THE INFLUENCE OF ADRENALIN IN PHLORHIZIN DIABETES. ¹

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In 1901, Blum² made the very important discovery that the suprarenals contain a substance which, when injected into the circulation of animals, produces glycosuria. This substance which he later³ found to be identical with adrenalin, when given by stomach, produces no effect on the carbohydrate metabolism. The glycosuria appeared in animals from whose diet all carbohydrates were excluded and in one dog’s urine (Experiment 19) after seventeen days of starvation, he obtained 0.4 per cent. of sugar. In a subsequent work,⁴ however, Blum found that out of seven animals which had fasted for eight days, only one reacted to adrenalin. The others did not react at all, or reacted very slightly. But, if after a period of nine days of starvation, he fed the animals for several days with olive oil, administration of adrenalin subcutaneously was followed by the appearance of from 1 to 1.5 per cent. of sugar in the urine. These facts led Blum to the conclusion that the carbohydrate excreted was derived from fat.

In a recent paper, Eppinger, Falta and Rudinger⁵ report a series of experiments, which according to their interpretation, confirm Blum’s theory of the source of carbohydrate in adrenalin glycosuria. They starved a dog for three days; made him run in a tread-mill one hour daily during these three days; then injected 0.01 gram of adrenalin (one milligram per kilo) subcutaneously. This was followed by an excretion in the urine of 2.83 grams of sugar in a period of eight hours.

¹ Received for publication November 10, 1909.
² Blum, Deutsches Arch. f. klin. Med., 1901, lxxi, 146.
³ Blum, Arch. f. d. ges. Physiol., 1902, xc, 617.
⁴ Loc. cit.
To a second dog, they gave 200 grams of butter during the course of seventy-two hours. They followed this by a subcutaneous injection of 0.01 gram of adrenalin, and obtained 2.8 grams of sugar during the first period of five hours, and 3.9 grams during the second period of seven hours. The authors attribute this increase in the sugar elimination to the ingestion of the butter.

One must not, however, consider these experiments as conclusively proving the conversion of fat into carbohydrate. Blum as well as Eppinger, Falta and Rudinger take it for granted that the animals, in the experiments cited, were glycogen free after fasting for seventeen days in the dogs of the former, and after three days with one hour of daily work in those of the latter. But Pflüger has shown that a dog after fasting for twenty-eight days and after losing 23 per cent. of its body weight still contains glycogen enough to give rise to 100 grams of sugar, and Prausnitz reports that a dog weighing 22 kilograms after fasting for twelve days and after excreting 287 grams of sugar in the urine, brought about by phlorhizin injections, has still contained 25 grams of glycogen in its tissues. These two experiments show absolutely, that unless a more effective method—like convulsions, excessive work, or exposure to cold—is employed in addition, a long period of fasting does not suffice to free an animal of its glycogen.

In the experiments in which animals were fed with olive oil, the extra output of sugar after adrenalin administration, may be accounted for in the following manner. After a period of fasting, the animal body always exhibits a marked tenacity for its glycogen, and any fat available will be burnt in preference to it. The feeding of olive oil or butter to such an animal, may serve to spare the store of glycogen, even more than will body fat, and will cause its retention in the tissues. Administration of adrenalin after ingestion of fat may, therefore, be followed by a greater excretion of sugar in the urine.

In another series of experiments, Eppinger, Falta and Rudinger extirpated the pancreas of several dogs, starved them for two days, and determined the D:N ratio during this period. Then they

*Prausnitz, Zeit. f. Biol., 1892, xxix, 188.
administered adrenalin subcutaneously. Their results are here tabulated:

**TABLE 17.**
**Brown Dog, 8.4 Kilograms. Pancreas Extirpated on December 27, 1907, at 9 A. M.**

<table>
<thead>
<tr>
<th>Date</th>
<th>Period in hours</th>
<th>Remarks</th>
<th>Total N</th>
<th>Total D</th>
<th>D : N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dec. 27</td>
<td>11</td>
<td>Dog fasting</td>
<td>2.11</td>
<td>2.75</td>
<td>1.38</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td></td>
<td>5.57</td>
<td>13.77</td>
<td>2.52</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td></td>
<td>1.90</td>
<td>3.52</td>
<td>1.85</td>
</tr>
<tr>
<td>Dec. 28</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dec. 29</td>
<td>2</td>
<td></td>
<td>2.12</td>
<td>4.98</td>
<td>2.35</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>0.008 gm. of adrenalin administered subcutaneously</td>
<td>0.4</td>
<td>0.87</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Dog fasting</td>
<td>3.86</td>
<td>17.85</td>
<td>4.84</td>
</tr>
<tr>
<td></td>
<td>93%</td>
<td></td>
<td>1.87</td>
<td>5.87</td>
<td>3.1</td>
</tr>
</tbody>
</table>

**TABLE 18.**
**Dog's Weight, 13.9 Kilograms. Pancreas Extirpated on December 31, 1907, at 10 A. M.**

<table>
<thead>
<tr>
<th>Date</th>
<th>Period in hours</th>
<th>Remarks</th>
<th>Total N</th>
<th>Total D</th>
<th>D : N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dec. 31, '07</td>
<td>10½</td>
<td>Dog fasting</td>
<td>0.31</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11½</td>
<td></td>
<td>2.87</td>
<td>4.53</td>
<td>2.99</td>
</tr>
<tr>
<td>Jan. 1, '08</td>
<td>13</td>
<td></td>
<td>3.75</td>
<td>6.54</td>
<td>1.77</td>
</tr>
<tr>
<td>Jan. 2</td>
<td>11½</td>
<td></td>
<td>3.85</td>
<td>5.50</td>
<td>1.43</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td></td>
<td>3.44</td>
<td>7.05</td>
<td>2.33</td>
</tr>
<tr>
<td>Jan. 3</td>
<td>9½</td>
<td></td>
<td>2.24</td>
<td>4.65</td>
<td>2.07</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>0.012 gm. adrenalin injected subcutaneously</td>
<td>1.36</td>
<td>8.55</td>
<td>6.11</td>
</tr>
<tr>
<td></td>
<td>8½</td>
<td>Dog fasting</td>
<td>2.34</td>
<td>6.49</td>
<td>2.76</td>
</tr>
<tr>
<td>Jan. 4</td>
<td>4½</td>
<td>50 gm. of butter + 5 gm. of pancreatin</td>
<td>1.484</td>
<td>2.814</td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td>5½</td>
<td>Dog fasting</td>
<td>1.61</td>
<td>2.69</td>
<td>1.6</td>
</tr>
</tbody>
</table>

After the adrenalin injections, they obtained a D : N ratio of 5.2 (after six hours) and 6.1 (after four hours) respectively in Tables 17 and 18. Since the usual D : N ratio in depancreatized dogs is 2.8, the authors come to the conclusion that all the extra sugar is unquestionably derived from fat.

This appears to be true only upon a superficial examination of the figures, but upon a closer analysis an entirely different conclusion may be drawn.

During the first two days of the first experiment cited (Table 17), the animal excreted 11.8 grams of nitrogen and 25.89 grams of sugar. The D : N ratio was 2.19.4. This ratio shows that the

animal was not completely diabetic and that 7.15 grams of sugar were either oxidized or stored as glycogen. During the twenty-four hours following the injection of adrenalin, the animal excreted 8.7 grams of nitrogen and 39.28 grams of sugar. The D:N ratio was 4.51. From this we see that there was an extra elimination of 14.92 grams of sugar. This extra sugar, which was about 0.2 per cent. of the body weight, may have come from the fluids of the body; because after adrenalin injection, the blood sugar content very often sinks to subnormal (Vosburgh and Richards). Or else it may have been derived from the glycogen, which had not yet been liberated from the tissues, since the diabetes was not complete.

In the second experiment (Table 18), we find that the animal excreted during the foreperiod 16.15 grams of nitrogen and 29.76 grams of sugar, with a D:N ratio of 1.84, which also signifies an incomplete diabetes, and shows that the animal either burnt or stored 15.46 grams of sugar. During the twenty-three hours following the adrenalin injection the animal excreted 6.79 grams of nitrogen and 20.51 grams of sugar. The D:N ratio was 3.02, (not 6.11 as in the first four hours of this period)—a not unusual ratio for pancreas diabetes (Minkowski).

In the foregoing, we have seen that the most important arguments in favor of the theory that adrenalin converts fat into carbohydrates may have been based upon false premises from the beginning. No experiments in Professor Lusk's laboratory have ever furnished the slightest reason to believe that sugar can be produced from the metabolism of body fat. To investigate further the correctness of this view, several experiments were performed in accordance with the following principle.

Professor Lusk has shown that if dogs be placed completely under the influence of phlorhizin, diabetes results. The glycosuria bears a constant relationship to the nitrogen, i. e., for every gram

\[
1 (1.18 \times 2.8) - 25.89 = 7.15.
\]

\[
9 (39.28 - (8.7 \times 2.8)) = 14.92.
\]

\[
10 Vosburgh and Richards, American Jour. of Physiol., 1903, ix, 35.
\]

\[
11 (16.15 \times 2.8) - 29.76 = 15.46.
\]

\[
12 \text{ Loc. cit.}
\]

\[
13 \text{ Lusk, American Jour. of Physiol., 1908, xxii, 163.}
\]

\[
14 \text{ Stiles and Lusk, American Jour. of Physiol., 1903, x, 67.}
\]
of nitrogen excreted in the urine, we find approximately 3.65 grams of sugar. If we take an animal like this, and by exposing it to cold render it glycogen free, any intraperitoneal injection of adrenalin, ought to be followed by a rise in the D:N ratio, provided the theory of a conversion of fat into carbohydrate is true. That this is not the case will be seen from the accompanying protocols.

METHODS.

The adrenalin used was that prepared by Parke, Davis & Co. In six of the seven dogs experimented on, the dose given was the same as that employed by Eppinger, Falta and Rudinger, i.e., one milligram per kilogram of body weight. But this dose proved fatal within twenty-four hours in all cases except in Dog V. So in Dog VII the dose was reduced to 0.5 milligrams per kilogram.

The phlorhizin used was that prepared by Merck. It was administered subcutaneously in two gram doses three times a day, dissolved in warm 1.2 per cent. sodium carbonate solution.

The total nitrogen was determined by Kjeldahl method and the total sugar by Allihn's gravimetric method.

<table>
<thead>
<tr>
<th>Time</th>
<th>Dog No. 5</th>
<th>Dog fasting.</th>
</tr>
</thead>
<tbody>
<tr>
<td>March 6, '09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>March 7, '09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>March 8, '09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>March 9, '09</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time</th>
<th>Dog No. 5</th>
<th>Dog fasting.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>TABLE I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>10:15 A. M.</td>
</tr>
<tr>
<td>1 : 15 P. M.</td>
</tr>
<tr>
<td>1 : 15 P. M.</td>
</tr>
<tr>
<td>8 : 45 A. M.</td>
</tr>
</tbody>
</table>

*Lusk: Loc. cit.*

*At 4:10 P. M. and 10:45 P. M., 2 gm. of phlorhizin were injected subcutaneously.*
Influence of Adrenalin in Phlorhizin Diabetes.

This animal was kept in a cold room for five and a half hours following a period of four days of starvation, inclusive of two days of phlorhizin diabetes. This has apparently rendered the animal glycogen free. Administration of adrenalin, therefore, produced no change in the D:N ratio.

April 10, '09.  
Dog fed last.  
Dog starving.

April 11, '09.  
Dog starving.  
2 gm. of phlorhizin at 8:50 A.M., at 4 P.M. and at 11 P.M.

April 12, '09.  
Dog starving.  
2 gm. of phlorhizin at 8:50 A.M., at 4 P.M. and at 11 P.M.

April 13, '09.  
Dog starving.  
2 gm. of phlorhizin at 8:50 A.M., at 4 P.M. and at 11 P.M.

April 14, '09.  
Dog starving.  
2 gm. of phlorhizin at 8:50 A.M., at 4 P.M. and at 11 P.M.

April 15, '09, 8:50 A.M.  
Dog starving.  
2 gm. of phlorhizin injected subcutaneously.

April 15, '09, 10:25 A.M.  
Catheterized and bladder washed.  
Dog's weight 8.76 kg.

TABLE II.

<table>
<thead>
<tr>
<th>Time</th>
<th>No. of hours</th>
<th>Weight</th>
<th>Period</th>
<th>Condition</th>
<th>Total N</th>
<th>N per hour</th>
<th>Total sugar</th>
<th>Sugar per hour</th>
<th>D:N</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>10:25 A.M.</td>
<td>5:00</td>
<td>8.76</td>
<td>I</td>
<td>Phlorhizin</td>
<td>2.264</td>
<td>0.453</td>
<td>7.248</td>
<td>1.4496</td>
<td>3.2</td>
<td>(at 3:25, injected 0.005 gr. adrenalin intra-peritoneally)</td>
</tr>
<tr>
<td>3:25 P.M.</td>
<td>17:00</td>
<td></td>
<td>II</td>
<td>Adrenalin and</td>
<td>6.297</td>
<td>0.37</td>
<td>30.176</td>
<td>1.775</td>
<td>4.79</td>
<td></td>
</tr>
<tr>
<td>8:25 A.M.</td>
<td></td>
<td></td>
<td></td>
<td>phlorhizin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>April 16, 8:25 A.M.-3:40 P.M.</td>
<td>7:15</td>
<td></td>
<td>III</td>
<td>Phlorhizin</td>
<td>2.973</td>
<td>0.41</td>
<td>9.376</td>
<td>1.29</td>
<td>3.12</td>
<td>(at 3:40, 0.005 gr. adrenalin injected)</td>
</tr>
<tr>
<td>3:40 P.M.</td>
<td>17:00</td>
<td></td>
<td>IV</td>
<td>Adrenalin and</td>
<td>7.129</td>
<td>0.419</td>
<td>23.92</td>
<td>1.407</td>
<td>3.35</td>
<td></td>
</tr>
<tr>
<td>8:40 A.M.</td>
<td></td>
<td></td>
<td></td>
<td>phlorhizin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>April 17, 8:40 A.M.-3:40 P.M.</td>
<td>7:00</td>
<td></td>
<td>V</td>
<td>Phlorhizin</td>
<td>2.973</td>
<td>0.426</td>
<td>9.264</td>
<td>1.323</td>
<td>3.116</td>
<td>(at 3:40, 0.005 gr. adrenalin injected)</td>
</tr>
<tr>
<td>3:40 P.M.</td>
<td>17:00</td>
<td></td>
<td>VI</td>
<td>Adrenalin and</td>
<td>6.689</td>
<td>0.393</td>
<td>21.824</td>
<td>1.284</td>
<td>3.26</td>
<td>(at 3:40, 0.005 gr. adrenalin injected)</td>
</tr>
<tr>
<td>8:40 A.M.</td>
<td></td>
<td></td>
<td></td>
<td>phlorhizin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Throughout the course of the experiment the phlorhizin was injected regularly at 8:00, 3:45 and 11:30.

April 19, death of dog.
This animal was treated in a similar manner to Dog No. 5, but, because the April night was not as cold as the night of March, this dog was not sufficiently chilled to exhaust it of all its glycogen. The first administration of adrenalin was, therefore, followed by a rise in the D:N ratio, showing that a sweeping out or "Aus-

schwemmung" of the carbohydrates of the tissues took place. The second and third administration of adrenalin, however, failed to produce any extra sugar elimination, because the first one had, undoubtedly, removed all the glycogen that was present.

THE MECHANISM OF ADRENALIN GLYCOSURIA.

A number of theories have been advanced by the different investigators with regard to the mechanism of adrenalin glycosuria. That it is not of renal origin, like phlorhizin glycosuria has been shown by Zuelzer, and this has been corroborated by Metzger. Both authors obtained a decided hyperglycemia on injecting adrenalin after nephrectomy. Vosburgh and Richards found that the hyperglycemia is more intense in well-fed animals than in starved ones. They also found that the blood of the hepatic vein contains a higher percentage of reducing substances than the portal vein, suggesting very strongly that the liver is responsible for the hyperglycemia. Herter believes that adrenalin exerts a toxic effect on the cells of the pancreas, by interfering with its function in some unknown way. Eppinger, Falta and Rudinger attribute to adrenalin a series of functions. They believe that it has the power of mobilizing the carbohydrates, and, at the same time, of inhibiting the production of the internal secretion of the pancreas. The glycosuria, therefore, results from the lack of a corresponding increase in the pancreatic ferments. Underhill and Closson think that the adrenalin stimulates the nervous system, probably the sym-

"Zuelzer, Berliner klin. Woch., 1901, xlvi, 1209.
"Metzger, Münch. med. Woch., 1902, xii, 478.
"Loc. cit.
"Herter, Medical News, 1902, lxxx, 865; lxxxi, 769; Herter and Wakeman, Virchow's Arch., 1902, clxix, 479; Herter and Richards, Medical News, 1902, lxxx, 201.
"Loc. cit.
"Underhill and Closson, American Jour. of Physiol., 1906, xvii, 42."
pathetic. This stimulation causes the liver and the other glycogen
storehouses to throw out their glycogen in the form of dextrose.
More dextrose than can be cared for appears suddenly in the blood
and glycosuria is the result.

Opposed to the above theories are the results obtained by Straub24
and Ritzmann.25 They found that a continuous infusion of an
adrenalin solution with a concentration of 1:2,000,000, flowing at
a rate of two cubic centimeters per minute, i.e., an increase in
0.000001 gram of adrenalin secretion into the blood per minute,
may go on indefinitely without producing any glycosuria. Kretsch-
mer26 found this amount and rate of flow to be below the minimum
that is required to bring about a rise in blood pressure. On the
other hand, the infusion of the same adrenalin solution at a rate
of four cubic centimeters per minute, which according to Kretsch-
mer produces a considerable rise in blood pressure, results in an
almost immediate appearance of sugar in the urine. Straub and
Ritzman also found a constant relationship existing among the
amount of adrenalin injected into the blood and the degree of in-
creased blood pressure and the amount of sugar in the urine.

This suggests very strongly that the glycosuria following adrena-
lin injections is the result of an anemia produced by the constriction
of the blood vessels. The anemic condition of the tissues results
in imperfect oxidation, and whenever this condition occurs there is
a demand on the glycogen reserve of the body, so that hyperglyce-
mia may arise, and both sugar and lactic acid appear in the urine
(Zuntz).27 This hyperglycemia and glycosuria, which is similar
to the hyperglycemia and glycosuria obtained in asphyxiation (Mac-
leod)28 outlasts the stimulus.

The writer's thanks are due to Professor Lusk, at whose sugges-
tion and under whose direction this investigation was conducted.

26 Kretschmer, Arch. f. exper. Path. und Pharm., 1907, lvii, 423.
28 Macleod, American Jour. of Physiol., 1909, xxiii, 278.
CONCLUSIONS.

I. Intraperitoneal injections of adrenalin into animals which are completely under the influence of phlorhizin and which are free from glycogen do not result in any extra elimination of sugar. This proves that adrenalin does not cause a conversion of fat into carbohydrates, as is maintained by Blum and by Eppinger, Falta and Rudinger.

II. The high D:N ratio 5.2 and 6.1 reported by Eppinger, Falta and Rudinger after adrenalin injections in depancreatized dogs, which were obtained after short periods of six hours and four hours respectively, can be explained by the elimination of carbohydrates present in the organism.

III. These results confirm the work of Straub and Ritzmann which indicates that adrenalin, by its constricting effect on the blood vessels, produces anemia of the tissues, resulting in imperfect oxidation, and this anemia is followed by the conversion of glycogen into dextrose by hyperglycemia and consequently by glycosuria.