THE RELATION OF THE LIVER TO FAT METABOLISM.*

I. EFFECT OF LIVER LACK ON FAT COMBUSTION AND THE RESPIRATORY QUOTIENT.

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It is generally agreed that the liver is active in fat metabolism in many ways. As early as 1886 this became evident to Nasse (1). Subsequent systematic studies by Noel Paton (2), Leathes (3, 4), Leathes and Raper (5), Raper (6), Mottram (7), Rosenfeld (8), Bloor (9, 10, 11) and others, have resulted in a mass of evidence, demonstrating various liver activities in the metabolism of fat. But are these functions performed solely by the liver and are they vital to the organism? Can fat combustion be carried on at all in the absence of the organ? These are the chief questions concerning the role of the liver in fat metabolism. Their answer waits upon a demonstration of the absence or continued presence of fat combustion in animals deprived of the liver or otherwise brought into a state of extreme hepatic insufficiency. In the present communication we will report experiments upon this theme. Rabbits were chosen for the work and total liver ablations done (12) by a method already described. For the induction of a partial but pronounced liver insufficiency, removal of approximately 90 per cent of the liver was practiced (13).

The Respiratory Quotient of Rabbits with Partial Liver Insufficiency.

Earlier workers have shown that the respiratory quotient of fasting animals, previously well fed, is low (14), indicating a body metabolism largely that of fat. What now will the quotient be after removal of the liver, or in conditions of hepatic insufficiency?

* A preliminary report upon some of the findings given herein has already appeared in the Proceedings of the Society for Experimental Biology and Medicine, 1927, xxv, 151.
Well nourished rabbits on a mixed diet, and weighing 2 to 3 kilos, were fasted 48 to 72 hours and subjected to a preliminary determination of the respiratory quotient by the method outlined below. The respiratory quotient was low in such fasting animals indicating a pronounced combustion of fat. Then liver insufficiency was induced.

Method.

The Respiratory Quotient. The Apparatus.—All respiratory quotient determinations were made by the closed circuit method with the rabbits sealed in an air tight respiration chamber, a very large desiccator, submerged in a constant temperature bath. The chamber was just large enough to allow the animals the normal crouching posture. The closed circuit consisted of the animal respiration chamber, two parallel absorbing systems with shut-off clamps, a mercury pump which afforded a continuous circulation of air, and a set of valves permitting the air to pass through the circuit in one direction only. The total volume of the apparatus was 11 liters. The absorbing systems, for the removal of water vapor and CO2, were each made up of an ascarite1 tube connected at both ends with sulfuric acid absorption bottles. The weight of the ascarite tube in one of these systems was carefully determined, and so too was that of the second sulfuric acid bottle which the air entered after passing through the ascarite. The circulating air could be shunted at will through either of these absorption circuits. From a reservoir of known volume, oxygen entered the closed circuit between the absorbers and the pump. At this point too, connections were made with an auxiliary oxygen reservoir. At frequent intervals the apparatus was tested for leaks, by raising the pressure by an amount equal to that of 100 cm. of water in addition to the atmospheric pressure and ascertaining that no volume change occurred in the circuit within 5 minutes.

The Respiratory Quotient Determination.—The respiration chamber containing the experimental animal was submerged in the constant temperature bath and the air within the system circulated at the rate of 3 liters a minute. But one of the absorption systems was employed in the circuit and oxygen was used from the auxiliary oxygen reservoir. After 20 minutes the pump was stopped and the pressure within the system adjusted to that of the room atmosphere. The barometric pressure was noted at the same time. Upon starting the circulation of air again the current was deflected through the second train of absorbers containing the weighed ascarite tube and weighed sulfuric acid adsorption bottles. Oxygen was now allowed to enter the closed system from the measured reservoir until about 1.5 liters had been consumed. This required about 1 hour and 20 minutes with the average 2 to 2.5 kilo rabbit. At the end of this period the pump was

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stopped, the pressure in the closed system adjusted again to that of the room atmosphere, the barometric pressure observed, and the volume of oxygen added to the system during the period was noted. By reweighing the ascarite tube and second sulfuric acid bottle the amount of CO₂ produced was determined. The volume of oxygen added during the period of the experiment, plus or minus the correction for changes in barometric pressure, temperature and vapor pressure, represented the oxygen consumed.

The rabbits remained quiet within the respiration chamber. It was not necessary to prevent all motion on the animal's part for calorimetry studies were not contemplated and only the gas exchange was measured. However the animals sat so tranquilly that we were able, in later work, to give them continuous intravenous injections of glucose while in the chamber, despite the fact that the injecting needle once placed in an ear vein could not be readjusted during the period of the respiratory quotient determination. In over 20 such experiments no animal ever moved sufficiently to dislodge the needle from the vein. The method will be described further on.

Technique.—When it had been established that the respiratory quotient of a fasted rabbit was definitely low, indicating that fat combustion was taking place, blood specimens were taken from an ear vein for sugar, hemoglobin and hematocrit estimations, and immediately thereafter 90 per cent of the liver was ablated under ether. 5 to 7 hours later, when the immediate effects of operation and anesthesia had worn off, a second determination of the respiratory quotient was made. Immediately preceding the animal's entrance into the respiration chamber and at once following its removal therefrom, samples of venous blood were taken by cardiopuncture from the right ventricle for CO₂ and sugar analyses.

As we have shown in a preceding paper the blood sugar concentration falls rapidly after removal of 90 per cent of the liver, reaching the lethal minimum 6 to 10 hours after the operation. As the second respiratory quotient determinations were made in the latter part of this period the blood sugar level was invariably found low, between 60 and 70 mg. per cent. Often the animals collapsed and became moribund while in the respiration chamber the second time. In such instances the experiments were discontinued.

In four instances a third respiratory quotient was determined on the following day, 24 hours or more after the removal of 90 per cent of the liver. These animals, of course, received glucose during the night in amounts just sufficient to keep the blood sugar level slightly above the minimum required to keep them free from convulsions. Blood sugar analyses were made before the final respiratory quotient was taken to rule out instances in which the giving of too much glucose might have brought the blood sugar concentration to normal or above. It seemed conceivable in this event, indeed it has been shown by our later work, that the utilization of glucose by the animal might mask or entirely supplant the combustion of fat. In one instance, Table I, No. 4, the blood sugar concentration was found high (0.099 per cent) on the day following operation and the respiratory quotient determination was duly postponed several hours, until it had fallen to 0.079 per cent.
### TABLE I.

*Respiratory Quotient, Metabolic Rate*<sup>1</sup> and Blood Sugar Findings in Rabbits Deprived of 90.6 Per Cent of the Liver.

<table>
<thead>
<tr>
<th>No.</th>
<th>Respiratory quotient</th>
<th>O₂ consumption</th>
<th>Blood sugar</th>
<th>Respiratory quotient</th>
<th>O₂ consumption</th>
<th>Blood sugar</th>
<th>Respiratory quotient</th>
<th>O₂ consumption</th>
<th>Blood sugar</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mcg. per min.</td>
<td>mcg. per cent</td>
<td></td>
<td>mcg. per min.</td>
<td>mcg. per cent</td>
<td></td>
<td>mcg. per min.</td>
<td>mcg. per cent</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.740</td>
<td>27.5</td>
<td>0.114</td>
<td>0.720</td>
<td>27.8</td>
<td>0.064</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.766</td>
<td>20.7</td>
<td>0.119</td>
<td>0.757</td>
<td>18.5</td>
<td>0.069</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.783</td>
<td>19.3</td>
<td>0.118</td>
<td>0.720</td>
<td>18.9</td>
<td>0.077</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.729</td>
<td>28.0</td>
<td>0.122</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>0.731</td>
<td>32.6</td>
<td>0.079</td>
</tr>
<tr>
<td>5</td>
<td>0.782</td>
<td>33.6</td>
<td>0.128</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>0.745</td>
<td>31.9</td>
<td>0.056</td>
</tr>
<tr>
<td>6</td>
<td>0.768</td>
<td>30.0</td>
<td>0.125</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>0.735</td>
<td>29.5</td>
<td>0.046</td>
</tr>
<tr>
<td>7</td>
<td>0.760</td>
<td>25.5</td>
<td>0.122</td>
<td>0.739</td>
<td>25.0</td>
<td>0.059</td>
<td>0.743</td>
<td>26.1</td>
<td>0.066</td>
</tr>
<tr>
<td>8</td>
<td>0.826</td>
<td>29.9</td>
<td>0.128</td>
<td>0.751</td>
<td>27.7</td>
<td>0.085</td>
<td>0.714†</td>
<td>29.6</td>
<td>0.051</td>
</tr>
</tbody>
</table>

* Expressed in terms of O₂ consumption per minute.  
† 10 hours after operation.

### TABLE II.

*Blood CO₂ of Rabbits Immediately before and after the Period of Respiratory Quotient Determination.*

<table>
<thead>
<tr>
<th>No.</th>
<th>Before entering respiration chamber</th>
<th>After entering respiration chamber</th>
<th>Hours after operation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>vol. per cent</td>
<td>vol. per cent</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>48.1</td>
<td>48.3</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>46.8</td>
<td>47.6</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>39.6</td>
<td>39.9</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>47.5</td>
<td>47.2</td>
<td>24</td>
</tr>
<tr>
<td>5</td>
<td>40.1</td>
<td>40.5</td>
<td>24</td>
</tr>
<tr>
<td>6</td>
<td>42.7</td>
<td>43.1</td>
<td>26</td>
</tr>
<tr>
<td>7</td>
<td>44.4</td>
<td>44.4</td>
<td>5</td>
</tr>
<tr>
<td>8</td>
<td>41.6</td>
<td>40.6</td>
<td>24</td>
</tr>
<tr>
<td>8</td>
<td>46.0</td>
<td>45.6</td>
<td>6</td>
</tr>
<tr>
<td>8</td>
<td>45.8</td>
<td>45.5</td>
<td>10</td>
</tr>
</tbody>
</table>

As an additional routine measure, blood specimens from the ear vein were taken before operation and at variable intervals thereafter for sugar estimation by the Hagedorn-Jensen (15) method. After operation, blood specimens for CO₂ analysis were taken immediately preceding, and at once following the sojourn of
the animals in the respiration chamber. They were obtained by cardiopuncture of
the right ventricle, under oil, and in paraffined tubes. The CO2 estimations were
carried out by the method of Van Slyke and Sendroy (16, 17). These latter
findings for the instances shown in Table I are presented separately in Table II.
As the respiration chamber was small and the animals quiet, differences in the
metabolic rate could be roughly determined in terms of oxygen consumption per
minute.

Only those instances have been considered in which the metabolic
rate remained constant before and after operation (see Table I). All
experiments have been ruled out, too, in which any significant change
in the concentration of blood CO2 was found. The results given below
must be attributed to the true gas exchange of the animal and not to
mere retention or blowing off of CO2 during the periods of experi-
mentation.

In these experiments, which were of relatively brief duration, no
significant hemoglobin or hematocrit changes were observed.

Findings.

The preliminary respiratory quotients of 25 fasted rabbits averaged
0.755, with variations between 0.722 and 0.826, indicating a great
combustion of fat. In Table I the respiratory quotient, blood sugar
and oxygen consumption data are given in 8 of these instances which
constitute experiments free from objection, in which neither blood CO2
changes nor significant variations in the metabolic rate appeared.
The magnitude and character of the individual variations are self-
evident. When about 90 per cent of the liver of the animals was
ablated, the respiratory quotient 6 to 8 hours later averaged 0.737,
with individual variations between 0.720 and 0.757. The respiratory
quotients of 4 of these rabbits taken again the following day averaged
0.738, with only slight variations,—0.731 to 0.745.

In 4 other successful experiments, not shown in the table, the respira-
tory quotient and blood sugar findings were similar but the metabolic
rate showed some retardation, the animals requiring 1 3/4 to 2 hours,
even 2 1/2 hours in one instance, to consume the quantity of oxygen used
prior to operation in about 1 1/4 to 1 1/2 hours. These latter instances are
merely corroborative and hence need be mentioned no further.

From the findings reported so far we conclude that fat combustion
can be carried on as readily and as rapidly in the rabbit after ablation of 90 per cent of the liver as before, in spite of the fact that the animals suffer from extreme liver insufficiency, eventually dying therefrom (13).

The Respiratory Quotient of Rabbits Deprived of the Entire Liver.

With these facts established, it became essential to determine whether fat combustion could continue in the absence of the entire liver. In the experiments just described, there was the possibility that the findings depended upon some activity of the small remnant of the liver. For this reason we repeated the experiments, as described above, but employed rabbits deprived of the entire organ according to the method described in an earlier paper (12).

One important change in technique was forced upon us. The rabbits deprived of the entire liver required glucose prior to the postoperative estimation of the respiratory quotient. For the fall in blood sugar concentration took place more rapidly in them than in those animals retaining 10 per cent of the organ. In the liverless rabbit given no glucose death from low blood sugar occurs in some instances within 2 to 3 hours after operation; and it seemed wise to wait at least 4 hours before determinations of the respiratory quotient since both metabolism and respiratory quotient might have been disturbed by the ether anesthesia and laparotomy. Preliminary experiments were made to determine the minimum amount of glucose which would maintain hepatectomized rabbits. These experiments will be detailed in a following communication. Suffice it to say here that 100 to 130 mg. of glucose per kilo of body weight per hour answers the purpose, when given by continuous injection during the first 8 hours after hepatectomy. This small amount of glucose only was given in the later work, since a larger dosage might conceivably have acted to mask an existing fat consumption.

Technique.

For the respiratory quotient experiments a technique was used similar to that just described, with certain minor modifications. Rabbits of about 2 kilos were subjected to subtotal ligations of the portal vein and vena cava to establish a collateral circulation about the liver (12). 3 to 5 weeks later the animals were fasted for 72 hours and given water which they drank freely. The long fasting period was found necessary, for the respiratory quotient of a previously well nourished rabbit, which is fasted, does not fall in less than 3 days. At the end of this time if a preliminary respiratory quotient determination was found to be low, as it usually was, blood specimens were taken for sugar estimations and hepatectomy done under ether anesthesia.
At once after operation blood sugar determinations were again made and a continuous intravenous injection, of isotonic (5.4 per cent) glucose solution, begun. The change in the blood sugar percentage found at this second estimation deter-

**Text-fig. 1. The Blood Sugar Concentration of Rabbits Deprived of the Entire Liver and Given Small Amounts of Glucose during the Interval between the Preoperative and Postoperative Respiratory Quotient Determinations.**

The blocked in areas indicate the period during which respiratory quotient determinations were made and their height above the base line the blood sugar levels. Blood sugar estimations were done after each of the preoperative respiratory quotient determinations and their level plotted accordingly. In each instance a blood sugar estimation was made again immediately after the operation for hepatectomy. The changes in concentration are shown by the dotted lines. At various intervals thereafter the blood sugar concentration was determined in each animal and the variations depicted by the continuous lines. As the blood sugar levels were known both before and after the postoperative respiratory quotient determinations were made, the chart shows the approximate level of blood sugar concentration during those periods. It is obvious that the blood sugar concentration fell during the postoperative respiratory quotient determinations.

Determined how much glucose was later given, the amount being that deemed necessary just to maintain the blood sugar concentration above the level of 100 mg. per cent. Experience soon taught us that it was safer to give too much glucose than
too little, for in two experiments the animals entered the state of hypoglycemic collapse while in the respiration chamber before the respiratory quotient determinations could be made. These experiments, of course, were ruled out. Three of the instances plotted in Text-fig. 1 received slightly too much glucose and a distinct rise in the blood sugar level followed. At various intervals blood sugar determinations were made as guides to the rate at which glucose was injected later.

After the operation, during the continuous glucose injection, the animals sat quietly on a warmed pad, with only occasional shifting movements.

About 5 to 6 hours after removal of the liver a second estimation of the respiratory quotient was begun; and in one instance a third was made 24 hours after hepatectomy. Ordinarily the animals remained in the respiratory quotient chamber about 1½ hours. The glucose injection was continued during this period, the fluid entering the chamber through a glass tube connected in turn with fine rubber tubing about 8 inches long, to which the needle was attached. The needle inserted in the ear vein was kept in place by two weak bulldog clips and the rubber tube supported along the animal's back by an adhesive strip to prevent its occlusion by a kink should the rabbit shift its position. In all of the experiments the glucose injection was successfully carried out.

To determine changes in the blood CO₂ and sugar, specimens of venous blood were taken in every instance, immediately before and again after the animal's sojourn in the respiration chamber. To obtain blood samples in these experiments cardiopuncture was not necessary since the animals presented greatly enlarged collateral abdominal veins from which blood was taken, under oil, in paraffined syringes.

As in the previous experiments, we shall consider only the cases in which the metabolic rate remained high after operation and no significant blood CO₂ changes could be demonstrated.

Findings.

It was deemed sufficient to carry on experiments with hepatectomized rabbits until 6 instances had been obtained which fulfilled the conditions mentioned above. Table III gives a survey of the findings with the 6 different animals, on one of which (No. 4) a third respiratory quotient was obtained 24 hours after operation. In Text-fig. 1, we have charted the blood sugar curves of these animals in such a way as to show the probable blood sugar level during the period of respiratory quotient determinations.

Of the 6 instances, 4 showed practically no change in the respiratory quotient after liver removal, although in 1 of these (No. 4) a late determination was made as long as 24 hours after the operation. In
### TABLE III.

*The Respiratory Quotient and Metabolic Rate* in Rabbits Deprived of the Entire Liver.

The respiratory quotients of 6 fasted rabbits before and after removal of the liver are shown, together with the rate of oxygen consumption during each respiratory quotient determination. After hepatectomy all these animals received glucose. In Columns 4 and 9 the "noncarbohydrate" respiratory quotient has been calculated as explained in the text.

<table>
<thead>
<tr>
<th>No.</th>
<th>Preoperative</th>
<th>Postoperative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. respiration</td>
<td>O(_2) consumption</td>
</tr>
<tr>
<td></td>
<td>rate, per min.</td>
<td>vol. per cent</td>
</tr>
<tr>
<td>1</td>
<td>0.751</td>
<td>17.22</td>
</tr>
<tr>
<td>2</td>
<td>0.772</td>
<td>20.53</td>
</tr>
<tr>
<td>3</td>
<td>0.779</td>
<td>18.03</td>
</tr>
<tr>
<td>4</td>
<td>0.783</td>
<td>19.84</td>
</tr>
<tr>
<td>5</td>
<td>0.765</td>
<td>17.82</td>
</tr>
<tr>
<td>6</td>
<td>0.786</td>
<td>21.12</td>
</tr>
</tbody>
</table>

* Expressed in terms of O\(_2\) consumption per minute.
† Excess of glucose given as described in text.
‡ Did not receive enough glucose during respiratory quotient determination.
§ Received too much glucose before and during respiratory quotient determination. Blood sugar high.

### TABLE IV.

*Blood CO\(_2\) of Rabbits Deprived of Total Liver Immediately before and after the Period of Respiratory Quotient Determination.*

<table>
<thead>
<tr>
<th>No.</th>
<th>Before entering respiration chamber</th>
<th>After entering respiration chamber</th>
<th>Hours after operation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>vol. per cent</td>
<td>vol. per cent</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>43.35</td>
<td>43.14</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>39.35</td>
<td>38.98</td>
<td>5‡</td>
</tr>
<tr>
<td>3</td>
<td>40.18</td>
<td>39.95</td>
<td>5‡</td>
</tr>
<tr>
<td>4</td>
<td>41.63</td>
<td>41.34</td>
<td>5‡</td>
</tr>
<tr>
<td>4</td>
<td>44.80</td>
<td>45.40</td>
<td>24</td>
</tr>
<tr>
<td>5</td>
<td>37.16</td>
<td>37.58</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>45.60</td>
<td>45.42</td>
<td>5‡</td>
</tr>
</tbody>
</table>

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2 instances an appreciable rise in the respiratory quotient occurred. It may here be remarked again that of necessity all the animals received continuous intravenous glucose injections during the interval between the operation and the completion of the respiratory quotient estimation.

In both of the animals in which a rise in the respiratory quotient occurred, Nos. 5 and 6, a marked fall in blood sugar was noticed immediately after the liver ablation (see Text-fig. 1). To prevent the development of hypoglycemic symptoms, much more glucose was given to these animals than to the others. In Rabbit 6, far too much glucose was given, 200 mg. per kilo per hour, and the blood sugar level stood at 159 mg. per cent at the beginning of the respiratory quotient determination. The other instance showing a rise in the respiratory quotient (No. 5) also received much more glucose per kilo per hour than those in which no rise was found. As Text-fig. 1 shows, the blood sugar concentration in this instance was abnormally low after operation. The animal was consequently given 185 mg. of glucose per kilo per hour instead of the usual 100 to 130 mg. Although the blood sugar concentration in the animal was not high immediately before the period of respiratory quotient estimation, it is to be noted that the animal had received this excess sugar.

The findings show beyond doubt that fat combustion continues actively in the animal without a liver.

**The Effect of Increased Sugar Administration on the Respiratory Quotient of Hepatectomized Rabbits.**

During the respiratory quotient determinations, the period that is to say when the blood sugar level could not be ascertained, the amount of glucose given was arbitrarily cut down to avoid the production of a sugar combustion sufficient to mask any existing one of fat. On the assumption that this glucose, given during the periods of respiratory quotient estimation, was burned we have calculated the hypothetical "non-carbohydrate-burning respiratory quotients," shown in Columns D and H of Table III. These approach closely in some cases the figure 0.71, that of a wholly fat burning respiratory quotient. As Text-fig. 1 shows, the blood sugar concentration of each animal was lower at the end of the respiratory quotient determination than before,
a finding which would support the assumption that the sugar introduced had been used up.

In calculating the hypothetical "non-carbohydrate-burning respiratory quotient" of Columns D and H in Table III we are for the moment assuming that the administration of glucose raised the respiratory quotient. To test the point one experiment was done.

In the experiment on Rabbit 1 a respiratory quotient of 0.757 was obtained between the 6th and 7th hours after operation. For 6 hours prior to this the animal had been given 100 mg. of glucose per kilo per hour by continuous intravenous injection. The blood sugar level fell from 126 mg. per cent 1 hour after liver removal to 0.098 just before the respiratory quotient determination. During the period of the respiratory quotient estimation the glucose dosage was further decreased to 80 mg. per kilo per hour, causing a further fall in the blood sugar level to 0.085, as Text-fig. 1 shows.

The animal was then given an intravenous injection of 5 cc. 5.4 per cent glucose and the rate of the continuous injection increased to the level of 300 mg. per kilo per hour. 20 minutes later another respiratory quotient determination was begun. This required 1½ hours, during which glucose was given at the rate of 300 mg. per kilo per hour. The quotient rose to 0.852. To avoid confusion with the findings in the other instance the latter part of the experiment has been omitted from Text-fig. 1.

DISCUSSION.

It is not to be inferred from our findings that the respiratory quotient must be low under all conditions after removal of the entire liver or a 90 per cent fraction of it. In this paper we wish to emphasize merely that the organism deprived of the liver is still capable of burning fat adequately for its needs. An existing fat combustion may be easily masked, as shown by our experiments in which too much glucose was administered, purposely or inadvertently to the liverless animals. And the respiratory quotient may be high in a variety of circumstances after hepatectomy. Thus, for example, if it is high before operation, it will tend to remain so thereafter. One of our "unsuccessful" experiments serves to illustrate this point.

Ablations of 90 per cent of the liver were carried out on two rabbits which had been fasted but 36 hours. This was done following the preliminary respiratory quotient estimations but before the results had been calculated. At operation the stomachs of the animals were found moderately distended with food. The preliminary respiratory quotients were 0.865 and 0.851, respectively. In both
instances, the respiratory quotient was found high 6 to 8 hours after operation, 0.811 and 0.826, respectively. Autopsy disclosed quantities of undigested food in the stomachs, sufficient reason for the high quotients. In another experiment, a freshly fed rabbit on a carbohydrate diet was subjected to the same procedure. The respiratory quotient which was close to unity (0.951) remained at this figure 6 hours later.

In another rabbit with a preliminary respiratory quotient of 0.731 the second determination was purposely taken 2 hours after operation and found to be 0.840. Guided by this finding we considered it advisable as routine to wait several hours after hepatectomy before attempting the second respiratory quotient estimations.

From the evidence given here one can only say with certainty that fat combustion continues unaffected after removal of the liver of animals already burning fat before operation. The state in which they are burning fat can be brought about by fasting, for about 3 days, animals previously well fed. The freshly fed rabbit on a carbohydrate diet shows as a rule a high respiratory quotient, and so does one fasted for less than 48 hours. On the other hand the fasting period should not be unduly prolonged. For one would of course expect a respiratory quotient indicative of protein combustion in an animal suffering from severe inanition.

Some experimenters have in the past employed the respiratory quotient as an indicator of the type of metabolism existing in animals after attempted exclusion of the liver from the general circulation by the ligation of vessels. In 1910 Porges (18) and Porges and Solomon (19) found a rise in the respiratory quotient of rabbits and depancreatized dogs following ligation of the abdominal aorta, the inferior vena cava, the portal vein and the hepatic veins. They concluded that the oxidation of fat and protein proceeds within the body only in the presence of the liver. In these experiments the animals lived but a few hours, rapidly becoming moribund. Rolly (20), too, reported changes in the respiratory quotient after interferences with the circulation of the liver but found them inconstant. Verzar (21, 22) obtained inconstant results after partial exclusion of the liver by anastomosis of the portal vein with the inferior vena cava. Grafe and Fischler (23) reported no change in the respiratory quotient of dogs with Eck fistulas. Fischler and Grafe (24) ligated the hepatic artery in Eck fistula dogs and observed usually a rise in the respiratory quotient within 6 hours of the operation. But it is to be noted that the respiratory quotient returned to the preoperative figure in the animals surviving more than 6 hours. Bohm (25) excluded the abdominal organs in depancreatized dogs and found but little rise in the respiratory quotient. Still later Grafe and Denecke (26) extirpated the liver in dogs several weeks after an Eck fistula had been formed and found the respiratory quotient low—in one instance 0.774 after operation.
Several explanations for these varying results have since come to hand. As is now well known, from the work of Mann (27) and others, an evident liver lack can only be brought about by almost complete removal or destruction of the organ. Rich (28) has recently demonstrated the futility of attempted exclusion of the liver from the circulation through the methods practiced by most of the earlier workers. Murlin, Edelmann and Kramer (29) have pointed out that radical ligations, excluding as they do much blood and tissue, should be carefully controlled. These authors have demonstrated that changes in the relationships of the blood gases follow sudden clamping of the abdominal aorta which are of themselves sufficient to account for the results of the earlier workers without the need to invoke, as explanation, a change in the metabolism of the animals.

Although no radical circulatory interference, such as complicated these various findings, has been brought about in our experiments we have thought best to rule out the possibility of errors due to changes in the blood CO2 and have done so by considering only instances in which no variations of the sort occurred.

Mann (27, 30) has reported a series of carefully conducted studies upon the respiratory quotient of hepatectomized dogs. In his experiments the respiratory quotient tended to approach unity after removal of the liver. That the quotient in dogs need not necessarily be close to unity after hepatectomy is shown by the work of Markowitz (31). From our findings on rabbits and the figures given in his paper we believe that the respiratory quotient of hepatectomized dogs would be found low 6 hours after the operation if fat combustion were duly established before liver removal and the giving of glucose afterwards reduced to a minimum.

SUMMARY.

Fat combustion is carried on adequately in rabbits deprived of the liver or brought into a condition of extreme liver insufficiency. Even 24 hours after hepatectomy fat combustion goes on as well as in the normal animal. Evidently the liver plays no essential part in the breaking down of fat.

Following the completion of this work, F. C. Mann and W. M. Boothby reported experiments in the American Journal of Physiology, 1928, lxxxvii, 486, which show an increase in the respiratory quotient of dogs immediately after removal of the liver. A subsequent return of the respiratory quotient 17 hours later to a figure but slightly above the preoperative one was also observed.
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