THE MECHANISM OF EPINEPHRINE ACTION.
I. THE INFLUENCE OF EPINEPHRINE ON THE CARBOHYDRATE METABOLISM OF FASTING RATS, WITH A NOTE ON NEW FORMATION OF CARBOHYDRATES.

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Dudley and Marrian (1) were the first to show that liver glycogen disappears in fasting animals when insulin is injected. Cannon, McIver, and Bliss (2) found that insulin hypoglycemia leads to an increased discharge of epinephrine. Furthermore, there was general agreement that epinephrine mobilizes liver glycogen. By linking these three facts together, a strong case was made out for the assumption that the disappearance of liver glycogen in insulinized animals was due to the discharge of epinephrine. This assumption is contradicted by the recent observation (3) that insulin mobilizes liver glycogen in adrenalectomized animals; that is, in animals with an abolished or at least strongly reduced epinephrine secretion. A decrease in liver glycogen in adrenalectomized rats following insulin injections has been found independently by Artundo (4).

The results of Cannon and his collaborators and of other investigators are accepted as evidence that insulin evokes an increased discharge of epinephrine, while the observations on adrenalectomized animals referred to above are taken as evidence that the disappearance of liver glycogen following insulin injections is not connected with this increased release of epinephrine. In view of this it was difficult to see how the antagonistic action of insulin and epinephrine on blood sugar was brought about. The following question presented itself. If insulin alone is capable of a rapid glycogen mobilization in the liver, and if epinephrine has its chief point of attack on liver glycogen, how does epinephrine antagonize the insulin hypoglycemia? There
was the possibility that epinephrine, whether released by the adrenals or injected, speeded up the mobilization of liver glycogen. However, there was no marked difference in the rate of disappearance of liver glycogen in normal and adrenalectomized animals, when insulin was injected. This made it unlikely that the antagonistic action between insulin and epinephrine occurred in the liver; indeed, it seemed more probable that the chief antagonistic action between these two hormones took place outside of the liver. A detailed study of the literature gave no definite clue as to the influence of epinephrine on the carbohydrate metabolism of the peripheral tissues. It appeared that the hepatic action of epinephrine had been overemphasized, with the result that an extrahepatic point of attack of this hormone was not taken into consideration. This made it desirable to supplement our knowledge of epinephrine in this respect. As in the case of insulin, the most promising approach in the investigation of an extrahepatic action, seemed by way of a sugar balance. Experiments involving a sugar balance were carried out on sugar-fed, on rats in the postabsorptive state, and on 24 hour fasting rats. They were made in the chronological order just given, but for reasons of greater ease of presentation, the order in which these experiments are published is reversed.

**Note on the New Formation of Carbohydrates.**

The following observation involves the problem of new formation of carbohydrates. It was found that the glycogen content of rats undergoes only a slight diminution between the 24th and 48th hour of fasting. This is shown in the summary in Table I, which was calculated from previous experiments (5-7), including the present series of glycogen determinations in Table II. The average deviations from the mean are given in Table I in order to...
to illustrate the extent of individual variation. It will be noted that there is a diminution of only 22 mg. of glycogen between the 24th and the 48th hour of fasting, in spite of the fact that the animals perform muscular work during that time. It seems clear that 22 mg. of glycogen can provide only a small fraction of the lactic acid needed for the performance of muscular work, and it is therefore evident that much more than 22 mg. of glycogen is split into lactic acid during a period of 24 hours. Nevertheless, the glycogen content of the rats remains practically constant. This may have two causes. Either glycogen is not used up, because the oxidation of fat furnishes the energy for the reconversion of lactic acid into glycogen, or glycogen is formed from non-carbohydrate material as fast as it is used up. In the latter case sugar formed from non-carbohydrate sources in the liver must be transported to the muscles by means of the blood stream.

The view that fat oxidation may furnish the energy for the reconversion of lactic acid is held by Lusk (8). Krogh and Lindhard (9), in their study of muscular work, came to the conclusion that the R.Q., as determined, is always a mixture of anabolic and catabolic processes. With an R.Q. above 0.9 sugar is converted in part into fat; with an R.Q. below 0.8 the reverse process takes place. A number of investigators came to regard the conversion of fat into sugar as a proved fact, even though the Danish authors stated expressly that they were proposing only a working hypothesis. According to this hypothesis, part of the fat undergoing oxidation passes through a carbohydrate stage before it appears as CO₂ and H₂O. There can be no objection to this view, because the sugar stage in the breakdown of the fat molecule is conceived as transitory and is regarded as taking place in the same cell in which the oxidation of fat is completed. A transportation of the sugar formed from fat, from one part of the body to another, is not postulated. If such a transportation would take place, the sugar formed from fat should give rise to the excretion of sugar under special conditions. The view of Krogh and Lindhard is, therefore, not necessarily opposed to the fact that the catabolism of fat does not lead to the excretion of sugar in the diabetic organism.

The constancy of the glycogen of fasting rats is best explained either by the view of Lusk, or by the conception of Krogh and
Lindhard. Those, who believe that the energy for the reconversion of lactic acid into glycogen can come from the oxidation of carbohydrates only, will favor the latter view. The constancy of the glycogen is less satisfactorily explained by the assumption of Chaikoff and Macleod (10). These authors believe that the liver converts fat into sugar and has therefore an R.Q. of about 0.3. The sugar formed from fat in the liver is carried to the muscles where it undergoes oxidation with an R.Q. of unity. The R.Q. of the whole animal is then the algebraic sum of the R.Q.'s of the liver and muscles. Numerous measurements have shown that the R.Q. of 24 and 48 hour fasting rats is invariably in the neighborhood of 0.71. In order to explain these R.Q.'s by Macleod's theory, one has to assume that the new formation of sugar in the liver and the oxidation of this sugar in the muscles are exactly synchronized. If at any time the sugar formed from fat were to accumulate in the body, the R.Q. would fall markedly below 0.71, which has not been observed. The same consideration applies to the diabetic R.Q. The sugar formed from fat in the diabetic organism, instead of being excreted in the urine, must be carried to the muscles and must be oxidized as fast as it is formed. If any sugar formed from fat would escape in the urine, the R.Q. would fall to a low level. Lusk (11) writes that the establishment of the diabetic quotient at a level of 0.69 carries the refutation of the idea that fat may be converted into sugar. The amino acids, which are convertible into glucose in the liver of the diabetic animal, appear as sugar in the urine. It is difficult to see why the sugar formed from fat in the liver, as postulated by Macleod's theory, should not have the same fate.

It is proposed to make a distinction between sugar formation from non-carbohydrate sources as an intermediary step of oxidation, and gluconeogenesis (or new formation of carbohydrates). The former case may be called intermediary sugar formation, denoting the molecule from which the sugar is formed (fat, protein, etc.). The latter term should be reserved for cases where the sugar formed from non-carbohydrate sources becomes stabilized and is, therefore, capable of becoming blood sugar and of being transported to other parts of the body. The conception of Krogh and Lindhard affords an example for intermediary sugar formation from fat. An example for gluconeogenesis is sugar
formation from protein in the diabetic animal. The authors believe that it is permissible to speak of intermediary sugar formation from fat in the same way as one discusses various possibilities for intermediary stages of carbohydrate and protein oxidation. However, gluconeogenesis from fat is still awaiting experimental verification.

**Experiments with Epinephrine.**

The foregoing discussion may serve as a background for the changes observed in liver and body glycogen and in respiratory metabolism in 24 hour fasting rats, following the subcutaneous injection of epinephrine. Rats of 125 to 145 gm. of body weight were fasted for 21 hours. A metabolism fore period of 3 hours was made, 0.02 mg. of epinephrine per 100 gm. of body weight was injected, and immediately a second metabolism period of 3 hours was started. The animals were killed 3 hours after the injection, and the glycogen in the liver and the rest of the body was determined in the usual manner. The amount of glycogen present in liver and body at the time of the epinephrine injection was determined on a series of control rats (Table II).

In the experiments with epinephrine in Table III the average R.Q. of the fore period was 0.715, corresponding to a non-protein R.Q. of 0.704. This R.Q. allows for no oxidation of preformed carbohydrates. The validity of this R.Q. is established by the observation recorded in Table I, that there is a disappearance of only 22 mg. of glycogen between the 24th and the 48th hour of fasting. The average

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**TABLE II.**

**Glycogen Content of 24 Hour Fasting Rats.**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>In liver.</td>
<td>In other tissues.</td>
</tr>
<tr>
<td>gm.</td>
<td>mg.</td>
<td>mg.</td>
<td>mg.</td>
</tr>
<tr>
<td>123</td>
<td>3.42</td>
<td>3.0</td>
<td>123.0</td>
</tr>
<tr>
<td>132</td>
<td>3.58</td>
<td>4.2</td>
<td>129.8</td>
</tr>
<tr>
<td>130</td>
<td>3.62</td>
<td>9.9</td>
<td>144.1</td>
</tr>
<tr>
<td>141</td>
<td>3.48</td>
<td>7.1</td>
<td>114.9</td>
</tr>
<tr>
<td></td>
<td>3.52</td>
<td>6.0</td>
<td>128.0</td>
</tr>
</tbody>
</table>

was made, 0.02 mg. of epinephrine per 100 gm. of body weight was injected, and immediately a second metabolism period of 3 hours was started. The animals were killed 3 hours after the injection, and the glycogen in the liver and the rest of the body was determined in the usual manner. The amount of glycogen present in liver and body at the time of the epinephrine injection was determined on a series of control rats (Table II).
Epinephrine in Fasting Rats

R.Q. of the epinephrine period remained unchanged as compared with the fore period, while the O₂ consumption rose in every experiment, corresponding to an average increase in calorie production of 17.3 per cent. Epinephrine produced an increase in heat production in 24 hour fasting rats at the expense of fat oxidation,

TABLE III.
Influence of Epinephrine on Carbohydrate Metabolism of 24 Hour Fasting Rats.

Average body weight 135.0 ± 7 gm. Values calculated per 100 gm. of body weight per 3 hours.

<table>
<thead>
<tr>
<th>O₂</th>
<th>n.q.</th>
<th>Total calories</th>
<th>O₂</th>
<th>n.q.</th>
<th>Glycogen.</th>
<th>In liver.</th>
<th>In rest of body.</th>
<th>Total.</th>
<th>Urine N.</th>
<th>Blood sugar</th>
<th>Total calories</th>
<th>Increase in calories over basal per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>gm.</td>
<td></td>
<td>g m.</td>
<td>mg.</td>
<td></td>
<td>mg.</td>
<td>mg.</td>
<td>mg.</td>
<td>mg.</td>
<td></td>
<td></td>
<td>g m.</td>
<td></td>
</tr>
<tr>
<td>0.660</td>
<td>0.710</td>
<td>2.27</td>
<td>0.799</td>
<td>0.722</td>
<td>28.4</td>
<td>58.4</td>
<td>86.8</td>
<td>8.81</td>
<td>105</td>
<td>2.61</td>
<td>15.0</td>
<td></td>
</tr>
<tr>
<td>0.768</td>
<td>0.734</td>
<td>2.50</td>
<td>0.844</td>
<td>0.717</td>
<td>50.2</td>
<td>81.9</td>
<td>132.1</td>
<td>7.00</td>
<td>105</td>
<td>2.75</td>
<td>10.0</td>
<td></td>
</tr>
<tr>
<td>0.632</td>
<td>0.699</td>
<td>2.05</td>
<td>0.768</td>
<td>0.717</td>
<td>45.9</td>
<td>65.5</td>
<td>111.4</td>
<td>8.40</td>
<td>137</td>
<td>2.50</td>
<td>21.9</td>
<td></td>
</tr>
<tr>
<td>0.654</td>
<td>0.720</td>
<td>2.13</td>
<td>0.782</td>
<td>0.718</td>
<td>43.1</td>
<td>76.5</td>
<td>119.6</td>
<td>7.96</td>
<td>104</td>
<td>2.55</td>
<td>19.7</td>
<td></td>
</tr>
<tr>
<td>0.648</td>
<td>0.711</td>
<td>2.10</td>
<td>0.770</td>
<td>0.714</td>
<td>32.6</td>
<td>62.8</td>
<td>95.4</td>
<td>11.76</td>
<td>100</td>
<td>2.50</td>
<td>19.0</td>
<td></td>
</tr>
<tr>
<td>0.703</td>
<td>0.714</td>
<td>2.28</td>
<td>0.830</td>
<td>0.701</td>
<td>51.8</td>
<td>77.2</td>
<td>129.0</td>
<td>11.37</td>
<td>110</td>
<td>2.72</td>
<td>19.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.677</td>
<td>0.718</td>
<td>2.22</td>
<td>0.800</td>
<td>0.716</td>
<td>42.0</td>
<td>71.0</td>
<td>113.0</td>
<td>9.22</td>
<td>110</td>
<td>2.60</td>
<td>17.3</td>
</tr>
</tbody>
</table>

TABLE IV.
Average Glycogen Content in Mg. per 100 Gm. of Rat.
Calculated from Tables II and III.

<table>
<thead>
<tr>
<th></th>
<th>Liver.</th>
<th>Rest of body.</th>
<th>Total.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>6 ± 2</td>
<td>128 ± 9</td>
<td>134 ± 10</td>
</tr>
<tr>
<td>3 hrs. after epinephrine</td>
<td>42 ± 8</td>
<td>71 ± 8</td>
<td>113 ± 15</td>
</tr>
<tr>
<td>Difference</td>
<td>+36</td>
<td>-57</td>
<td>-21</td>
</tr>
</tbody>
</table>

since an increased nitrogen elimination in the urine was not observed. This indicates that the calorigenic action of epinephrine is not necessarily connected with an increased combustion of carbohydrates.

There was a slight but unmistakable rise in blood sugar. The control rats in Table II showed an average of 87 mg. per cent,
while 3 hours after the epinephrine injection the blood sugar averaged 110 mg. per cent. The r.q. of the fore period and of the 3 hour period during which epinephrine acted, showed no indication of carbohydrate oxidation. Nevertheless, profound changes were produced in the distribution of glycogen by the epinephrine injections. This is the more remarkable because these changes occurred in animals which were in a state of glycogen equilibrium. It will be seen from a comparison of the glycogen values in Tables II and III that epinephrine leads to a marked increase in liver glycogen and to a diminution of body glycogen in every experiment. On an average, the glycogen in the rest of the body is found to have decreased a little more than the liver glycogen has increased (−57 against +36 mg.). This is shown in the summary in Table IV, which was calculated from Tables II and III. The liver glycogen which had accumulated during the 3 hours of epinephrine action, was found to have disappeared again when the rats were killed 16 hours after the injection.

An increase in liver glycogen after epinephrine has been observed previously by Loeper and Crouzon (12), by Pollak (13), and by Kuriyama (14). None of these authors determined the glycogen so soon after the epinephrine injections as in the present experiments. Pollak made rabbits glycogen-free by fasting and strychnine poisoning. After daily injections of epinephrine, a considerable amount of liver glycogen (up to 4.5 per cent) was formed, in spite of the continued fasting. Kuriyama found that the livers of rabbits which were fasted and submitted to daily epinephrine injections, contained a much larger amount of glycogen than those of merely fasted animals. On an average, the muscle glycogen of the injected rabbits was lower than that of the control rabbits. The interval between the last epinephrine injection and the glycogen determination varied between 7 and 24 hours. A single injection of epinephrine into fasted rabbits also caused an increase in liver glycogen. Recently, Markowitz (15) observed that repeated epinephrine injections into fasted, strychnine-treated rabbits lead to an accumulation of liver glycogen. Since a complete carbohydrate balance was not made, this author arrived at the conclusion that the newly formed glycogen in the liver was derived from fat.

The present experiments reveal that muscle glycogen is another
possible source for the newly formed liver glycogen. It is now
definitely known, especially from the work of Mann and Magath
(16) on hepatectomized dogs, that muscle glycogen is not a di-
rect source of blood sugar after epinephrine injections, or under
any other conditions. When muscle glycogen is split, the presence
of the glycolytic ferment causes an immediate change of the split
products into lactic acid (Lohmann (17)). The course of events
in 24 hour fasting rats would then be that epinephrine mobilizes
muscle glycogen and that lactic acid enters the blood stream and
is carried to the liver where it is deposited as glycogen. If the
disappearing muscle glycogen (57 mg.) were oxidized, the R.Q.
should be 0.74, while the R.Q. actually observed was 0.715.

Before considering this explanation further, it was necessary to
determine whether lactic acid was able to form liver glycogen.
\(d\)-Lactic acid in the free state or as sodium salt, as well as \(r\)-sodium
lactate, when fed by stomach tube to 24 hour fasting rats, gave
rise to the formation of considerable amounts of liver glycogen
(18). Sodium lactate, when injected subcutaneously, was far
less effective in forming liver glycogen. A detailed report of these
experiments will be presented in a later paper. Abramson, Eggle-
ton, and Eggleton (19) reported recently that \(r\)-sodium lactate,
when injected intravenously, does not form liver glycogen. It
would seem that their experimental procedure was not favorable
for the detection of glycogen formation from lactic acid.

With the demonstration that lactic acid forms liver glycogen,
one possible objection to the explanation here proposed has been
eliminated. An older observation gains special significance in
the light of the present work. It was found that epinephrine
injections lead to a marked increase in the blood lactic acid of
rabbits and cats (20). Tolstoi, Loebel, Levine, and Richardson
(21) observed an increase in blood lactic acid in men after epi-
nephrine injections. An increase was also found, to a lesser ex-
tent, in the rats used for the present experiments.

There is the possibility that the liver glycogen accumulating
during epinephrine action is derived from non-carbohydrate
sources, in other words, that one is dealing with gluconeogenesis
according to the definition given in the preceding section. If this
were the case, one would have to assume that the glycogen disap-
ppearing from the rest of the body is oxidized. The simultaneous
occurrence of the two processes (anabolic and catabolic) would also result in the R.Q. actually observed. The average nitrogen elimination in the 3 hour epinephrine period was 9.2 mg. If one assumes a conversion into glucose corresponding to a D:N ratio of 3.65, 34 mg. of glucose could have been derived from the catabolism of protein. The increase in liver glycogen of 36 mg. is of the same magnitude. This indicates that it is unnecessary to assume gluconeogenesis from fat in order to explain the increase in liver glycogen after epinephrine injections. We believe that gluconeogenesis does not explain the results, because an increase in liver glycogen was also observed in rats in the postabsorptive state in which gluconeogenesis should be in abeyance on account of previous carbohydrate feeding and an R.Q. above 0.8. The increase in blood lactic acid is also in favor of the first explanation.

The experiments on 24 hour fasting rats recorded in this paper show in a definite way that epinephrine influences the carbohydrate metabolism of the peripheral tissues, since it leads to the disappearance of muscle glycogen. The experimental demonstration of glycogen formation in the liver from lactic acid supports the conclusion that glycogen mobilized in the muscles is converted into liver glycogen with lactic acid as an intermediary stage. Muscle glycogen is therefore an indirect source of blood sugar if the liver is present and if there is an escape of lactic acid from the muscles. Epinephrine injections, violent exercise, strychnine and insulin convulsions, asphyxia, decerebration, and a variety of other conditions lead to an escape of lactic acid from the muscle. The loss of muscle glycogen incurred under these different conditions is repaid, in part at least, by the liver in terms of glucose. It remains an established fact that the liver is the only direct source of blood sugar in the body. In the absence of the liver, muscle glycogen is unable to contribute sugar to the blood, because lactic acid cannot be converted into liver glycogen.

SUMMARY AND CONCLUSIONS.

1. Between the 24th and 48th hour of fasting, the glycogen content of rats diminishes by only 22 mg. This constancy of the glycogen during fasting is discussed from the standpoint of the new formation of carbohydrates. It is proposed to make a
sharp distinction between carbohydrate formation from protein or fat as an intermediary step in the complete oxidation of these molecules and gluconeogenesis. The latter term should be reserved for cases where the sugar formed from non-carbohydrate sources becomes stabilized.

2. The R.Q. of 24 hour fasting rats of 0.715 remained unchanged when epinephrine was injected. The $O_2$ consumption rose in each experiment, corresponding to an average increase in heat production of 17.3 per cent.

3. 3 hours after the subcutaneous injection of epinephrine (0.02 mg. per 100 gm. of rat), the body glycogen (mainly muscle glycogen) diminished on an average by 57 mg., while the liver glycogen increased by 36 mg.

4. The increase in liver glycogen after epinephrine injections is explained by the conversion of muscle glycogen into liver glycogen with lactic acid as an intermediary stage. This explanation is supported by the fact that the oral administration of lactic acid has been found to lead to the deposition of liver glycogen. Another possibility which has been considered is the conversion of protein into liver glycogen, with a simultaneous oxidation of the glycogen disappearing in the muscles. The combination of the two processes (anabolic and catabolic) would also result in the R.Q. actually observed.

5. Accepting the first explanation as the better supported one, it follows that muscle glycogen is an indirect source of blood sugar, if the liver is present and if there is an escape of lactic acid from the muscles.

6. Epinephrine influences the carbohydrate metabolism of the peripheral tissues, since it leads to the disappearance of muscle glycogen.

BIBLIOGRAPHY.

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