THE EFFECT OF EXERCISE ON THE EXCRETION OF URIC ACID

WITH A NOTE ON THE INFLUENCE OF BENZOIC ACID ON URIC ACID ELIMINATION IN LIVER DISEASES

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No satisfactory explanation has been offered for the uricacidemia which is apt to occur in such clinical conditions as eclampsia, chloroform poisoning, cardiac failure, and pneumonia, but interestingly in these same conditions an elevation of the lactic acid of the blood is not uncommon (1). In view of the fact that ingested lactic acid causes a temporary decrease in the excretion of uric acid as Gibson and Doisy (2), and the writer (3) have observed, the possibility exists that accumulation of lactic acid in the body may be one of the causes for uric acid retention. As a means of testing whether excessive production of lactic acid can influence the excretion of uric acid, the effect of strenuous exercise was studied.

EXPERIMENTAL

All experiments were carried out during the morning, since the hourly excretion of uric acid during this period under standardized conditions is fairly constant. Strenuous exercise consisted mainly of jumping and running to the extent of mild exhaustion and breathlessness. The analytical methods were the same as those previously used (3).

DISCUSSION

Strenuous exercise produced a marked drop in the excretion of uric acid as seen in Table I. A similar decrease was observed by
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Burian (4), Kennaway (5), Hartmann (6), and Lucke (7). All failed to offer any definite explanation except Burian, who at-

TABLE I

Excretion of Uric Acid during Rest, and Mild and Strenuous Exercise

<table>
<thead>
<tr>
<th>Time</th>
<th>Rest</th>
<th>Walking*</th>
<th>Brisk walking†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Urine volume</td>
<td>Uric acid</td>
<td>Creatinine</td>
</tr>
<tr>
<td>9.00 -10.00 a.m.</td>
<td>33</td>
<td>26.7</td>
<td>59</td>
</tr>
<tr>
<td>10.00 11.00 &quot;</td>
<td>152</td>
<td>25.0</td>
<td>60</td>
</tr>
<tr>
<td>11.00 a.m.-12.00 m.</td>
<td>235</td>
<td>26.0</td>
<td>59</td>
</tr>
<tr>
<td>12.00 m. - 1.00 p.m.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brisk walking†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10.00 -11.00 &quot;</td>
<td>183</td>
<td>26.1</td>
<td>55</td>
</tr>
<tr>
<td>11.00 a.m.-12.00 m.</td>
<td>75</td>
<td>24.8</td>
<td>55</td>
</tr>
<tr>
<td>12.00 m. - 1.00 p.m.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strenuous exercise</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetoacetic acid† and strenuous exercise</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strenuous exercise</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Exercise carried out from 10.00 to 11.00 a.m.
* Walking 3 miles per hour.
† Walking 4 miles per hour.
‡ Diuresis produced by drinking 500 cc. of water.
§ 10 gm. of acetoacetic acid (sodium salt) ingested at 10.00 a.m.
|| Before exercise: uric acid, 2.5 mg.; non-protein nitrogen, 35.3 mg.; lactic acid, 6.8 mg. per 100 cc. of blood. After exercise: uric acid, 2.7 mg.; non-protein nitrogen, 34.1 mg.; lactic acid, 28.4 mg. per 100 cc. of blood.

tributed the decrease to the diminished volume of urine. This explanation does not appear to be valid, for it has been repeatedly found that the excretion of uric acid is practically independent of
urine volume. Even increasing the volume 7-fold failed to increase the output of uric acid in the first experiment of Table I. It will be further observed that the drop in uric acid output during exercise is always greater than the decrease in the volume of urine. Further evidence that exercise causes a retention of uric acid is contributed by Lucke (7), Levine, Gordon, and Derick (8), and Rakestraw (9), who studied the blood and found an elevation of the uric acid after exercise. Curiously, Rakestraw found that although there was an increase in whole blood, the uric acid of the corpuscles showed a slight decrease. In view of the fact that the combined uric acid is present only in the corpuscles, this observation may perhaps be significant. It will be observed in Table I that when acetoacetic acid is administered before the exercise, the drop in uric acid excretion is more precipitous than with exercise alone, thus suggesting a definite summation of effects. The creatinine excretion during vigorous exercise was found to remain constant. Schulz (10) and Eichelberger (11) have reported an increased output of creatinine during exercise. In the present study, only in mild exercise such as walking was there a slight stimulation of creatinine output. Significantly, mild exercise does not appear to influence the excretion of uric acid, which is interesting since Cook and Hurst (12) have recently reported that walking even at the rate of 4½ miles per hour for 30 minutes did not increase the lactic acid concentration of the blood. This suggests that an oxygen deficit must occur before lactic acid accumulates and presumably a retention of uric acid becomes manifest.

In the last experiment of Table I it can be seen that a definite increase in the lactic acid of the blood occurs during an hour of exercise which was considered strenuous. Simultaneously, there was a small but definite rise in the blood uric acid together with a marked drop in the hourly excretion. Since ingested lactic acid can decrease the output of uric acid, the most probable explanation for the retention during vigorous exercise is the excessive production of lactic acid; though direct evidence for this conclusion is still lacking. The question how lactic acid affects uric acid excretion is difficult to answer because little is known concerning the mechanism whereby uric acid is eliminated. Unlike that of the other common urinary constituents, the excretion of uric acid is specifically influenced by a variety of agents, which the writer has previously discussed.
Neither lactic acid nor strenuous exercise seems to affect kidney function, as demonstrated by the constant rate of creatinine excretion and the absence of a rise in the non-protein nitrogen of the blood. It seems rather unlikely that the retention of uric acid can be attributed to a specific inhibitory effect of lactic acid on kidney function. It appears more probable that the retention is in some manner linked with the metabolism of lactic acid and that the liver is a factor to be considered.

### TABLE II

**Effect of Benzoic Acid on Excretion of Uric Acid in Liver Diseases**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Uric acid excretion</th>
<th>Hippuric acid output in terms of benzoic acid*</th>
<th>Per cent of normal†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 hr.</td>
<td>2 hrs.</td>
<td>3 hrs.</td>
</tr>
<tr>
<td>Normal</td>
<td>7.4</td>
<td>8.2</td>
<td>15.8</td>
</tr>
<tr>
<td>&quot;</td>
<td>21.4</td>
<td>11.7</td>
<td>16.7</td>
</tr>
<tr>
<td>Common duct obstruction</td>
<td>25.8</td>
<td>16.3</td>
<td>20.9</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>13.2</td>
<td>10.3</td>
<td>11.2</td>
</tr>
<tr>
<td>Carcinoma of colon with metastasis to liver</td>
<td>10.0</td>
<td>8.5</td>
<td>4.1</td>
</tr>
<tr>
<td>Catarrhal jaundice</td>
<td>23.4</td>
<td>12.3</td>
<td>13.0</td>
</tr>
<tr>
<td>&quot;</td>
<td>25.0</td>
<td>9.6</td>
<td>11.3</td>
</tr>
<tr>
<td>Acute hepatitis</td>
<td>34.8</td>
<td>10.9</td>
<td>7.5</td>
</tr>
<tr>
<td>Atrophic cirrhosis</td>
<td>9.8</td>
<td>3.0</td>
<td>3.0</td>
</tr>
</tbody>
</table>

* In 4 hours after the ingestion of 6 gm. of sodium benzoate.
† Based on a normal excretion of 3 gm. of benzoic acid as hippuric acid in 4 hours.

Studies of the effect of aromatic acids on uric acid elimination also suggest that the liver plays a part in the excretory process. Ingestion of benzoic acid will inhibit the excretion of uric acid as Lewis and Karr (13), Swanson (14), and the author (15) have found, but this drug will not cause retention of any other common constituent of the urine. Experimental evidence indicates that in man the conjugation of benzoic acid is primarily dependent on the liver, and that in various hepatic diseases the production of hippuric acid is greatly diminished (16). The normal adult will excrete approximately 3 gm. of benzoic acid as hippuric acid in 4 hours following the ingestion of 6 gm. of sodium benzoate, but
patients with impaired livers may have a greatly diminished output. In these patients with damaged livers the period of uric acid retention following the taking of sodium benzoate is invariably prolonged, but the severity of the retention does not run parallel with the diminished output of hippuric acid, as seen in Table II. The significance of this discrepancy cannot yet be evaluated, but eventually it is hoped that such data will be useful in increasing the clinical value of the hippuric acid test. It is interesting to note that in the severe case of hepatitis in which the output of hippuric acid was only 17 per cent of normal, the uric acid excretion dropped to approximately 8 mg. per hour, whereas in another case with atrophic cirrhosis, in which the hippuric acid production was 37 per cent of normal, the hourly excretion of uric acid was only 3 mg. Many more data are necessary before one can attempt to correlate these results, but it seems fairly evident that the liver must be concerned with the excretion of uric acid; otherwise liver damage should not intensify the depressing action of benzoic acid on uric acid output.

Both lactic acid and benzoic acid can diminish the excretion of uric acid; theoretically, therefore, they may be factors in the pathological retention of uric acid. Whether the increased blood uric acid in eclampsia and chloroform poisoning is the result of an accumulation of lactic acid or a disturbance of its metabolism due to liver damage cannot be answered but offers an interesting speculation. Likewise, it is difficult to say whether sufficient benzoic acid and other aromatic acids can be produced in intestinal putrefaction to influence the excretion of uric acid. It must be remembered, however, that when the liver is injured, its conjugating power is diminished and the depressing effect of aromatic acid on uric acid excretion is increased.

SUMMARY

Strenuous exercise markedly diminishes the excretion of uric acid without affecting the output of creatinine. Mild exercise has no appreciable influence on uric acid. A possible explanation for the retention of uric acid during exercise is the overproduction of lactic acid, since even ingestion of this compound brings about a decrease in the output of uric acid.

The inhibitory effect of benzoic acid on uric acid excretion is
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prolonged and often pronounced in patients with liver diseases, but the degree of this retention does not run parallel with the diminution in the rate of hippuric acid production.

BIBLIOGRAPHY

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