THE RENAL TUBULAR REABSORPTION OF GLUCOSE IN THE NORMAL DOG

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It is known that glucose is filtered through the glomerulus in the same concentration as it is present in the water of the plasma (Walker and Reisinger, 1933), and that its absence from the urine at normal plasma concentrations is due to the circumstance that it is reabsorbed by the tubule. In the amphibian kidney, this reabsorption is effected by the proximal segment (Walker and Hudson, 1937). In mammals the reabsorptive process is never complete, a small amount of glucose being present in the urine at normal plasma glucose levels (Harding, Nicholson and Archibald, 1936). Frank glycosuria at elevated plasma glucose levels is due, not to the complete cessation of reabsorption, but to the fact that more glucose is filtered than can be reabsorbed (Ni and Rehberg, 1930).

Ni and Rehberg (1930) have given a quantitative description of the reabsorption process, but we believe that their data are unsuitable for this purpose because venous blood was used for the calculation of the rate of glucose filtration in their experiments, because there were marked variations in the rate of filtration, and because significant errors were introduced by very rapidly changing plasma glucose concentrations. The present observations, also directed towards a quantitative description of the reabsorptive process, have been made in such a manner as to eliminate these sources of error.

EXPERIMENTAL PROCEDURE. Observations have been made upon two normal, well trained female dogs which were loosely restrained upon a comfortable animal board, and upon four dogs decerebrated under ether and chloroform anesthesia some hours prior to their use. Constant creatinine and varying glucose concentrations in the plasma were obtained by means of constant intravenous infusions. Urine collections were made by an inlying catheter, and at the end of each period the bladder was emptied as completely as possible and washed with warm water, this wash fluid being added to the urine prior to the final dilution for analysis. In the decerebrate dogs the ureter was cannulated and the urine delivered directly into a collecting vessel through a glass tube of small volume.
All bloods were obtained at the mid-period by puncture of the femoral artery.

Chemical Methods. Potassium oxalate was used in minimal quantities as an anticoagulant. The bloods were centrifuged immediately and the plasma precipitated within ten minutes of withdrawal from the animal, using the ferric sulphate-barium carbonate method (Steiner, Urban and West, 1932). The diluted urines were precipitated by the same method. Glucose was determined by the Folin (1929) method on plasma and urine filtrates diluted so that the actual concentration of glucose was close to 15 mgm. per cent. In the lower ranges of plasma glucose (i.e., below 500 mgm. per cent) all figures for urine glucose are given as the difference in copper reduction before and after absorption on yeast (Somogyi, 1928). Plasma and urine glucose has been taken as the observed glucose concentration minus 0.2 times the concentration of creatinine, a correction factor based on determinations of the reducing power of creatinine, using the above methods of precipitation and glucose analysis. The correction is of quantitative importance only in the range of plasma glucose at and below the level of frank glycosuria.

Creatinine determinations on plasma and urine filtrates were performed by the Folin and Wu (1919) method. The Jaffe reaction yields slight color with glucose in the concentrations involved in these experiments (Shannon, Jolliffe and Smith, 1932); we have avoided errors due to this circumstance by maintaining the plasma creatinine concentrations at 30 to 40 mgm. per cent, and reading the creatinine determinations in small groups between 10 and 14 minutes after the addition of the alkaline picrate. With these precautions the error in the determination of the creatinine clearance is negligible at moderate plasma glucose levels, and it does not increase appreciably at the higher glucose levels since the urine filtrates are diluted to the U/P ratio of creatinine, and consequently contain almost as much glucose as do the plasma filtrates. If the clearance of glucose or creatinine for any period, as calculated from each set of duplicate analyses, did not agree within two per cent, a third set was analyzed and the two showing best agreement were accepted. The values used for our calculations were the means of these duplicate analyses.

Experimental results. The experiments on normal dogs consisted of several groups of two or three observations made at successively higher plasma glucose concentrations. The procedure was such that the plasma glucose concentration was maintained at a nearly steady level in each group of observations and the creatinine clearance was essentially constant throughout the experiment. A typical series of observations of this type, made upon the normal dog, is given in table 1 and figure 1. A summary of five experiments is given in figure 2.

The absolute quantity of glucose reabsorbed by the tubules per unit
time is given by the difference between the rate of excretion and the rate of filtration of the sugar. This last term is given by the product of the plasma concentration and the creatinine clearance. Calculations made in this manner reveal that the tubular reabsorption of glucose is limited by the existence of a maximal rate. So long as the rate of filtration is such as to deliver glucose to the tubules at less than this maximal rate,

### TABLE 1

*An experiment on a normal dog showing the relationship between glucose plasma concentration and its renal tubular reabsorption*

Dog C, 24.0 kgm.

<table>
<thead>
<tr>
<th>PERIOD</th>
<th>TOTAL CONCURRENT TIME</th>
<th>URINE FLOW</th>
<th>PLASMA LEVEL</th>
<th>CLEARANCE</th>
<th>CLEARANCE RATIO</th>
<th>GLUCOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>cc. per min.</td>
<td>mgm. per cent</td>
<td>cc. per min.</td>
<td>mgm. per cent</td>
<td>cc. per min.</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>1000 cc. water by stomach tube, 3 grams creatinine intravenously, infusion 5 per cent glucose, 0.55 per cent creatinine at 8 cc. per minute</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>30-39</td>
<td>2.45</td>
<td>31.6</td>
<td>126</td>
<td>115.0</td>
<td>145</td>
</tr>
<tr>
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<td>30-10</td>
<td>2.30</td>
<td>32.4</td>
<td>128</td>
<td>117.5</td>
<td>150</td>
</tr>
<tr>
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<td>115-125</td>
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<td>238</td>
<td>112.4</td>
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</tr>
<tr>
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<td>4.75</td>
<td>33.6</td>
<td>246</td>
<td>116.3</td>
<td>2.24</td>
</tr>
<tr>
<td>4</td>
<td>134</td>
<td>4.00</td>
<td>31.8</td>
<td>462</td>
<td>110.0</td>
<td>54.7</td>
</tr>
<tr>
<td>5</td>
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<td>8.50</td>
<td>32.1</td>
<td>437</td>
<td>114.2</td>
<td>52.3</td>
</tr>
<tr>
<td>6</td>
<td>211-220</td>
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<td>31.8</td>
<td>462</td>
<td>110.0</td>
<td>54.7</td>
</tr>
<tr>
<td>7</td>
<td>221</td>
<td>110.4</td>
<td>1234</td>
<td>121</td>
<td>98.2</td>
<td>0.812</td>
</tr>
<tr>
<td>8</td>
<td>300-308</td>
<td>30.4</td>
<td>31.7</td>
<td>1234</td>
<td>121</td>
<td>98.2</td>
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<td>308-317</td>
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<td>1316</td>
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<td>95.2</td>
</tr>
<tr>
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<td>317-326</td>
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<td>31.3</td>
<td>1410</td>
<td>117.0</td>
<td>68.8</td>
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reabsorption is essentially complete, as shown by the crossed symbols in figure 2, which indicate observations where less than one per cent of the filtered glucose is excreted. When delivery exceeds the maximal rate all the excess glucose is allowed to pass into the urine (see fig. 1a).

It is because of the existence of a maximal rate of reabsorption that the glucose clearance is essentially zero at low plasma levels, and that as the plasma level is raised glucose suddenly makes its appearance in
the urine, the glucose clearance thereafter rising and approaching the creatinine clearance (rate of glomerular filtration) as an upper limit (see fig. 1b). The point of transition in glucose reabsorption from the limitation imposed by the rate of filtration to the limitation imposed by the maximum rate of reabsorption is so abrupt that its exact experimental definition is very difficult or impossible. Individual experiments do show, however, that a small but significant amount of glucose first appears in the urine when the plasma concentration is 10 to 20 mgm. per cent below the level at which the maximal rate of reabsorption is reached.

![Fig. 1. Graphic analysis of the reabsorption and excretion of glucose (see table 1).](image)

1a. Glucose filtration, reabsorption and excretion (mgm. per min.) per 100 cc. of glomerular filtrate. Curve B, the glucose filtered at various plasma concentrations; curve A (solid dots), rate of glucose excretion; curve C (open circles), rate of glucose reabsorption.

1b. In consequence of the relationship shown here, the glucose/creatinine clearance ratio (the fraction of filtered glucose which is excreted) rises as the plasma level is increased and approaches 1.0 as a limiting value. The curve is calculated on the assumption that 234 mgm. of glucose (per each 100 cc. of glomerular filtrate) can be reabsorbed.

The above experiments have consisted of successive observations made at progressively higher plasma glucose levels, the last observations being made at the highest plasma level. It is practically impossible to examine the reversibility of the reabsorptive system in such experiments by lowering the plasma glucose rapidly, nor can the examination be made on a falling plasma concentration following a single injection of a large quantity of glucose; the rapidity at which the plasma concentration falls, and the changes in glomerular filtration due to circulatory disturbance, so complicate the renal picture that such experiments are uninterpretable. It is possible, however, to obtain observations in a single experiment at high plasma glucose levels (800 to 1000 mgm. per cent) and then at low
levels (300 to 400 mgm. per cent); or at intermediate plasma levels (400 to 500 mgm. per cent) shortly after the elevation of the plasma glucose to this level (i.e., starting within 10 minutes) and again several hours later, the plasma concentration being maintained constant meanwhile by a constant intravenous infusion. Observations such as these invariably show a constant value for the rate of glucose reabsorption, and

![Graph showing relationship between glucose reabsorption and plasma concentration and the genesis of the glucose threshold. The maximal rate of glucose reabsorption in each of seven experiments has been taken as the mean of the individual observations at plasma concentrations above the level of frank glycosuria. The rate of glucose reabsorption in each period of the experiment has then been expressed as the fraction of this mean value. The broken line shows the relationship to be expected in dog G, taking into account the mean rate of filtration and maximal reabsorption in this dog, and assuming that all filtered glucose is reabsorbed up to the maximal rate. The crossed symbols indicate observations where more than 99 per cent of the filtered glucose has been reabsorbed.

A curve calculated from equation 2, using $K = 0.2$, would follow closely the two lines in this figure. At plasma concentrations 20 mgm. per cent below the point of intersection of the two lines, reabsorption would be 99 per cent complete; at 20 mgm. per cent above the point of intersection the rate of reabsorption would be within 99 per cent of the maximal rate.

indicate that the reabsorptive mechanism is characterized by both physiological stability and reversibility. At no time have we discovered evidence that this mechanism is subject to "fatigue" in consequence of continued hyperglycemia.

Furthermore, the magnitude of the glucose reabsorptive maximum is fairly constant for any one dog over fairly long periods of time when the animal is maintained on the same diet, and it is not necessarily affected
by spontaneous changes in rate of glomerular filtration. Consequently glycuresis may occur at different plasma glucose levels in the same animal, not because of changes in the reabsorptive mechanism but because of changes in the rate of filtration and hence in the amount of glucose delivered to the reabsorptive system (Govaerts, 1936). A summary of data on two dogs examined over a period of five months is given in table 2.

Ni and Rehberg (1930) have suggested that the limiting factor in glucose reabsorption is a limit in the diffusion pressure which the tubule cells are capable of producing (or withstanding) between tubular urine and blood. This question has been specifically examined in decerebrate dogs in which the kidney had been denervated and an adjustable clamp attached to the aorta just below the diaphragm. The rate of glucose reabsorption was determined at the normal filtration rate (using plasma glucose of 700 mgm. per cent), again after the filtration rate had been reduced by about 50 per cent by tightening the aortic clamp, and lastly after the

<table>
<thead>
<tr>
<th>Date</th>
<th>Number of periods</th>
<th>Filtration rate</th>
<th>Reabsorption maximum</th>
<th>Date</th>
<th>Number of periods</th>
<th>Filtration rate</th>
<th>Reabsorption maximum</th>
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<td>220</td>
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<td>211</td>
<td>6-9</td>
<td>7</td>
<td>115.2</td>
<td>268</td>
</tr>
</tbody>
</table>

1 In arriving at this conclusion Rehberg made the assumption that glucose reabsorption takes place prior to water reabsorption; if such were the case the existence of a maximal rate of reabsorption at a constant rate of glomerular filtration would produce a constant difference (diffusion pressure) between the tubular urine and the blood at various glucose plasma concentrations. This assumption is, however, unsupported by any evidence and possibly incorrect.

2 The decerebrate dog yields the same results as the normal animal when subjected to an experimental routine similar to that in table 1. The results of two such experiments are shown as triangles in figure 2. These experiments indicate that decerebrate dogs may safely be used in the further examination of the glucose reabsorptive mechanism.
filtration had been restored to normal by removal of the clamp. If the limitation of glucose reabsorption were the diffusion gradient between the tubular urine and the blood, as suggested by Ni and Rehberg, the amount of glucose reabsorbed per unit time should have been lowered in proportion to the rate of filtration. As shown in table 3, the rate of glucose reabsorbed at normal and at reduced filtration rates was but slightly

### Table 3

**An experiment on a decerebrate dog showing that the diffusion gradient established by glucose reabsorption cannot be the factor that limits this process**

Two hours before the start of the experiment ether anesthesia was induced and 20 minutes later operative procedure began, carotids tied, skull trephined, decerebrated; clamp applied to upper abdominal aorta; left ureter cannulated, right tied off; femoral arteries isolated, left connected to mercury manometer through a citrate system. Male dog; 11.0 kg. Kidney weight 46.0 grams.

<table>
<thead>
<tr>
<th>PERIOD</th>
<th>TOTAL CONCURRENT TIME</th>
<th>URINE FLOW</th>
<th>PLASMA LEVEL</th>
<th>CLEARANCE</th>
<th>CLEARANCE RATIO</th>
<th>GLUCOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>cc. per min.</td>
<td>mgm. per cent</td>
<td>cc. per min.</td>
<td>cc. per cent</td>
<td>mgm. per min.</td>
</tr>
<tr>
<td>0</td>
<td>30-35</td>
<td>2.6</td>
<td>30.6</td>
<td>706</td>
<td>23.2</td>
<td>11.33</td>
</tr>
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<td>35-40</td>
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<td>31.0</td>
<td>717</td>
<td>21.7</td>
<td>10.90</td>
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<td>40-45</td>
<td>2.9</td>
<td>31.7</td>
<td>724</td>
<td>22.4</td>
<td>10.95</td>
</tr>
<tr>
<td>50</td>
<td>Aortic clamp tightened. Left femoral blood pressure 50-66 mm. Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>100-110</td>
<td>0.95</td>
<td>34.3</td>
<td>921</td>
<td>11.4</td>
<td>3.70</td>
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<td>3.94</td>
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<td>36.5</td>
<td>956</td>
<td>10.5</td>
<td>3.23</td>
</tr>
<tr>
<td>135</td>
<td>Aortic clamp released. Left femoral blood pressure 125-130 mm. Hg</td>
<td></td>
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<tr>
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<td>34.1</td>
<td>836</td>
<td>20.3</td>
<td>11.05</td>
</tr>
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</table>

different, and we conclude that it is not the diffusion pressure, but an actual maximal rate, that limits the reabsorptive process.

Our observations on the dog kidney differ from those of Clark (1932) and Walker and Hudson (1933), who have concluded that the plasma glucose level is a specific determinant in the reabsorption of glucose by the amphibian kidney. The difference between the two animals may
be due to the method of examination, to differences in the permeability
to the Amphibian and mammalian tubule, or to differences in the mech-
anism of glucose reabsorption. We are inclined to dismiss the last sugges-
tion as improbable.

It should perhaps be stressed that our observations have all been made
at relatively constant glucose plasma concentrations, under which condi-
tions the reabsorptive system may be considered to be in kinetic equilib-
rium with the concentrations of glucose in the tubular urine and the renal
interstitial fluid. This circumstance minimizes any error or physiological
disturbance that might arise from rapid changes in the glucose concen-
tration in either of these fluids.

Discussion. The demonstration that there exists a maximal rate in
the tubular reabsorption of glucose is especially significant in view of the
fact that the tubular excretion of many substances is limited in a similar
manner. Certain aspects of tubular activity have been discussed elsewhere
in terms of an hypothesis which treats the limitations of this activity in
terms of the mass law (Shannon, 1938a). Applying this hypothesis to
the present observations, we would suggest that in the process of reab-
sorption glucose enters into reversible combination with some element in
the tubule cells, present in constant but limited amount, and that the
subsequent decomposition of this complex limits the rate of glucose trans-
fer from tubular urine to blood. The conditions to be satisfied require
two consecutive reactions:

\[ A + B \rightleftharpoons AB \rightarrow T_r + B \]

where \( A \) is the glucose in the tubular lumen, \( B \) the cellular element, \( AB \)
the compound formed by the reversible combination of these two, and
\( T_r \), the glucose distal to the initial reaction. The equation which
relates the arterial plasma concentration, \( a \) (mgm. per cent), the rate of
glucose reabsorption, \( T_r \) (mgm. per min.) and the maximum rate of glucose
reabsorption, \( T_m \) (mgm. per min.) in terms of this hypothesis, is

\[ K = \frac{(a - T_r/V)(T_m - T_r)}{T_r} \]

where \( K \) is the equilibrium constant and \( V \) is the volume of glomerular
filtrate in 100 cc. per minute. The application of this equation to our

3 The data in the present report and that of other workers do not permit a further
analysis of the reactions of transfer or the identification of the substance we have
designated as \( B \) in our equations. Nor do we feel it advisable to attempt such an
analysis by analogy to the process of glucose transfer by the intestinal mucosa.
The dissimilarity of the two processes and their inhibition precludes the use of such
an analogy in the reconstruction of the reactions of transfer (see Lundsgaard, 1935;
Verzar, 1936, and Walker and Hudson, 1937).
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data is discussed in the legend of figure 2. The hypothesis appears to be as applicable to the tubular reabsorption of glucose as to the tubular excretion of various foreign substances. It is the limitation imposed upon the reabsorptive system by the amount of glucose contained in the glomerular filtrate, on the one hand, and the maximum rate of glucose reabsorption, on the other, that gives rise to the phenomenon of the "glucose threshold." According to (2) it is to be expected that small concentrations of glucose will appear in the urine at normal plasma glucose levels, that there will be little increase in the rate of excretion as the plasma level rises until the maximal rate of reabsorption is approached, and that the maximal rate of reabsorption will thereafter be rapidly attained (see legend, fig. 2). In view of the anatomy of the nephron it is recognized that as the tubular urine moves distally from the glomerulus there is progressive saturation of the reabsorptive capacities of the tubule cells and that frank glycuresis occurs only when the distal cells of the reabsorptive system are presented with more glucose than they are capable of reabsorbing per unit time. By taking the equilibrium concentration of glucose in the tubular urine to be \((a - T_c/V)\) we are neglecting the above fact; consequently \(K\) in equation 2 has an artificially elevated value. This method of analysis is unavoidable at the present time, but adequate for the over-all description of the reabsorptive system.

SUMMARY

1. The tubular reabsorption of glucose has been examined by the simultaneous determination of glucose and creatinine clearances at various arterial plasma glucose concentrations in the normal dog.

2. The essential limitation in the reabsorptive process lies in the circumstance that the tubules are able to transfer only a certain maximal quantity of glucose from the tubular urine to the blood per unit time. When the rate of glomerular filtration of glucose is such that glucose is delivered to the tubules at less than this maximal rate, reabsorption is essentially complete.

3. This relationship has been discussed in relation to an hypothesis suggested to describe a similar limitation in the tubular excretion of certain substances.

REFERENCES

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4 Reabsorption of water in the proximal tubule would increase the concentration \((a - T_c/V)\) by some multiple which automatically becomes incorporated in the constant, \(K\).
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WALKER, A. M. AND C. L. HUDSON. This Journal 118: 130, 1937.