The metabolism of the acetone substances in the intact organism has been the subject of numerous investigations, but researches on the function of individual organs have been relatively meager. Embden and his collaborators (1, 2) concluded from experiments on excised tissue perfused with the animal's own blood that the liver was the source of acetone bodies. Chaikoff and Soskin (3) showed that injected acetoacetic acid remained longer in the blood of depancreatized dogs than in normal dogs, despite the fact that the muscles of the two types of experimental animals utilized the ketone acids with equal facility. They concluded that the liver of the depancreatized animal produced acetone substances.

In a previous paper (4) the function of the liver, striated muscle, and the gastrointestinal tract was investigated by means of analyses of afferent and efferent blood samples for total acetone substances. The liver was found to be the most constant source of acetone substances, regardless of the action of the other organs. Blood samples drawn simultaneously from striated muscle and the gastrointestinal tract showed that these organs had the same qualitative effect on the blood concentration of total acetone substances in most experiments. In the present work, the observations were extended to include the heart, brain, and testicle.

**Methods**

Experimental diabetes was induced in eighteen dogs after a preliminary fast which lasted from 24 to 72 hours. Ten animals

* The expenses of this research were met in part by a grant from the Research Fund of the Yale University School of Medicine.
Ketone Substances in Diabetes

were phlorhizinized (5) and eight were depancreatized (6). Blood samples were drawn from the phlorhizinized animals after definite amounts of acetone substances appeared in the urine, and from the depancreatized dogs 2 to 5 days after operation. The animals were anesthetized with amytal.

Since the concentration of acetone substances is the same throughout the arterial system, the femoral artery was used as a convenient source of afferent blood for all the organs. The efferent blood samples of the striated muscles and heart were obtained from the femoral vein and coronary sinus respectively. Observations on the brain were made by means of a window trephined in the cranium which exposed the superior longitudinal sinus, from which the brain efferent blood was sampled. The venous blood of the testicle was drawn from the left spermatic vein caudal to the point at which it empties into the left renal vein. In every case a separate arterial blood sample was taken at the same time as the venous sample.

The method of Van Slyke and Fitz (7) with their modification (8) was employed for the analysis of total acetone substances of the blood. The error of a single determination was ±0.8 mg. per cent.

Results

In the course of obtaining data from the various organs, the femoral arterial blood of each animal was analyzed from three to seven times at varying intervals. It was thus possible to determine the variation in the concentration of acetone substances in arterial blood. Several typical experiments are presented in Table I. The fluctuations observed made it necessary to take an arterial blood sample each time a venous sample was drawn.

Differences in the concentration of acetone substances in the afferent and efferent blood which exceeded 3 times the experimental error were taken as significant. Smaller differences were listed as "no change."

Heart—Afferent and efferent blood samples were obtained from the heart and striated muscle simultaneously, so that a comparison might be made between the actions of the two types of muscle tissue. This comparison is presented in Table II. The number of experiments in which the acetone balance of striated muscle
was negative, zero, or positive, is presented in Column 2. The
effect of heart muscle in each set of experiments listed in Column
2 is noted in Columns 3 to 5. In the eight observations in which
striated muscle had a positive balance, that of the heart was
positive six times, negative once, and zero once. Striated muscle
was found to add acetone to the blood in two experiments, and

### TABLE I

Variations of Acetone Concentration in Arterial Blood

<table>
<thead>
<tr>
<th>Experiment 34</th>
<th>Experiment 33</th>
<th>Experiment 31</th>
<th>Experiment 27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time Acetone</td>
<td>Time Acetone</td>
<td>Time Acetone</td>
<td>Time Acetone</td>
</tr>
<tr>
<td>min. mg. per cent</td>
<td>min. mg. per cent</td>
<td>min. mg. per cent</td>
<td>hrs. mg. per cent</td>
</tr>
<tr>
<td>0 37 0 49</td>
<td>0 24 0 11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 14 20 31 41 29 5 9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 13 45 27 90 6 7 5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 5 60 45 105 22 11 10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>55 9 75 21 450 49 11.5 5</td>
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<td></td>
</tr>
<tr>
<td>90 26 460 30</td>
<td></td>
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</tr>
</tbody>
</table>

### TABLE II

Correlation of Changes of Blood Acetone Produced by Muscle with Those
Produced by Heart

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Heart</th>
</tr>
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<tbody>
<tr>
<td>(1)</td>
<td>(2)</td>
</tr>
<tr>
<td>Added</td>
<td>Added (3) No change (4) Removed (5)</td>
</tr>
<tr>
<td>No change</td>
<td>2 2 0 0</td>
</tr>
<tr>
<td>Removed</td>
<td>5 0 3 2</td>
</tr>
<tr>
<td>Total</td>
<td>15 3 4 8</td>
</tr>
</tbody>
</table>

The readings are for the number of experiments in which acetone was
added to, remained unchanged, or was removed from the blood.

simultaneously the heart also was found to add acetone twice. The
arteriovenous difference of striated muscle was within 3 times
the experimental error in five cases, while the heart removed
acetone from the blood twice, and made no change three times.
Thus, in eleven of fifteen determinations, cardiac and striated
muscle exhibited the same acetone balance.
Brain—Ten observations were made on the brain in six depancreatized dogs, and thirteen afferent and efferent blood samples were obtained from five phlorhizinized animals. Table III contains the results of these experiments in summary. In eighteen of twenty-three cases, no change occurred in the concentration of ketones in the blood passing through the brain. In the five experiments in which the difference was greater than 3 times the

<table>
<thead>
<tr>
<th>Type of diabetes</th>
<th>Added</th>
<th>No change</th>
<th>Removed</th>
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</thead>
<tbody>
<tr>
<td>Phlorhizin</td>
<td>0</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>2</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>2</td>
<td>18</td>
<td>3</td>
</tr>
</tbody>
</table>

The readings are for the number of experiments in which acetone was added to, remained unchanged, or was removed from the blood.

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Added</th>
<th>No change</th>
<th>Removed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Added</td>
<td>5</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>No change</td>
<td>6</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Removed</td>
<td>4</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>1</td>
<td>8</td>
</tr>
</tbody>
</table>

The readings are for the number of experiments in which acetone was added to, remained unchanged, or was removed from the blood.

experimental error, the acetone balance was positive three times and negative twice. No simultaneous observations were taken on muscle, since in most cases, the brain had no effect on the concentration of acetone substances in the blood.

Testicle—It seemed desirable to compare the effect of the testicle and striated muscle on blood acetone, since a similarity between the actions of striated muscle and the gastrointestinal tract had
been noted (4). Blood was drawn from the femoral artery, femoral vein, and spermatic vein and the effect of the two organs was compared. This correlation is presented in Table IV. In the five experiments in which the acetone balance of striated muscle was positive, the testicle added acetone once and removed it four times. Muscle made no change six times, while the testicle made no change five times and removed acetone once. Of the four experiments in which muscle removed acetone, testicle removed it once and made no change in three of these experiments. In only one case of a total of fifteen did the testicle cause an increase in the ketone concentration of the blood passing through it.

The observations were usually made on two or three organs simultaneously, which made it possible to calculate the coefficients of correlation of the actions of the various viscera. The coefficients are presented in Table V. There is a significant positive correlation between striated muscle and the gastrointestinal tract, and between striated muscle and cardiac muscle. The coefficients for striated muscle and liver, and striated muscle and testicle indicate that these organs act in complete independence.

DISCUSSION

In the present experiments a study was made of the acetone production of the various organs of the dog. It was observed that the concentration of ketones in the arterial blood was not constant, but varied within wide limits (Table I). Such variations might be due to the fact that each of the organs of the body can affect the acetone concentration of the blood. The arterial blood concentration would thus be the resultant of the changes effected by all the organs.

In a previous paper (4) it was demonstrated that the liver was...
the organ of the body most prone to ketosis during deprivation of carbohydrate. This may be due in part to its large energy requirement (9) which is probably satisfied by fat in the diabetic organism, and by fat and glucose in normal individuals. The fat may be oxidized to the 4-carbon stage without the simultaneous catabolism of carbohydrate. In diabetes, because less glucose is oxidized, the liver cannot completely catabolize the acetone substances, which therefore diffuse out into the venous blood.

The brain was in acetone equilibrium eighteen out of the twenty-three times it was tested. The respiratory quotient of unity found for the brain (10) might result from the oxidation of glucose, acetoacetic acid, lactic acid, or a combination of the above three substances. There is considerable evidence to show that the cerebral cortex does not oxidize glucose either in the normal or diabetic organism (10, 11). In the present experiments we have been unable to demonstrate the removal of acetone substances by the brain. Thus, it may be said that the brain oxidizes mainly lactic acid, and that the amounts of acetoacetic acid it may oxidize are too small to be detectable with our method.

The character of the food mixture oxidized by the testicle was investigated by Krebs (12). The evidence indicates that this organ, like the cerebral cortex, can oxidize carbohydrate only after its conversion to lactic acid. Unlike the cerebral cortex, however, the testicle can oxidize fat (13). The food mixture oxidized by the testicle in diabetes also consists of fat and lactic acid, since insulin is probably not required for the oxidation of lactic acid (10). Satta (14) has shown that lactic acid is an antiketogenic substance. Therefore the acetone balance of the testicle would be determined by the proportions of the two foodstuffs oxidized, fat and lactic acid. In those cases in which the antiketogenic value of the lactic acid metabolized exceeded the ketogenic value of the fat, the testicle would remove acetone substances from the blood and oxidize them to carbon dioxide and water. In studying the acetone balance of the testicle, either a positive or a zero balance was observed in fourteen of fifteen observations. In those experiments in which there was a positive balance, it is probable that there was more than enough lactic acid oxidized to permit the complete oxidation of the fat used by the testicle. This excess permitted the removal and the oxidation of acetone substances from the blood.
The actions of the gastrointestinal tract, which consists in part of smooth muscle, and striated and cardiac muscle in these experiments showed a high degree of correlation (Table V). These three organ systems have therefore been grouped together in the following discussion. It is possible that the acetone substances which are apparently removed or discharged at various times might depend on the storage of the ketones at one time, and a return to the blood stream at a later time. However, it is also possible that the ketone acids which were removed were oxidized; and those cases in which the organs added acetone substances to the blood might be due to the incomplete oxidation of the fatty acids. There is some evidence in favor of the latter possibility. Chaikoff and Soskin (3) have demonstrated that the muscles of depancreatized dogs can oxidize acetoacetic acid. Sweet and Quick (15) found that depancreatized dogs oxidized butyric acid. Our own experiments indicate that the liver added 12 to 100 gm. of acetone substances per day to the blood, and only a small fraction was eliminated through the kidneys and lungs. Thus, it is not improbable that the acetone substances removed from the blood by muscle were oxidized, despite the fact that presumably no glucose was oxidized (16, 17). As in the case of the testicle, so with muscle, the oxidation of ketone acids may be due to the oxidation of lactic acid (18). In this regard, it is interesting to recall that the liver, the only organ which cannot split glucose to lactic acid (19), is likewise the only organ which is consistently ketogenic.

**SUMMARY**

1. The influence of various organs on the concentration of acetone substances in the blood passing through them was studied in eight depancreatized and ten phlorhizinized dogs. In eight of fifteen experiments the heart removed acetone substances from the blood and on three other occasions added ketone acids to the blood. The brain made no change in the ketone acids in eighteen of twenty-three experiments. The testicle removed acetone from the blood six times, and made no change eight times in fifteen experiments.

2. These results give some indication of the character of the foodstuffs oxidized by the individual organs. Thus, only organs which oxidize fat and carbohydrate, the latter in the form of glucose, are capable of producing acetone substances in diabetes.
This applies to skeletal muscle, gastrointestinal tract, cardiac muscle, and the liver. The testicle oxidizes fat and lactic acid. Lactic acid is ketolytic and therefore the testicle frequently removes acetone from the blood. Brain cortex is unique in that it does not oxidize fat, and has no demonstrable effect on the acetone concentration of the blood.

3. The observations were made on two or more organs simultaneously, so that it was possible to correlate the effects obtained. The testicle and liver each had effects independent of those of striated muscle. Striated muscle, heart, and the gastrointestinal tract, on the other hand, exhibited a high degree of correlation, indicating a similarity in the metabolic processes of these tissues. In approximately one-third of the experiments muscle was removing acetone substances despite the constant addition of these substances by the liver.

BIBLIOGRAPHY

KETONE SUBSTANCE PRODUCTION
AND DESTRUCTION IN CERTAIN
TISSUES OF DIABETIC DOGS
Walter Goldfarb and Harold E. Himwich

*J. Biol. Chem.* 1933, **101**:441-448.

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