case of a normal boy of 17 still excreting creatine, and undoubtedly there must be many cases where creatine has disappeared at an age earlier than the average.

As far as our figures show, there is no distinct influence of sex in the early years. Apparently, however, there is a slight divergence in later years (Group C), but the figures are not sufficiently numerous to permit of the drawing of decided conclusions. The well known results of Tracy and Clark (12) on the low creatinine coefficients of normal women as contrasted with normal men, would however, incline us to believe that taken on the average, the majority of women would show creatinuria on a high protein diet. This, we believe, in spite of the negative results of Rose (4) and Rose, Dimmitt, and Bartlett (13). In this connection, we think that an examination of the results shown by the two girls of Group C is of interest. Both girls, of the same age and upon the same diet excrete almost the same amount of nitrogen. L. G. has a low creatinine coefficient and is a fat, heavy girl. It might therefore be expected that she would continue to excrete creatine for at any rate a longer period of her life.
than her companion C. A., especially as her excretion under identical conditions is nearly 50 per cent higher. Such a prediction should be true for the average case. Girl C. A., however, possesses an exceptionally high total creatine coefficient and would need to develop an exceptionally vigorous muscular system in order to attain a creatinine coefficient equivalent to 27.6. While we believe that on the average, the height of the creatinine coefficient gives a method of predicting the presence or absence of a creatinuria upon a high protein diet we have no means of foretelling the exact height of the total creatine coefficient in the individual.

Total Creatine Coefficient in Some Pathological Conditions.

In order to see whether the conclusions drawn from a study of the creatine excretion in children are applicable to creatinuria in pathological conditions when on high protein diets, we have tabulated in Table II some results of our own, and such results in the literature as we could find, and in which were reported the requisite data. It will be seen that with two exceptions, creatinuria in pathological conditions shows the same general rule as creatinuria in children. The total creatine coefficient averages 21.9, a figure very close to that given as the average for children of 22.7, and that the variations in the coefficient cover the same range as does the creatinine coefficient in normal man. This, we think is remarkably good agreement, as the conditions of diet were not uniform, and the investigators, including ourselves at the time of the observations, were quite unaware of the constancy of this figure. The two exceptions are possibly to be explained by the exceptionally heavy weight of the boy O. Sch., and that child D. R. was on so low a protein diet, that some of the creatine may be of starvation origin.

Particular interest attaches itself to the observations in the hyperthyroid cases reported by ourselves, Denis, and Denis and Minot. Owing to the experimental work on creatinuria in this condition, a great deal of attention has been centered on the thyroid, and Gross and Steenbock (14) have made the function of this gland an essential part of their theory of the origin of creatine from arginine. It would not appear from the results we have just given that the thyroid gland plays any direct rôle
**TABLE II.**

Calculation of Creatinine and Total Creatine Coefficients in Some Pathological Conditions.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Subject</th>
<th>Sex</th>
<th>Age (yrs)</th>
<th>Weight (kg)</th>
<th>Average N intake</th>
<th>Creatinine coefficients</th>
<th>Total creatine coefficients</th>
<th>Observer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperthyroid</td>
<td>L. B.</td>
<td>F</td>
<td>53</td>
<td>40.3</td>
<td>10.5</td>
<td>10.3</td>
<td>21.9</td>
<td>Harding and Gaebler,*</td>
</tr>
<tr>
<td>&quot;</td>
<td>P. S.</td>
<td>&quot;</td>
<td>45</td>
<td>50.7</td>
<td>7.9</td>
<td>9.3</td>
<td>17.3</td>
<td>&quot;</td>
</tr>
<tr>
<td>&quot;</td>
<td>A. S.</td>
<td>&quot;</td>
<td>41</td>
<td>65.2</td>
<td>12.4</td>
<td>12.9</td>
<td>27.5</td>
<td>&quot;</td>
</tr>
<tr>
<td>&quot;</td>
<td>V. E.</td>
<td>&quot;</td>
<td>29</td>
<td>61.2</td>
<td>10.1</td>
<td>14.0</td>
<td>20.1</td>
<td>&quot;</td>
</tr>
<tr>
<td>&quot;</td>
<td>M.</td>
<td>M</td>
<td>33</td>
<td>55.2</td>
<td>8.25</td>
<td>12.6</td>
<td>22.5</td>
<td>Denis (15)</td>
</tr>
<tr>
<td>&quot;</td>
<td>II</td>
<td>M</td>
<td>35</td>
<td>58.0</td>
<td>13.53</td>
<td>21.7</td>
<td>34.9</td>
<td>&quot;</td>
</tr>
<tr>
<td>&quot;</td>
<td>III</td>
<td>F</td>
<td>21</td>
<td>59.0</td>
<td>9.47</td>
<td>13.7</td>
<td>23.0</td>
<td>&quot;</td>
</tr>
<tr>
<td>&quot;</td>
<td>IV</td>
<td>&quot;</td>
<td>46</td>
<td>52.3</td>
<td>8.76</td>
<td>12.2</td>
<td>16.6</td>
<td>&quot;</td>
</tr>
<tr>
<td>&quot;</td>
<td>V</td>
<td>&quot;</td>
<td>23</td>
<td>54.5</td>
<td>9.97</td>
<td>12.8</td>
<td>18.9</td>
<td>&quot;</td>
</tr>
<tr>
<td>&quot;</td>
<td>III</td>
<td>&quot;</td>
<td>32</td>
<td>45.0</td>
<td>13.97</td>
<td>16.1</td>
<td>27.0</td>
<td>Denis and Minot (16)</td>
</tr>
<tr>
<td>&quot;</td>
<td>IV</td>
<td>&quot;</td>
<td>22</td>
<td>41.0</td>
<td>10.91</td>
<td>15.2</td>
<td>24.0</td>
<td>&quot;</td>
</tr>
<tr>
<td>&quot;</td>
<td>V</td>
<td>&quot;</td>
<td>28</td>
<td>51.0</td>
<td>12.11</td>
<td>10.5</td>
<td>21.3</td>
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<tr>
<td>&quot;</td>
<td>VI</td>
<td>&quot;</td>
<td>27</td>
<td>63.3</td>
<td>17.31</td>
<td>11.2</td>
<td>23.5</td>
<td>&quot;</td>
</tr>
<tr>
<td>Muscular dystrophy</td>
<td>O. Sch.</td>
<td>M</td>
<td>15</td>
<td>90.0</td>
<td>9.62</td>
<td>2.82*</td>
<td>10.3*</td>
<td>Gibson, Martin, and Buell (17).</td>
</tr>
<tr>
<td>&quot;</td>
<td>B. McD.</td>
<td>&quot;</td>
<td>22</td>
<td>53.0</td>
<td>11.38</td>
<td>19.48</td>
<td>25.6</td>
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</tr>
<tr>
<td>&quot;</td>
<td>L. W.</td>
<td>&quot;</td>
<td>25</td>
<td>63.0</td>
<td>9.92</td>
<td>19.7</td>
<td>25.4</td>
<td>&quot;</td>
</tr>
<tr>
<td>&quot;</td>
<td>J. Sch.</td>
<td>&quot;</td>
<td>6</td>
<td>18.2</td>
<td>4.62</td>
<td>7.56</td>
<td>20.7</td>
<td>&quot;</td>
</tr>
<tr>
<td>&quot;</td>
<td>D. R.</td>
<td>&quot;</td>
<td>8</td>
<td>21.8</td>
<td>3.96</td>
<td>13.53</td>
<td>38.2†</td>
<td>&quot;</td>
</tr>
</tbody>
</table>

Average....................................................... 13.8 21.9

* The authors wish to thank Dr. W. Campbell of the Toronto General Hospital for his cooperation in these cases.
† Excluded from averages.
V. J. Harding and O. H. Gaebler

in the production of creatinuria. Acromegaly, muscular dystrophies, and children all show a power to produce the same amount of creatine per kilo body weight as the normal adult. Only in so far as the activities of the thyroid alter the proportion of muscular mass to total body weight, does that gland contribute a quota to the production of a creatinuria.

BIBLIOGRAPHY.

15. Denis, W., J. Biol. Chem., 1917, xxx, 47.
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