STUDIES ON THE CONDITIONS OF GLUCOSE EXCRETION IN MAN

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The application of the filtration reabsorption theory to the explanation of glucose excretion has been of great importance for our knowledge of the factors involved in this process. In normal and pathologic conditions the quantity of glucose excreted is dependent only on three factors: the level of the capillary blood sugar, the filtration rate and the glucose threshold.

We may assume that the glucose level of the glomerular filtrate is the same as that of the arterial plasma. The quantity of the filtered glucose is determined by two factors: the level of the arterial blood sugar and the quantity of the filtration rate. Under normal circumstances, the glucose is almost completely reabsorbed by the tubules. In a unit of time only a constant, maximal quantity of glucose can be transported by the tubular cells, as Shannon and Fisher (14) demonstrated for the normal dog, Govaerts and Muller (3) for the diabetic dog. Under normal conditions this reabsorbing capacity of the tubules is not fully utilized and the excretion of glucose is almost zero. When the blood sugar, and in consequence the filtered quantity of glucose, has been increased or has just risen to the full utilization of the reabsorbing capacity, the blood sugar has reached the threshold. The quantity of the maximal reabsorbed glucose therefore depends on two factors: the level of the threshold and the quantity of the filtration rate.

If the blood sugar rises above this threshold, the maximal capacity of reabsorption is surpassed and the glucose appears in the urine. Glucose filtered — glucose reabsorbed = glucose excreted. This excess glucose, which has not undergone reabsorption, is now concentrated at the same rate as other substances which are neither reabsorbed nor secreted from the tubules, such as insulin or endogenous creatinine. One can express this relationship by the following equation (2):

\[
\text{creatinine excreted, mgm. per minute} = \frac{\text{glucose excreted, mgm. per minute}}{\text{plasma creatinine, mgm. per cent}} \times \left(\frac{\text{blood sugar — threshold}, \text{mgm. per cent}}{\text{urine sugar, mgm. per cent}}\right)
\]

So far, the threshold in man has been determined by oral administration of glucose. The blood sugar is tested at close intervals and the appearance of sugar is noted in the urine. The disadvantage of this procedure lies in the fact that the rise of the blood sugar curve may be very rapid, and the peak very brief. Most of the authors have observed a high ascending and a low descending threshold. In this article we will not discuss whether this difference really exists or whether it is due only to the experimental conditions (cf. Govaerts and Muller (2), Peters and Van Slyke (9), Falta (1)). Moreover, it is only possible to provoke glycosuria by oral administration in a certain percentage of subjects (16).

To avoid these difficulties, we tried to fix the threshold by another method, that is, as already stated, by the determination of that part of the blood sugar which is treated like a substance that has neither been reabsorbed nor secreted. To render this possible, the existence of a frank glycosuria is indispensable. When glycosuria was absent, it was produced by intravenous infusion of glucose in order to obtain a constant plasma level of glucose. For the following reasons it is impossible to compare the results of this method with the aforesaid oral administration method without certain considerations.

From their experiments with dogs Shannon and Fisher (14) have reached an equation "according to which it is to be expected that small
concentrations of glucose will appear in the urine at normal plasma glucose levels, that there will be a 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.” Govaerts and Muller (2, 3) obtained exactly the same results. They called that level of blood sugar at which the first traces of glucose appear “seuil d’apparition,” according to the definition of C. Bernard, whereas they called the higher level of blood sugar, above which there exists a direct proportionality between “supralimite” blood sugar and the amount of glucose excreted, the “seuil maximum.”

With our method we have not determined the threshold of appearance, but the maximum threshold. It is rather probable, however, that these two thresholds are not very different from each other. Experiments in dogs show “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.” One of our experiments seems to demonstrate that this difference is not greater in man, and that between the level of the threshold of appearance and that of the maximum threshold only very small amounts of glucose are excreted. These amounts are not important for the excretion rate of glucose in diabetic patients.

METHODS

In patients with a spontaneous glycosuria technic A was employed. Urine and blood were collected as described by Möller, McIntosh and Van Slyke (6) for the urea clearance. At the beginning, in the middle, and at the end of the test, the capillary blood sugar was determined by the method of Hagedorn and Jensen. The results of these determinations must not differ very much from each other. The sugar in urine was determined by polariscopic examination after previous precipitation with lead acetate. The creatinine in blood plasma and urine was determined by the method of Popper and Mandel (10). Patients with acetonuria were excluded from the test, as the values of creatinine in plasma and urine increased considerably in the presence of acetone. An attempt was made to remove the acetoacetic acid and the acetone by boiling the picric acid filtrate, but the results were not satisfactory since, in spite of the removal of acetone, the chromogenic substance increased slightly, even during a short boiling period.

Glucose was introduced in patients without glycosuria by an intravenous infusion, and the period was started if a frank glycosuria was present (technic B). In some cases the inulin clearance was determined simultaneously (technic C). The collection of urine and blood, the technic of infusion and the analytical methods were the same as described in the previous paper (15). The amount of glucose necessary to produce a glycosuria was approximately the same as described by Sansum and Woodyatt (13). Glucose was given as a 20 per cent solution at a rate of 5 cc. per minute. After 25 to 30 minutes glucose appeared in the urine, and the first period began.

Increased plasma glucose gives a faint color reaction with the modified Selivanoff’s reagent (11). According to the increase of blood glucose during the experiment, glucose was added to the fasting blood filtrate in order to compensate for this color. The value of extinction of this blank analysis was subtracted from the other values. Glucose in blood and urine was determined as already described. Only in experiments with inulin was the sugar in urine determined by the reduction of titrated Benedict’s reagent.

Normal subjects

Table I shows the results in 4 normal subjects. The maximum threshold in these subjects lies between 200 and 280 mgm. per cent. In Case 4 we tried to determine the difference between the threshold of appearance and the maximum threshold. After a priming infusion of 10 per cent glucose with 5 per cent inulin, a second infusion of 10 per cent glucose with 1 per cent inulin was given at a rate of 5 cc. per minute until the blood sugar remained constant between 173 and 179 mgm. per cent. At the same time the filtration rate was determined. Then a third infusion of 20 per cent glucose with 1 per cent inulin was given at the same rate. The first glucose could be found in the urine at a blood sugar level between 194 and 209 mgm. per cent. At a blood sugar level of 220 mgm. per cent the same value for the threshold was found. Unfortunately, the patient was not able to bear the infusion any longer but it seems probable that the threshold would not have increased much at higher blood sugar levels.

Diabetes renalis

We were recently able to examine 4 cases of true renal glycosuria. As these cases are relatively rare, a short report will be of interest. The results of these cases are given in Table II.
CONDITIONS OF GLUCOSE EXCRETION

TABLE I
Normal subjects

<table>
<thead>
<tr>
<th>Technic</th>
<th>Subject</th>
<th>Age</th>
<th>Urine flow</th>
<th>Creatinine</th>
<th>Sugar in urine</th>
<th>Supra-liminary blood glucose</th>
<th>Blood sugar</th>
<th>Threshold</th>
<th>Reabsorbed glucose</th>
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<tbody>
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Case 1. Münevver is a female of 27 years. Towards the end of the first pregnancy sugar was found in the urine during a casual examination. At a second examination some weeks after the delivery sugar was found again and assumed to be lactose. Three months after the delivery the patient was admitted to the hospital. The daily sugar output fluctuated between 35 and 50 grams, the fasting blood sugar level being 88 mgm. per cent. The sugar was identified as glucose as follows:

1. Reduction and polariscope examination gave the same quantity of glucose.
2. The fermentation with yeast began quickly. After complete fermentation the capacity of reduction disappeared.
3. The tests of Rubner, Wöhlk and Malfatti for lactose were negative (8).
4. The characteristic formation of mucic acid was negative.
5. The phenylosazone was formed quickly and copiously during heating. Lactosazone, however, is soluble in the heat.

The results of tests 2 to 5 proved the absence of lactose.

The oral administration of 50 grams of glucose was followed by a quite normal blood sugar curve. The sugar in urine rose to 6.3 per cent. After the injection of 12 units of insulin the blood sugar decreased during 3 hours from 109 to 69 mgm. per cent. At this level the glucose excretion ceased.

During the time of hospitalization the daily excretion of sugar was 30 to 50 grams at an intake of 250 grams of carbohydrates. The fasting blood sugar level was always normal. During the observation time, from April to December 1938, no change occurred.

Case 2. Shevket is a male of 30 years. Sugar was found in the urine during a casual examination. The glucose tolerance test had been performed in another hospital and had been followed by a normal blood sugar.

TABLE II
Diabetes remalis

<table>
<thead>
<tr>
<th>Date</th>
<th>Technic</th>
<th>Subject</th>
<th>Age</th>
<th>Urine flow</th>
<th>Creatinine</th>
<th>Sugar in urine</th>
<th>Supra-liminary blood glucose</th>
<th>Blood sugar</th>
<th>Threshold</th>
<th>Reabsorbed glucose</th>
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<td>A</td>
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<td>207</td>
<td>3850</td>
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<td>Shevket</td>
<td>30</td>
<td>0.51</td>
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<td>600</td>
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<td>1000</td>
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<td>137</td>
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<td>19.1</td>
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<td>19.1</td>
<td>87</td>
<td>68</td>
<td>79.5</td>
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</table>
curve, with abundant sugar excretion in the urine. We
had no occasion to study this case more completely.
Case 3. Agop is a boy of 17 years. The first ex-
amination took place on April 20, 1935. Some time
before this date a glycosuria was found incidentally
and the existence of a diabetes mellitus was assumed.
The result of the glucose tolerance test at that time was
normal, but the sugar excretion rose to 3 per cent. The
tolerance test with 100 grams of white bread gave a
similar result. Since then we saw the patient only at
irregular intervals. The daily glucose output was al-
ways about 20 grams, the fasting blood sugar being
normal. The determination of the threshold was made on
April 20, 1939.
Case 4. Ayshe is a female of 37 years. Four months
ago she had a delivery with forceps. Twenty-five days
later a manifestation of syphilis was found in her mouth.
The Wassermann test was positive. Treatment with
neosalvarsan and bismuth was begun. During the treat-
mant sugar was found in her urine for the first time.
The doctor assumed a diabetes mellitus, but dietetic treat-
tment was without success. She was hospitalized on May
31, 1939. The sugar in the urine was identified as glucose
as described in Case 1. As the resident physician had at
first believed the case to be a diabetes mellitus, a fasting
day and afterwards a vegetable day were ordered. On the
following day, June 2, the threshold of glucose was found
at 52 mgm. per cent at a glycosuria of 0.14 per cent. Now
the patient was given usual food which contained more
than 250 grams of carbohydrates. The daily sugar ex-
cretion rose to 25 to 40 grams. The glucose tolerance
test on June 5 showed only a slight hyperglycemic re-
sponse. The blood sugar rose from 77 mgm. per cent to
119 mgm. per cent, at a sugar excretion up to 6.8 per cent.
The determination of the threshold was repeated on June
6, and 80 mgm. per cent were found at a sugar excretion
of 3.5 per cent. On June 8, 10 units of insulin were in-
jected into the fasting patient. The blood sugar fell from
71 mgm. per cent to 33 mgm. per cent. Even at this low
blood sugar level in urine, 0.2 per cent sugar was ex-
creted. After a week the determination of the threshold
was made once more and repeated each hour from morn-
ing to afternoon. The patient is still in the hospital.
Every day she excretes 20 to 35 grams of sugar at a
normal blood sugar level.

In all the cases there exists an obvious inability
of the tubules to reabsorb glucose in sufficient
quantities. No conclusions concerning a uniform
etiology can be drawn from these observations.
The anamnesis gave no evidence of hereditary
factors. The rôle of pregnancy in Cases 1 and
4 is not clear, as the non-existence of glycosuria
before pregnancy has not been proved.

Monasterio (7) was the first to detect an ana-
tomical anomaly of the renal tubules in one case of
renal glycosuria. An enormous dilatation of the
lumen with flattening of the tubular epithelium
was found. In our cases we had no occasion to
suggest an operation to the otherwise normal
patient. If further evidence from more cases
is added, it will perhaps be possible to charac-
terize some of the cases of renal glycosuria as
an anatomical anomaly of the kidney.

We will not discuss here the mechanism of the
failure of the tubular cells to transfer glucose.
The results of Ruhl and Thaddea (12), who
-treated 2 cases with adrenal cortex hormone, are
not yet very conclusive. Hoff (4) demonstrated the
influence of lactoflavine and corticosterone
on the phlorizin glycosuria.

The values of the threshold, determined during
insulin hypoglycemia as well as by the "supra-
limitary" blood glucose, agree very well in Case
1. In this case a difference between the threshold
of appearance and the maximum threshold does
not seem to exist. In Case 4, however, this
difference seems to be obvious. After 2 fasting
days the threshold is 52 mgm. per cent at a just
perceptible glycosuria. During insulin hypogly-
cemia the threshold appears to lie much lower still.
A complete renal diabetes seems to exist because
the greatest part of the blood sugar value of 33
mgm. per cent, determined by the method of
Hagedorn-Jensen, is formed by non-glucose-re-
substances. If glucose is filtered more
copiously, however, the threshold rises to 70 to
80 mgm. per cent.

Diabetes mellitus

The determination of the threshold in patients
with diabetes mellitus gave the same values as in
normal subjects (Table III). The tests of some
patients of advanced age and of patients whose
diabetes had existed for a very long time, how-
ever, sometimes gave much higher values. In
clinical practice this fact has been known for a
long time but until now an explanation for the
increased capacity to reabsorb glucose has not
been found.

Reduced kidney function

One patient with amyloidosis in the terminal
stage and with extremely low kidney function,
and 1 patient with malignant hypertension were
examined with technic B (Table IV). The de-
creased excretion of glucose in patients with reduced kidney function depends only on the reduction of the filtration rate. The filtered quantity of glucose decreases so much that the reduction of the filtering surface causes a retention of sugar. The reabsorbed quantity decreases in the same proportion. The glucose threshold remains absolutely unchanged within the same limits as in the normal subject. The only explanation for this fact is that a reduction of the filtration at glomerular lesions is accompanied by a corresponding reduction of whole functional units of nephrons. In Case 1 the filtration decreased to a minimal amount, whereas the capacity of glucose reabsorption in the still functioning nephrons remained normal. Suppose that in a normal subject the quantity of reabsorbed glucose is 300 mgm. per minute, at a number of 2,000,000 nephrons: then one of them reabsors 0.15 microgram. In our case only 3.6 mgm. glucose could
be reabsorbed per minute. If we assume that in this case only 2 to 3 per cent of still functioning nephrons exist, that is 40,000 to 60,000, the quantity reabsorbed from one nephron is nearly the same as in the normal one.

In cases with reduced kidney function caused by decrease of the number of functional units, glucose is retained like other constituents of the plasma. Only at very high blood sugar levels sufficient glucose is filtered to cause a frank glycosuria. We did not examine cases of diabetes with kidney disease, but it is beyond any doubt that the low glycosuria of these patients has to be explained in the same manner. In some patients who have suffered from diabetes for a long time, the glucose threshold is very high. If this condition is complicated by a kidney disease, a very high blood sugar will be necessary to produce a glycosuria.

Functional disorganization of the kidney

In certain conditions the filtration decreases temporarily by decrease of the blood pressure or by other extrarenal influences without any lesion of the single nephron itself. McCance and Widdowson (5) call this condition the “functional disorganization of the kidney.” The filtration rate in the single glomerulus decreases, but the function of those parts of the tubules where glucose is reabsorbed remains unaltered. The filtered quantity of glucose decreases, while the reabsorbed quantity remains constant, and the excretion of glucose is greatly reduced or ceases completely. Shannon and Fisher (14) have demonstrated this process by an instructive experiment in Table III of their paper. In a decerebrated dog the reabsorption of glucose is examined before, during and after the application of a clamp

<table>
<thead>
<tr>
<th>Condition</th>
<th>Glucose filtered</th>
<th>Glucose reabsorbed</th>
<th>Glucose excreted at</th>
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<tbody>
<tr>
<td></td>
<td>Blood sugar level</td>
<td>Filtration rate</td>
<td>Renal threshold</td>
</tr>
<tr>
<td>1. Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
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<tr>
<td>2. Phlorizin glycosuria</td>
<td>Normal</td>
<td>Normal or slightly reduced</td>
<td>Low or non-existent</td>
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<td>3. Diabetes renalis</td>
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<td>Normal</td>
<td>Low</td>
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<tr>
<td>4. Pregnancy glycosuria</td>
<td>Normal</td>
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<td>Low</td>
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<td>5. Diabetes mellitus</td>
<td>Increased</td>
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<td>Reduced by destruction of functional units</td>
<td>Normal</td>
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<td>8. Diabetes mellitus with reduced renal function</td>
<td>Increased</td>
<td>Reduced by destruction of functional units</td>
<td>Normal or increased</td>
</tr>
<tr>
<td>9. Functional disorganization of the kidney</td>
<td>Normal</td>
<td>Reduced with preserved tubular function</td>
<td>Extremely increased</td>
</tr>
<tr>
<td>10. Diabetic coma with functional disorganization of the kidney</td>
<td>Increased</td>
<td>Reduced with preserved tubular function</td>
<td>Extremely increased</td>
</tr>
</tbody>
</table>
to the upper abdominal aorta. During artificial
decrease of the blood pressure to 50 to 66 mm.
Hg, the maximal reabsorbed quantity of glucose
remains constant, in spite of the reduction of the
filtration rate and corresponding reduction of the
filtered quantity of glucose by half. The glucose
threshold, which before tightening the clamp lay
between 360 and 370 mgm. per cent, suddenly
rises to 620 to 650 mgm. per cent.
In the condition of functional disorganization
of the kidney two factors retard the appearance
of glucose in the urine. The first one is the
retention of glucose caused by the decrease of the
filtration; the second one is the unaltered re-
absorbing function of the tubules, by which they
are able to reabsorb glucose from the decreased
filtrate with an extremely high threshold value.
This condition may be called reabsorption hyper-
glycemia.
It has been known for a long time that often
in diabetic coma, in spite of extremely high blood
sugar values, only traces of sugar are found in the
urine. Sometimes, in spite of the presence of
all the other symptoms, the diagnosis may be
doubtful for the doctor because of the faint or
negative reaction of sugar in the urine. McCance
and Widdowson (5) have demonstrated that in
such cases glucose is reabsorbed at a normal rate
from a reduced glomerular filtrate.
The interaction of the three factors on which
depends the excretion rate of glucose under vari-
ous conditions is summarized in Table V.

SUMMARY

The appearance of glucose in urine depends on
three factors: the blood sugar level, the filtration
rate, and the renal threshold of glucose.
The tubular reabsorption of glucose has been
examined by simultaneous determination of the
endogenous creatinine clearance or the insulin
clearance, the glucose excretion and the blood
sugar level in 4 normal subjects, in 4 cases of
renal diabetes, in 12 cases of diabetes mellitus,
and in 2 cases of kidney disease.
The results of these various conditions have
been discussed.
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