GLYCOGEN FORMATION IN THE LIVER FROM d- AND l-LACTIC ACID.

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The question as to whether or not the liver is able to form glycogen from lactic acid is of importance for the relation between the carbohydrate metabolism of the muscles and that of the liver. It is known that the process glycogen \rightarrow lactic acid occurs in the muscles, while the process glycogen \rightarrow glucose occurs in the liver. Glucose derived from liver glycogen is convertible into muscle glycogen; it is, however, not definitely known whether lactic acid derived from muscle glycogen is convertible into liver glycogen. If this should prove to be the case, the glucose molecule would be capable of a complete cycle in the body; it could in turn be liver glycogen, blood sugar, muscle glycogen, blood lactic acid, and again liver glycogen. If, on the other hand, the liver is unable to form glycogen (or glucose) from lactic acid, this cycle would be interrupted as soon as the glucose molecule was deposited as muscle glycogen.

Mandel and Lusk (1) found that d-lactic acid, when administered to phlorhizinized dogs, leads to the excretion of extra glucose in the urine. This might be interpreted in the sense that, since lactic acid is convertible into glucose in the liver of the diabetic animal, it should also be able to form liver glycogen in the normal animal. However, the literature is contradictory on this point. Röhmann (2) states that ammonium and sodium lactate, when fed to rabbits fasted previously for 3 to 4 days, leads to glycogen deposition in the liver. Parnas and Baer (3) concluded that glycogen synthesis occurred during perfusion of the isolated turtle liver with sodium lactate. Barrenscheen (4), on the other hand, reported negative results in perfusion experiments on isolated livers of rabbits and dogs. Izume and Lewis (5) injected sodium lactate subcutaneously into two fasting rabbits and observed glycogen deposition in the liver. Takane (6) in Meyerhof's laboratory, obtained carbohydrate synthesis from sodium lactate which was added to sections of liver tissue suspended either in Ringer's solution...
or blood serum. It appears from a remark on p. 417 of Takane’s paper that
glucose rather than glycogen was formed from the added sodium lactate,
which this author ascribes to the special conditions of his in vitro experi-
ments. Abramson, Eggleton, and Eggleton (7), working on dogs anes-
thetized with ether and amytal, were unable to demonstrate glycogen syn-
thesis in the liver following intravenous injection of sodium r-lactate,
though the injection of glucose, under the same conditions, led to glycogen
formation in the liver.

The writers became interested in the question of glycogen forma-
tion from lactic acid when it was found that epinephrine when
injected into 24 hour fasting rats, causes a simultaneous disap-
pearance of muscle glycogen and an increase in liver glycogen in
approximately equivalent amounts (8). It was suggested that
part of the disappearing muscle glycogen was converted into liver
glycogen with lactic acid as an intermediary stage, since there was
no other obvious source for the newly formed liver glycogen and
since carbohydrate oxidation was too low to account for the muscle
glycogen which disappeared. In view of these results the experi-
ments reported in the present paper were undertaken.

Meyerhof and Lohmann (9) found a marked difference in the
utilization of d- and l-lactic acid in isolated mammalian tissues.
Whereas d-lactic acid, when added to sections of liver, kidney,
and brain tissue, increased the respiration, l-lactic acid had a
doubtful effect. Liver tissue was able to synthesize carbohydrate
from d-lactic acid but hardly from l-lactic acid.

The rate at which sodium d-lactate could be infused intrave-
nously into rats without causing an appreciable rise in the lactic
acid content of blood and urine was 95± 5 mg. per 100 gm. of
body weight per hour (10). When the experiments were repeated
with sodium r-lactate, a considerable amount of lactic acid was
excreted in the urine (10). This suggested that there was also a
difference in the utilization of the d- and l-lactic acid in the intact
animal. It was therefore decided to use both forms of lactic
acid in the investigation of glycogen formation in the liver and to
include observations about the rate of absorption from the in-
testine and lactic acid content of blood and urine.

Methods.

The experiments were made on male rats after a fasting period
of 24 hours. The weight of the animals at the time of feeding
varied between 100 and 160 gm. Sodium d-, r-, or l-lactate was fed by stomach tube in the manner described in a previous paper (11). The amount of fluid introduced was 2.2 cc. In some experiments 2.5 to 3.5 cc. of a 6 per cent solution of free lactic acid were fed without ill effects. When sodium lactate was injected subcutaneously, three equal doses were given with an interval of 1 hour between each injection. When it became desirable to feed a constant amount of lactic acid per unit of body weight, the following procedure was adopted. The concentration of the lactic acid in the stock solution was determined by titration with phenolphthalein as indicator and by the Friedemann, Cotonio, and Shaffer method (12) with very satisfactory agreement. The desired amount of lactic acid solution was delivered from a burette into a small beaker. After addition of a small drop of methyl red, the solution was neutralized with 20 per cent NaOH. The fluid in the beaker was drawn up with a syringe and injected through the catheter into the stomach. Beaker, syringe, and catheter were then washed out with a small quantity of water. All animals were killed 3 hours after the administration of lactic acid.

Blood for duplicate lactic acid determinations was collected after decapitation. The muscular movements during the collection of blood make the lactic acid values slightly too high, because, when blood is collected in the same manner from animals under amytal anesthesia, lower values for blood lactic acid are found. The average for six determinations on normal rats under amytal anesthesia was 26.8 mg. per cent (10), while in the present series of determinations in Table I the average was 41.5 mg. per cent. Urine was collected by placing the small wire screen cages, in which the animals were kept, on plates. Urine remaining in the bladder after the death of the animals was added to that voided spontaneously. The urine was made up to a volume of approximately 20 cc. in a 25 cc. volumetric flask, and 2.5 cc. each of 10 per cent CuSO₄ and 5 per cent Ca(OH)₂ were added in order to remove interfering substances. After 30 minutes standing the solution was filtered and analyzed. Extraction of the lactic acid from the urine with ether was found unnecessary, since the direct method gave only slightly higher values than after ether extraction.

After collection of blood, the liver was removed as quickly as
possible, frozen with CO₂ delivered from a tank, weighed in the frozen state, cut into small pieces, and introduced into boiling 60 per cent KOH. Glycogen was determined according to Pflueger's method. After hydrolysis of the glycogen with 2.2 per cent HCl, neutralization, and filtration, sugar was determined by means of the Bertrand method. If less than 10 mg. of sugar was present in 20 cc. of the solution to be analyzed, a known amount of glucose was added before the determination was carried out.

For the determination of the amount of lactic acid absorbed from the intestine, a method was used which had been worked out previously for the determination of sugar absorption (11). The difference between the amount of lactic acid fed and the amount of lactic acid recovered from the whole intestinal tract represents the amount of lactic acid absorbed. It is necessary to apply a slight correction because the intestine of a rat weighing 100 gm. contains on an average 10.9 mg. of lactic acid (Table I). After the death of the animal, the esophagus was tied and the whole intestinal tract was removed and placed in a beaker. Stomach and intestines were cut open and extracted with repeated portions of hot water on a water bath at 100°. The washings were poured into a 250 cc. volumetric flask, and before being made up to the mark, 12 cc. of colloidal iron and a few drops of a saturated solution of sodium sulfate were added. An aliquot part of the filtrate was treated with copper sulfate and lime in order to remove interfering substances. The final filtrate used for the lactic acid analysis was water-clear. Control experiments showed that lactic acid is not included in the colloidal iron precipitate.

All lactic acid determinations were carried out by the Friedemann, Cotonio, and Shaffer method (12). When this method was first used, and occasionally later, analyses of zinc lactate solutions containing known amounts of lactic acid were made. The recovery of lactic acid was of the same magnitude as reported by the above authors. Recently, the modification of Kendall and Friedemann (13), in which the permanganate used for the oxidation is substituted by colloidal manganese, was used with equal success.

**Preparation of d- and l-Lactic Acid.**

Pederson, Peterson, and Fred (14) found that certain bacteria produce only the d form of lactic acid from glucose. Dr. Peter-

1 The older designation of the sarcolactic acid as d-lactic acid is used in this paper.
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son kindly consented to isolate a sufficient quantity of d-lactic acid from the bacteria cultures for our purpose. His method of preparation was as follows: The fermented media, glucose-yeast water, were evaporated to a small volume, acidified, and the lactic acid extracted with ether. The acid was converted into the zinc salt by boiling with zinc carbonate. A sample for analysis gave 13.1 per cent water of crystallization. The zinc salt was dissolved in water, acidified, and extracted with ether. After the ether was removed, the solution was decolorized with norit and concentrated to about 38 per cent of lactic acid. A sample was converted into the zinc salt and an analysis gave 12.6 per cent water of crystallization. A sample of zinc lactate prepared by us 18 months later from the same d-lactic acid solution gave the following analytical results:

$$\text{Zn(C}_3\text{H}_4\text{O}_2)_2 + 2 \text{H}_2\text{O}.$$  

**Found.** H$_2$O, 13.06 per cent; ZnO, 29.09 per cent.  
**Calculated.** H$_2$O, 12.89 per cent; ZnO, 29.11 per cent.

(The racemic zinc lactate, which crystallizes with 3 molecules of water, yields 18.17 per cent H$_2$O and 26.73 per cent ZnO.) The rotation of a 2.5 per cent solution of the water-free salt in a 2.2 dm. tube was $\alpha = -0.45^\circ$. $[\alpha]_D^{25} = -8.2^\circ$. The magnitude of rotation of the d- and l-zinc lactate depends very much on the concentration. Jungfleisch and Godchot (15) reported for the same concentration (2.5 per cent of the water-free salt) $-8.0^\circ$. Meyerhof and Lohmann (9) found for the l-zinc lactate +8.1$^\circ$ and Neuberg (16) $+8.2^\circ$.

The L-lactic acid was prepared according to Irvine's method (17), consisting of a resolution of the racemic acid with morphine. A concentrated solution of c. 5. lactic acid was diluted to 20 per cent and was heated for 6 hours under a reflux condenser in order to destroy the anhydride. The hot solution was neutralized with morphine, filtered, and allowed to crystallize. A second crop of morphine l-lactate was obtained upon concentration of the mother liquor. The salt was recrystallized from 50 per cent alcohol, dissolved in water, and decomposed with ammonia. After filtration and acidification, the free lactic acid was extracted with

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2 Up to this point, the preparation was carried out by Dr. Pucher of the Department of Biochemistry of the University of Buffalo.
ether in a continuous extraction apparatus. After the ether was
removed, the solution was concentrated to 20 per cent of lactic
acid. A sample was converted into the zinc salt by boiling with
ZnCO₃ and was analyzed with the following results.

Air-dry (20 hours at 37°)...... 0.3146 gm. Zn(C₅H₇O₇)₂ + 2H₂O.
Heated for 4 hours at 120°...... 0.2737 "
Difference.......................... 0.0409 " = 13.00 per cent H₂O.
Air-dry before ashing............. 0.2649 "
After ashing...................... 0.0778 " = 29.37 per cent ZnO.
[α]₁₂= + 8.0° (c = 2.5 per cent of water-
free salt, l = 2.2 dm., α =
+ 0.44°).

TABLE I.
Glycogen Content of Liver of 24 Hour Fasting Rats.

Average body weight 116 ± 10 gm.

<table>
<thead>
<tr>
<th>Weight of liver (gm.)</th>
<th>Glycogen in liver (mg.)</th>
<th>Lactic acid in intestine (mg.)</th>
<th>Liver glycogen (per cent)</th>
<th>Blood lactic acid (mg. per cent)</th>
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<tr>
<td>3.73</td>
<td>4.2</td>
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<td>8.3</td>
<td>0.06</td>
<td>46.5</td>
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<td>3.35</td>
<td>2.8</td>
<td>12.0</td>
<td>0.08</td>
<td>34.8</td>
</tr>
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<td>3.40</td>
<td>1.8</td>
<td>10.7</td>
<td>0.05</td>
<td>43.4</td>
</tr>
<tr>
<td>3.46</td>
<td>4.0</td>
<td>11.2</td>
<td>0.11</td>
<td>42.5</td>
</tr>
<tr>
<td>3.43</td>
<td>2.9</td>
<td>11.0</td>
<td>0.08</td>
<td>35.1</td>
</tr>
<tr>
<td>3.25*</td>
<td>1.9</td>
<td>10.9</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>3.18*</td>
<td>7.7</td>
<td></td>
<td>0.24</td>
<td></td>
</tr>
<tr>
<td>3.38</td>
<td>3.4</td>
<td>10.9</td>
<td>0.10</td>
<td>41.5</td>
</tr>
</tbody>
</table>

* Fed 2.5 cc. of saline; killed 3 hours later.

Results.

The rats were subjected to a fasting period of 24 hours before lactic acid was fed in order to reduce the liver glycogen to a low level. The glycogen content of the liver of 24 hour fasting rats was determined on a series of eight control rats (Table I). The average was 0.1 per cent liver glycogen, or, since the liver weight was 3.38 per cent of the body weight, 3.4 ±1.4 mg. of glycogen for the liver of a 100 gm. rat. In previous determinations on 24 hour
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fasting rats the average for sixteen experiments was 0.2 per cent or 7 ±2 mg. of liver glycogen per 100 gm. of rat (8). The values found by Macleod and collaborators (18) on rats fasted previously for 24 hours are in substantial agreement. In forty-eight experiments the average glycogen content was 0.16 per cent. The liver weight was not recorded, but assuming it to be on an average the same as in our experiments, this would correspond to 5.4 mg. of liver glycogen per 100 gm. of rat. It need hardly be pointed out that the remarkable constancy of the liver glycogen of 24 hour fasting rats makes such animals well suited for a study of glycogen formation. This rules out many uncertainties which are met with when glycogen formation in the liver of larger species is investigated. The possibility of determining absorption in the rat is a further advantage.

A comparison of the data in Tables I and II shows that the liver is able to form glycogen from lactic acid. There was only a small difference in the amount of glycogen formed during absorption of d- and r-lactate (on an average 53 mg. against 41 mg.). It would, however, be wrong to conclude from this that l-lactic acid is able to form liver glycogen as rapidly as d-lactic acid. This is not the case, as will be shown later. In order to explain the small difference between d- and r-lactate, the absorption from the intestine must be taken into consideration. The rats receiving d-lactate absorbed on an average 89.7 mg., while the rats receiving inactive lactate absorbed 115.1 mg., one-half of which (57.5 mg.) is d-lactic acid. The difference between the absorption of 89.7 and 57.5 mg. is not great enough to affect appreciably the rate of glycogen formation in the liver. The same is true for the experiments in which free d-lactic acid was fed, where the average absorption amounted to only 62.7 mg., while the amount of glycogen formed in the liver was 43 mg.

The percentage of absorbed lactic acid which is retained as glycogen in the liver is surprisingly high (Table II). It amounted on an average to 61.8 per cent when sodium d-lactate was fed and to 72.2 per cent when free d-lactic acid was given. In two cases, more than 95 per cent of the absorbed lactic acid was retained in the liver as glycogen. The percentage retention after feeding racemic lactate is only 34.2 per cent, because one-half of the lactic acid absorbed, namely the l-lactic acid, forms practically no
liver glycogen. Of glucose, fructose, and dihydroxyacetone 18, 38, and 21 per cent respectively of the amounts absorbed are retained as liver glycogen (19). On a percentage basis d-lactic acid is therefore a better glycogen former in the liver than any of these three sugars. It should be mentioned however that sodium lac-

### Table II

**Glycogen Content of Liver 3 Hours after Lactic Acid Feeding.**

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>mg.</td>
<td>mg.</td>
<td>gm.</td>
<td>mg.</td>
<td>per cent</td>
<td>mg. per cent</td>
<td></td>
</tr>
<tr>
<td>89</td>
<td>69.6</td>
<td>3.31</td>
<td>66.7</td>
<td>2.01</td>
<td>95.8</td>
<td>115</td>
</tr>
<tr>
<td>116</td>
<td>86.7</td>
<td>3.20</td>
<td>36.8</td>
<td>1.15</td>
<td>42.4</td>
<td>100</td>
</tr>
<tr>
<td>125</td>
<td>90.1</td>
<td>3.28</td>
<td>57.8</td>
<td>1.76</td>
<td>64.1</td>
<td>113</td>
</tr>
<tr>
<td>138</td>
<td>112.4</td>
<td>3.76</td>
<td>50.4</td>
<td>1.34</td>
<td>44.8</td>
<td>108</td>
</tr>
<tr>
<td>117</td>
<td>89.7</td>
<td>3.39</td>
<td>52.9</td>
<td>1.56</td>
<td>61.8</td>
<td>109</td>
</tr>
<tr>
<td>148</td>
<td>84.0</td>
<td>3.05</td>
<td>25.0</td>
<td>0.82</td>
<td>28.8</td>
<td>105</td>
</tr>
<tr>
<td>172</td>
<td>91.3</td>
<td>3.06</td>
<td>24.8</td>
<td>0.81</td>
<td>27.2</td>
<td>96</td>
</tr>
<tr>
<td>251</td>
<td>135.2</td>
<td>3.74</td>
<td>54.6</td>
<td>1.46</td>
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<tr>
<td>267</td>
<td>150.0</td>
<td>3.65</td>
<td>58.8</td>
<td>1.61</td>
<td>39.2</td>
<td>108</td>
</tr>
<tr>
<td>209</td>
<td>115.1</td>
<td>3.37</td>
<td>40.8</td>
<td>1.18</td>
<td>34.2</td>
<td>106</td>
</tr>
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<td>98</td>
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<td></td>
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</tr>
<tr>
<td>102</td>
<td>43.1</td>
<td>3.65</td>
<td>34.3</td>
<td>0.94</td>
<td>79.5</td>
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<tr>
<td>112</td>
<td>40.5</td>
<td>2.76</td>
<td>24.0</td>
<td>0.87</td>
<td>51.6</td>
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<td>120</td>
<td>61.0</td>
<td>3.68</td>
<td>59.2</td>
<td>1.61</td>
<td>97.0</td>
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<tr>
<td>150</td>
<td>84.2</td>
<td>4.10</td>
<td>50.8</td>
<td>1.24</td>
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<tr>
<td>210*</td>
<td>79.0</td>
<td>3.55</td>
<td>57.2</td>
<td>1.61</td>
<td>72.3</td>
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</tr>
<tr>
<td>132</td>
<td>62.7</td>
<td>3.50</td>
<td>42.9</td>
<td>1.21</td>
<td>72.2</td>
<td></td>
</tr>
</tbody>
</table>

* One-half neutralized with NaOH.

tate is absorbed approximately 7 times more slowly than glucose and 3½ times more slowly than fructose.

The blood sugar level is hardly changed during lactic acid absorption and the same is true following subcutaneous injection of lactate. This confirms the work of Janssen and Jost (20), Riegel (21), and Abramson, Eggleton, and Eggleton (7), who in-
ject ed sodium lactate intravenously. Izume and Lewis (5) state that sodium lactate in doses less than 2.0 gm. per kilo did not induce any appreciable hyperglycemia in fasting rabbits, while larger doses produced an increase in blood sugar.

The mechanism of absorption of lactic acid needs further investigation. In marked contrast to glucose and other sugars (11), the rate of absorption of sodium lactate and of free lactic acid depends on the amount fed. This is shown in Table II, in which the experiments are arranged according to the amount fed. Another striking difference exists between the absorption of sugars and lactic acid. Whereas isomeric sugars are absorbed at widely different rates from the intestine, for instance, mannose is absorbed 5 times more slowly than glucose (11), d- and l-lactate are absorbed at nearly the same rate (Table III). There is still one point which should be mentioned in connection with the experiments in Table II. For an equal amount fed, free lactic acid is absorbed more slowly than sodium lactate, but this is probably due to the acid reaction in the former case rather than to an intrinsic difference.

In order to afford a better comparison between optically active and inactive lactate, a standard amount of lactic acid was fed in all further experiments, namely 170 mg. per 100 gm. of body weight (Table III). This led to the absorption of nearly the same amounts of lactic acid in the three cases, the average being 111 mg. for d-lactate, 124 mg. for l-lactate, and 108 mg. for r-lactate. For an equal amount absorbed, r-lactic acid forms definitely less liver glycogen than d-lactic acid (26.1 mg. against 43.8 mg.). This is due to the fact that glycogen formation from l-lactic acid is almost entirely absent. It will be noted in Table III that the livers of the rats receiving l-lactate contained 10 ± 2.8 mg. of glycogen, while the livers of the control rats in Table I contained 3.4 ± 1.4 mg. This is perhaps not an entirely negative result, though the difference is very slight indeed. The l-lactic acid used in these experiments, on the basis of the analyses made, is regarded as sufficiently pure to exclude an appreciable admixture of d-lactic acid, which, if it were present, would account for the small amount of liver glycogen formed. It is possible therefore that l-lactic acid is able to form liver glycogen at a very slow rate.
Another striking difference between d- and l-lactic acid is found when the figures for blood and urine lactic acid are compared (Table III). Whereas during 3 hours of absorption of d-lactate only 0.5 mg. of lactic acid is excreted, 36.5 mg. appear in the urine when l-lactate is fed. This corresponds to an excretion of 29.4 per cent of the amount absorbed. The increase in blood lactic acid after the l-lactate feeding corresponds to a retention of 18 per cent of the amount absorbed, if it is assumed that the blood lactic acid is in equilibrium with 50 per cent of the body weight.

### Table III.

Comparing d-, l-, and r-Lactic Acid.

170 mg. of lactic acid per 100 gm. of body weight were fed in each case. The rats were killed 3 hours after the feeding.

<table>
<thead>
<tr>
<th>Per 100 gm. body weight.</th>
<th></th>
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<tr>
<td>gm.</td>
<td>mg.</td>
<td>mg.</td>
<td>mg.</td>
<td>per cent</td>
<td>mg. per cent</td>
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<tr>
<td>3.78</td>
<td>108</td>
<td>0.4</td>
<td>52.0</td>
<td>1.37</td>
<td>48.1</td>
<td>43.6</td>
<td>Sodium d-lactate.</td>
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<td>3.59</td>
<td>103</td>
<td>0.4</td>
<td>56.5</td>
<td>1.57</td>
<td>54.8</td>
<td>53.8</td>
<td>Average body weight, 110 ± 9 gm.</td>
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<tr>
<td>3.60</td>
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<td>0.0</td>
<td>32.6</td>
<td>0.91</td>
<td>27.6</td>
<td>63.7</td>
<td>Sodium l-lactate.</td>
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<td>0.95</td>
<td>29.4</td>
<td>54.6</td>
<td>Average body weight, 103 ± 3 gm.</td>
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<td>3.64</td>
<td>111</td>
<td>0.5</td>
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<td>1.20</td>
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<td>53.9</td>
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Remarks.
This leaves roughly 50 per cent of the amount absorbed or 62 mg. of \( l \)-lactic acid which, presumably, were utilized in the body in the course of 3 hours. Since \( d \)-lactate may be injected intravenously at a rate of 95 mg. per 100 gm. of rat per hour without causing an appreciable increase in blood lactic acid, or excretion in the urine (10), \( l \)-lactic acid is utilized approximately 4 times more slowly in the rat than \( d \)-lactic acid. A comparison of the experiments with \( d \)- and \( l \)-lactate in Table III, when based on excretion in the urine, does not reveal that there exists such a marked difference in the utilization of \( d \)- and \( l \)-lactic acid. This is due to the fact that after \( r \)-lactate feeding only half as much \( l \)-lactic acid is absorbed as after \( l \)-lactate feeding. In the latter case the rate of absorption of \( l \)-lactic acid was found to be 50 per cent higher than the rate of utilization. In the former case the rate of absorption does not exceed the rate of utilization and consequently the excretion in the urine is very small.

It remains to be determined how far a kidney factor might be involved in the different utilization of \( d \)- and \( l \)-lactic acid. Hewlett, Barnett, and Lewis (22) found in men that the threshold for lactic acid excretion is between 30 and 40 mg. per cent of blood lactic acid. This coincides fairly well with the values observed on rats under amytal anesthesia, when \( d \)-lactate was infused intravenously (10). As stated under "Methods," the lactic acid values in the present paper are approximately 15 mg. per cent too high, because muscular movements during the collection of blood were not abolished by an anesthetic, but this does not affect the following considerations. In Table III the average blood lactic acid after \( d \)-lactate feeding was 12.4 mg. higher than that of the control rats in Table I. Since after \( r \)-lactate feeding only half as much \( d \)-lactic acid is absorbed, it might be assumed that the increase in blood lactic acid was almost entirely due to \( l \)-lactic acid. This would give a concentration of 28.5 mg. per cent of \( l \)-lactic acid in the blood, at which level no appreciable quantity of lactic acid is excreted in the urine. After \( l \)-lactate feeding the average blood lactic acid was 45.1 mg. per cent higher than that of the control rats, and at this concentration in the blood lactic acid was excreted in the urine. The threshold for the excretion...
of l-lactic acid is therefore not much different from that of d-lactic acid.

Experiments in which sodium d-lactate was injected subcutaneously are summarized in Table IV. A smaller amount of liver glycogen was formed after d-lactate feeding. This may be due in part to the fact that absorption from the subcutaneous tissue was not completed when the animals were killed.

**DISCUSSION.**

The main result of the present investigation is that d-lactic acid can be deposited as liver glycogen and that it is utilized several times faster in the rat than l-lactic acid. Also, the levo isomer is hardly able to form liver glycogen. This is another example of the discrimination of the body cells between two optical isomers. As stated in the introduction, Meyerhof and Lohmann (9) obtained the same results on isolated tissues of the rat. It is possible that narcosis abolishes the faculty of the liver to synthesize glycogen from lactic acid, because Abramson, Eggleton, and Eggleton (7) obtained negative results with dogs under ether and amytrial anesthesia. Another contributory factor was probably the strong
alkalosis which they produced in their animals by intravenous administration of sodium lactate. The fact that glucose was still able to form liver glycogen under these abnormal conditions does, of course, not prove that lactic acid is unable to do so under more physiological conditions. The same authors state that there is no marked difference in the utilization of d- and l-lactic acid in the dog. However, they performed most of their experiments with r-lactic acid and did not compare d- and l-lactic acid directly. In the present experiments in which samples of d- and l-lactic acid of known purity were used, the difference in utilization was very marked.

The demonstration of glycogen synthesis in the liver from lactic acid links together some recently established experimental results. Himwich, Koskoff, and Nahum (23) found on decerebrate dogs, by an analysis of the arterial and venous lactic acid content of various organs, that the main site of lactic acid formation was the muscle, while the organ chiefly concerned with the removal of lactic acid from the blood was the liver. It seemed very probable that the liver formed glycogen from the lactic acid escaping from the muscles. Olmsted and Coulthard (24) actually observed a prolonged increase in liver glycogen in decerebrate cats. They explained this by a new formation of glycogen from an unknown carbohydrate existing in the body, but what actually took place was a conversion of muscle glycogen via lactic acid into liver glycogen. Epinephrine injections, which cause a disappearance of muscle glycogen in normal rats, also lead to glycogen formation in the liver from lactic acid (8). Geiger and Schmidt (25) showed recently that extra sugar in phlorhizinized dogs following epinephrine injections can be accounted for by the muscle glycogen which disappears. They failed, however, to realize that it was lactic acid and not glucose which was carried away by the blood stream to be converted into glucose in the liver.

Formation of liver glycogen from lactic acid is thus seen to establish an important connection between the metabolism of the muscle and that of the liver. Muscle glycogen becomes available as blood sugar through the intervention of the liver, and blood sugar in turn is converted into muscle glycogen. There exists
therefore a complete cycle of the glucose molecule in the body, which is illustrated in the following diagram.

Epinephrine was found to accelerate this cycle in the direction of muscle glycogen to liver glycogen and to inhibit it in the direction of blood glucose to muscle glycogen; the result is an accumulation of sugar in the blood. Insulin, on the other hand, was found to accelerate the cycle in the direction of blood glucose to muscle glycogen, which leads to hypoglycemia and secondarily to a depletion of the glycogen stores of the liver. It will be investigated to what extent this cycle plays a role in the preservation of liver glycogen and hence of a normal blood sugar level during fasting. There is also a possibility that other hormones besides epinephrine and insulin influence this cycle.

**SUMMARY.**

1. Sodium \(d\)-lactate, when fed by mouth or injected subcutaneously, leads to glycogen deposition in the liver. Sodium \(l\)-lactate, though it is absorbed at the same rate from the intestine as the dextro isomer, hardly forms any liver glycogen. Of \(d\)-lactate 40 to 95 per cent of the amount absorbed in 3 hours is retained as liver glycogen.

2. Of \(l\)-lactate 30 per cent of the amount absorbed is excreted in the urine, while no excretion occurs during \(d\)-lactate absorption. It is estimated that \(l\)-lactic acid is utilized 4 times more slowly in the rat than \(d\)-lactic acid.

3. The role of the cycle, liver glycogen \(\rightarrow\) blood glucose \(\rightarrow\) muscle glycogen \(\rightarrow\) blood lactic acid \(\rightarrow\) liver glycogen, as an important phase of carbohydrate metabolism, is emphasized.
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GLYCOGEN FORMATION IN THE LIVER FROM \textit{d-} AND \textit{l-} LACTIC ACID

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