THE ACTION OF EXERCISE ON KETOSIS

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In recent years evidence has been accumulating that the ketone bodies are, on occasion, an important step in the catabolism of fat (1, 2). There is much support for the view that the liver at certain times partially oxidizes fatty acids to form these ketone bodies which are then supplied to the other tissues of the body as an important fuel (3, 4). A large fraction of the energy turnover of the muscles may under certain conditions be supplied by oxidation of these substances (1, 5). It would seem likely then that individuals in a state of ketosis would show a decrease in its intensity (which has ordinarily been measured by urinary ketone excretion) as a result of exercise. This has not been found to be entirely the case for periods of exercise lasting an hour or more (6, 7). These seemingly contradictory findings may be reconciled if we can accept the assumption already stated in papers from these laboratories (1) that muscular activity not only causes increased burning of these bodies but also increased production of them by the liver.

If these two effects are produced at the same time they would tend to balance each other and it would be very difficult to investigate them separately. If they are not simultaneous,—one being delayed,—it should be possible to follow the successive opposite effects. The increased utilization of ketone bodies by working muscles is immediate as is evident from the observations of Blixenkrone-Moller (5) on perfused isolated extremities and of Drury and Wick (8) on the intact subject. If there is an increased output by the liver and it has a delay of over half an hour it should be possible to follow it since it should give a post-exercise increase in the blood ketone curve. With the human subject we experienced difficulty in producing a "steady" ketosis state on which we could study this delayed effect of exercise. One can easily produce a definite ketonemia by a fast of 20 hours, but at this time the level is not constant, but has a distinct, though not necessarily steady upward gradient. Over a three day period this averages 0.82 mgm. per cent per hour (9). Our subject showed a gradient of 2.2 mgm. per cent per hour between the 10th and 20th hours. Under these conditions it is easy to study mechanisms which lower the
ketone content of the body, but it is difficult to follow those which increase it. One is forced to attempt to determine whether the post-exercise blood ketone curve has a steeper gradient than a control curve for the subject during the same period of fasting.

Human experiments. In all of our human experiments we produced ketonemia by having the subject go without food for at least 15 hours. This was easily carried out by having him take no food after the evening meal of the previous day and then starting observations at 9 a.m. or later. At this time the blood ketone level is beginning to rise and continues to do so for many hours (8). We then had the subject exercise or rest for varying periods to see how this upward gradient of blood ketones would be affected during the exercises and during the period which followed. Blood ketone determinations were done by the method of Barnes and Wick (10) and are expressed as total ketone bodies.

Light exercise. The first exercise studied was walking. This was studied on two separate days a week apart. Every attempt was made to keep conditions identical on the two occasions (character of food on previous day, times of eating and sleeping) and the only thing that was varied was the times of walking and resting.

Although the results of the first day might suggest an increase in utilization during walking with an increased production in the supervening rest period, the second day shows the same general upward trend at any comparable period regardless of whether the subject rested or walked, or had been walking just before. We may conclude then that if walking does increase the utilization of ketone bodies it does so to but a small extent, and this small increase would be compensated for by increased production by the liver.

Moderate exercise. A heavier form of exercise was next studied—tennis playing. Table 2 shows the results of our first experiment with this.
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It is apparent that playing tennis for this period has little demonstrable effect on the course of the blood ketone level. Its steadily rising trend may have been slightly flattened during playing. We, therefore, examined the effect of this form of exercise when continued for a longer period. Table 3 gives the results together with a control day on which conditions were identical except for exercise.

It would seem that exercise might have leveled out the upward trend of the blood ketones during the first hour and a half, but not after this. The rise between 11:04 and 12:20 may represent increased production by the liver. The differences from the control period, however, are so slight that it appears again that in moderate exercise one cannot demonstrate increased utilization of ketone bodies followed by increased production of these substances. Both may be increased but if so they offset each other very closely.

Heavy exercise. With a higher rate of exercise—running steadily at 10 miles per hour for 20 minutes—we obtained a definite decrease in the blood ketone level. This drop was followed by a sharp rise during the period after the exercise. See tables 4 and 5.

The examples show the drop during the heavy exercise and the sharp rise immediately after. The control days, however, have periods during
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which the blood ketone level rises just as steeply. We can conclude then that a short bout of heavy exercise can use up ketone bodies faster than they are being formed by the liver. It is not possible to tell whether the succeeding rise due to liver production is greater than what would ordinarily occur because the control periods show at times rises just as steep.

RAT EXPERIMENTS. It seemed to us that the occurrence of these sharp rises in ketonemia on the control days make it very difficult to find out whether there is an over-production of ketone bodies by the liver after exercise in the human. We decided then to study an animal that had a

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<td><strong>CONTROL DAY</strong></td>
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<td><strong>CONTROL DAY</strong></td>
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<td><strong>Time</strong></td>
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<td>12:10 p.m.</td>
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more slow and gradual rise in blood ketones during simple fasting (11, 12). The rat, which as an example may have an average rate of rise in the blood ketone level of 0.2 mgm. per cent per hour between the zero and ninety-sixth hour of fasting, satisfies this requirement. Even more important for the present problem, it is possible to fast these animals for periods adequate to arrive at a state in which the blood ketone level reaches a plateau and remains practically constant (13).

We made observations on 3 series of rats. For each series we selected a group of adult rats of common origin, of the same sex, approximately the same weight and within thirty days of the same age. They were all fasted
the same length of time, and then divided into two parts—one for the exercise and one for the control. The rats of the former group were given a short period of strenuous exercise (swimming) and at set times thereafter sub-groups of six were sacrificed for individual blood ketone determinations upon arterial blood. Similar sub-groups of six of the unexercised group were sacrificed at set times for control blood determinations. In all cases the liver glycogen content was also determined. Male rats were used in experiments A and B. In experiment A the rats (average body weight 281 grams) were used 48 hours after their removal from the stock diet ("Tioga dog Pellets", protein, 23; fat, 4; fiber, 4; ash, 12.5; moisture, 8.5; nitrogen free extract, 48). The rats in experiments B (average body weight 300 grams) and C (average body weight 202 grams) were on a low protein diet (13) for 15 and 16 days respectively and then fasted 3 days before using. Such a diet leads to a high fasting concentration for the blood acetone bodies (14).

The animals were exercised by swimming them in water (32°C) for five 2 minute periods with 1 minute rest between periods. With this amount of exercise the rats are completely exhausted and further swimming is generally impossible. The blood ketones were determined by the method of Barnes and Wick (10). Oxalated blood specimens were obtained from the abdominal aorta after the animals were anesthetized with sodium pentobarbital. Glycogen determinations were carried out on the livers according to the method of Good, Kramer and Somogyi (15).

The results are given in figure 1. Each point in a given experiment represents the average of the determinations for a group of six rats. The rats used in experiment A were evidently not fasted long enough to give a very high beginning blood ketone level, so the drop after exercise is not large. The subsequent over-production is quite definite. In the next series (B) we, therefore, made sure of an adequate beginning blood ketone level by feeding of a low protein diet and a longer fast. We also extended the time of post exercise observations. In this series we obtained a marked drop in blood ketone level immediately after the exercise, with a return to the control level one hour later. This is followed by an over-production phase, so that the level is much higher than the control two hours thereafter. At six hours after exercise the level has come back to that of the controls. In series C we produced a still higher beginning level, extended further the post-exercise period and determined the blood ketones every hour after the exercise. The results are even more pronounced than in experiment B. Two hours after exercise the over-production phase has not only made up for the immediate drop but has taken the level to well above the control. From then the level continues to rise slightly until the fifth hour. At the sixth and seventh hours the level is back to the control.

The changes in liver glycogen content pictured in figure 1 represent
weighted averages of the data for experiments A, B and C in which the changes were of the same general nature. The liver glycogen level was fairly low to begin with because the animals were fasting. During the brief exercise period it fell to a really low level and remained there throughout the period of observations. This is not surprising for in these glycogen depleted rats the only possible source of additional carbohydrate would be from protein catabolism. Although it has often been questioned, the old experiment of Pettenkofer and Voit (16), who found that in starvation exercise did not increase protein metabolism, has not been disproved. The energy for the exercise must be supplied by an increased metabolism of fat. The ketone bodies during exercise, when fasting, serve in part at least the functions of glucose during exercise in the fed organism (17–20).

Discussion. The results with the rat show that we can demonstrate clearly both increased utilization, and subsequent over-production of ketone bodies as a result of strenuous exercise in this animal. Heavy exercise also gives clear evidence of increased utilization with the human, and it is likely that a subsequent over-production would be clearly shown if we had fasted the subject until he had reached the blood ketone plateau. Evidently, demonstration of the two processes would be difficult for lower rates of exercise. Here the intensities of the two effects are less and in order to get the definite drop in blood ketone level that is needed to prove
increased utilization the exercise has to be continued for such an extended period that we get overlapping of the increased-production mechanism, and in this way the results of the two actions are balanced and consequently hidden.

Our results solve the problem presented by the finding of Blixenkrone-Moller that increased work by isolated muscles increases utilization of ketone bodies whereas increased muscular activity by the intact ketonic animal does not decrease the urinary excretion of ketone bodies in the 24 hour period. If the rate of exercise is high there is a reduction of ketones in the body and urine at the time, but this is compensated for by overproduction during a period of several hours following the exercise, so that the total excretion during the two periods is little changed from control periods. It is reasonable to assume that the same mechanisms account for the absence of effect of less strenuous exercise continued for longer periods. Here the supervening increased production would commence before the increased utilization due to the exercise had continued long enough to have had a demonstrable effect. Although we can only get a separation of the two effects with short strenuous exercise, we have every reason to believe that they occur in milder forms of activity, here co-existing and offsetting each other.

A word should be said as to the possible mechanism of the action of exercise on ketosis. The initial fall in the ketone body level of the blood which results from exercise is most reasonably explained by an increased rate of utilization. What then of the subsequent overproduction? In severe exercise epinephrine secretion is abundant (20, 21) and causes an increase in glycoigenolysis when carbohydrate for such is available. When there is a lack of carbohydrate, epinephrine increases ketone body formation (22). This may well be the cause of the over-production of ketone bodies during and immediately after severe exercise. Epinephrine may be an agent for increasing the production of ketone bodies when there is a condition that may require a lot of them (carbohydrate lack), similar to the way in which it increases glucose production when there is a need for it and an ample supply of glycogen is available.

**SUMMARY**

1. With rats, in a state of ketosis, a short bout of heavy exercise causes an immediate drop in the blood ketone level. During a period of three to four hours thereafter there is a phase of over-production of ketone bodies so that the blood values for exercised animals go to higher levels than in controls.

2. These results support the view that in ketosis states exercise increases the oxidation of ketone bodies and also causes the liver to produce them at a higher rate.
3. In man these changes were not demonstrated for light exercise. The drop during heavy exercise was obtained.

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