THE RATE OF UREA EXCRETION.

IV. THE EFFECT OF CHANGES IN THE VOLUME OF URINE ON THE RATE OF UREA EXCRETION.

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Since the concentration of urea in the blood influences the rate at which urea passes through the urea-secreting cells of the kidney, it seems likely that the concentration of urea in the urine in contact with the internal surfaces of these cells should also have an effect. A high concentration would tend to delay, and a low concentration to facilitate the discharge of urea from the cells, at least if the mechanism of this discharge depended on a process of diffusion. It is, of course, obvious that we cannot determine the actual urea concentration of the urine which lies next to the urea-secreting cells. The anatomical evidence given by Leschke,¹ which has been confirmed by Oliver,² demonstrates that urea is secreted by the cells of the proximal convoluted tubules. Since there is every reason to believe that a great part of the water of the urine passes through the glomeruli, we should expect that a series of different concentrations, increasing in proportion to the distance from the glomerulus, will be present along the reaches of each proximal tubule. And when, further, the possible occurrence of secretion and absorption of water at lower levels of the tubular system is remembered, it becomes apparent that we cannot assume any close or constant relationship between the urea concentration in urine collected from the bladder, and the urine as it lies in the proximal tubules. We have grounds, however, for believing that a rough general parallelism exists, and that when the urea concentration of collected urine is found to be greatly

² Oliver, J., J. Exp. Med., 1916, xxiii, 301.
decreased as the result of an increase in volume produced by water drinking, there will also be a decrease in the average concentration in the proximal tubules.

In observations on the volume of urine of subjects under constant dietary conditions, we found that the urine volume was increased when the rate of urea excretion was approximately doubled by the administration of urea. On the other hand, the rate of urea excretion was not increased when the urine volume was doubled by the administration of water. This raises the question as to whether there may not be a general relationship between rate of urea excretion and volume of urine of such a nature that the urea excretion influences the volume, in contradistinction to the idea of the volume influencing the urea, which is implied in the above mentioned theoretical considerations as to the possible effect of the urea concentration of the urine.

With the data at our disposal, we can determine whether there is evidence of any general relationship between the volume of urine and the rate of urea excretion, such as would lend support to either of these hypotheses. This might be accomplished by determining the net correlation between these two factors by means of a formula for partial correlation. But it was pointed out to us that the distribution in our material of the three variables (rate of urea excretion, volume of urine, and concentration of urea in the blood) was so far from normal as to render any coefficient of correlation somewhat misleading. It was therefore considered better to eliminate the factor of blood urea concentration by plotting the rates of urea excretion as plus or minus differences between the observed hourly rates and those which the curve shown in Fig. 1 of the preceding paper indicated as normal for the blood concentration found in each instance.

These differences are represented in Fig. 1 by the ordinate, while the abscissa measures the volume of urine per hour. It is apparent that there is no general relationship between the volume of urine and the rate of urea excretion, since there is no indication that the minus values occur predominantly with low volumes of urine, nor any clear tendency towards a gradual increase over the normal value to successively greater plus values.

Fig. 1. The absence of any direct relationship between changes in the volume of urine and the rate of urea excretion. Observations on a group of individuals. The circles indicate experiments in which no urea was given, and the triangles those in which urea was administered.
as the urine volume increases. This absence of relationship between volume and rate of excretion means that there is also no relation between the concentration of urea in the urine and the rate of excretion, because this concentration is the amount of urea in 1 hour's urine (the rate of excretion) divided by the hourly volume of urine.

In a recent paper\(^3\) we said we had evidence that under certain conditions the volume of urine was an important factor in determining the rate of urea excretion. The conditions we had in mind were those in which the volume of urine was unusually low because of abstention from water and was then suddenly increased by copious water drinking. We found that concomitantly with the rise in urine volume there was an acceleration of the rate of urea excretion which was not accounted for by any increase in blood urea concentration. But a more complete analysis of the figures showed such discrepancies between the degrees of increase in rate of urea excretion and volume that there cannot be said to be any indication of a causal relationship between them. In Table I we give the details of an experiment carried out under these conditions.

During the first period of this experiment, the hourly volumes of urine were small because the subject had taken no water or food for 12 hours. At the commencement of the second period 20 gm. of urea were taken in a concentration at about the maximum concentration the normal kidney is capable of secreting. This led to a call for an increase in the rate of urea excretion under conditions in which there would tend to be a relative insufficiency of water available for carrying out the added urea. During the third period the body was flooded with water by the ingestion of 1,500 cc. and the drinking thereafter every quarter of an hour of amounts of water equivalent to the volumes of urine excreted.

The outstanding feature of the experiment is the increase in the rate of urea excretion which accompanied the rise in urine volume induced by water drinking. The rates which during the first and second periods were all lower than the normal as given by the curve become higher than normal during the third period. There can be no question from the results of this and other experiments that abstention from food and water tends to lower, and the drinking of large quantities of water to increase the rate,
independently of the blood urea concentration. On the other hand, the want of parallelism between the volumes and the differences between the actual and normal rates is so complete that we cannot say that the rates increase because of the rise in urine volumes, or that the volumes increase because of the rise in the rate of urea excretion. The greatest increase over the normal rate occurs when the volume of urine is still not unusually large while when the diuresis is at its maximum the rate is less

<table>
<thead>
<tr>
<th>Period</th>
<th>Actual urea excretion per hr.</th>
<th>Blood urea concentration per 100 cc.</th>
<th>Normal urea concentration found</th>
<th>Difference between the actual and the normal rates</th>
<th>Volume of urine per hr.</th>
<th>Times between which urine was collected</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Nothing taken. No food or water during the previous 12 hours.</td>
<td>0.47</td>
<td>0.036</td>
<td>0.92</td>
<td>-0.45</td>
<td>29</td>
<td>9:42-10:45 a.m.</td>
</tr>
<tr>
<td></td>
<td>0.38</td>
<td>0.029</td>
<td>0.65</td>
<td>-0.27</td>
<td>25</td>
<td>10:45 a.m.-12:45 p.m.</td>
</tr>
<tr>
<td></td>
<td>0.48</td>
<td>0.030</td>
<td>0.70</td>
<td>-0.22</td>
<td>26</td>
<td>12:45-2:00 p.m.</td>
</tr>
<tr>
<td>2. At 2 p.m. 20 gm. of urea were taken in 5.6 per cent solution.</td>
<td>1.50</td>
<td>0.064</td>
<td>2.31</td>
<td>-0.81</td>
<td>68</td>
<td>2:00-3:00 p.m.</td>
</tr>
<tr>
<td></td>
<td>1.25</td>
<td>0.070</td>
<td>2.65</td>
<td>-1.40</td>
<td>41</td>
<td>3:00-4:00 p.m.</td>
</tr>
<tr>
<td>3. At 4 p.m. 1,500 cc. of water were taken and thereafter a quantity equal to the volumes of urine excreted.</td>
<td>2.37</td>
<td>0.067</td>
<td>2.48</td>
<td>-0.11</td>
<td>70</td>
<td>4:00-4:30 p.m.</td>
</tr>
<tr>
<td></td>
<td>3.67</td>
<td>0.066</td>
<td>2.42</td>
<td>+1.25</td>
<td>120</td>
<td>4:30-4:45 p.m.</td>
</tr>
<tr>
<td></td>
<td>3.30</td>
<td>0.066</td>
<td>2.24</td>
<td>+0.44</td>
<td>176</td>
<td>4:45-5:00 p.m.</td>
</tr>
<tr>
<td></td>
<td>2.64</td>
<td>0.066</td>
<td>2.42</td>
<td>+0.22</td>
<td>352</td>
<td>5:00-5:15 p.m.</td>
</tr>
<tr>
<td></td>
<td>2.40</td>
<td>0.066</td>
<td>2.42</td>
<td>-0.02</td>
<td>440</td>
<td>5:15-5:30 p.m.</td>
</tr>
</tbody>
</table>

Similar discrepancies are noted when the changes in the urea concentration of the urine are compared with the rate. Thus both the highest (+) and the lowest (−) rates occur in periods during which the urine concentration is 3 per cent.

We no longer believe, therefore, that we are justified in tracing a direct relationship between the volume of urine and rate of urea excretion. All that we can say is that conditions accompanied by low urine volumes are also frequently associated with
subnormal rates of urea excretion and that when a large quantity of water is drunk the rate of excretion may become greater than normal as the urine volume increases. But these two phenomena appear to be independent of one another. Both may be the result of some common cause, such as an alteration in the blood circulation through the kidneys or a change in the activity of the kidney cells. If changes in the free water content of the blood have an effect on urine volume comparable to that which alterations in its urea concentration have on the rate of urea excretion, it might be possible to demonstrate a parallelism between variations from normal volumes and normal rates under the influence of some such common cause.

CONCLUSIONS.

1. Changes in the volume of urine or in the urea concentration of the urine have no appreciable effect on the rate of urea excretion.

2. When no food or water have been taken for some time, the drinking of large quantities of water is followed by an increase in urine volume and by a synchronous acceleration of the rate of urea excretion which cannot be accounted for on the basis of changes in blood urea concentration. But there is no evidence that this increased rate is a result of the increased volume of urine for the degree of increase above the normal in the rate is quantitatively independent of the degree of increase in volume.
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