Carbohydrate metabolism and muscular exercise

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Courtice and Douglas (1936) showed that, although a prolonged period of moderate muscular work may be associated with some rise of respiratory quotient and an enhanced carbohydrate oxidation, a persistent low respiratory quotient and ketonuria may result during subsequent rest. They concluded that this low quotient and ketonuria were in the main attributable to the reduced ratio of carbohydrate to fat oxidized owing to the depletion of readily available carbohydrate in the body as a result of the preceding muscular exercise. A second period of exercise was, however, still capable of causing a distinct rise of the respiratory quotient which was maintained throughout the exercise, to fall again abruptly to a persistent low level when the exercise stopped. Finding in one subject (Courtice) that after the ingestion of sucrose, glucose or fructose during post-exercise rest there was distinct evidence of a reduction of sugar tolerance in comparison with observations made during an initial resting period before exercise, they suggested the possibility that the activity of the endocrine organs associated with carbohydrate metabolism may be correlated with the varying activity of the muscles and so afford a partial explanation of the changes of carbohydrate metabolism which result from muscular exercise.

Mills (1938) confirmed on Douglas the reduction of glucose tolerance which ensues after a prolonged period of muscular exercise, but in his own case obtained inconstant results, some experiments showing a lowered glucose tolerance, others no significant change. He also examined the influence of the carbohydrate content of the diet taken previous to the experiments, and tested the influence of intravenous injection of insulin on the subject without any previous exercise and after exercise.

We have now been able to continue these experiments in greater detail, and in particular to determine the respiratory exchange and quotient continuously by the bag method whilst obtaining blood samples for the determination of blood sugar, lactic acid and CO₂ combining power.

[ 41 ]
The exercise was the same as in the original experiments of Courtice and Douglas, viz. a walk of 10 miles on practically level ground at the rate of 4\(\frac{1}{2}\) m.p.h. In a few experiments the distance was increased to 15 miles. In every experiment the subject was in the post-absorptive state at the start. Courtice and Douglas acted as subjects.

**Methods**

*Glucose tolerance.* Preliminary determinations of the respiratory exchange and blood sugar were first made. Immediately afterwards 50 g. of glucose dissolved in 300 c.c. of water were taken and the respiratory exchange was determined continuously (by a succession of bags) during the first hour, and subsequently during the last 10 min. of each quarter of an hour for a further hour and a half. All samples of expired air were collected for approximately 10 min., and in the figures the respiratory quotient is plotted at the mid-point of each of these periods. The blood sugar was determined at 5 min. intervals for the first half hour, and subsequently at 15 min. intervals for a further two hours.

*Reaction to insulin.* Insulin solution (Burroughs, Wellcome and Co., made with crystalline insulin) was injected intravenously into the forearm, the respiratory exchange being determined continuously for one hour, twelve 5 min. bag samples being taken, and the blood sugar at 4 min. intervals for one hour.

*Reaction to adrenaline.* Adrenaline chloride (Parke, Davis and Co., 1 : 1000 solution) was injected subcutaneously into the upper arm. The respiratory exchange was then determined by a succession of 10 min. bag samples for 2\(\frac{1}{2}\) hr., with the exception of a 10 min. interval after the end of each half-hour. Blood-sugar determinations were made at 10 min. intervals for the first hour and subsequently every quarter of an hour.

In all experiments the determinations were made with the subject reclining at rest in a deck-chair. In experiments after muscular exercise the preliminary observations were made after the subject had been resting for 1 hr., so that the glucose or insulin was actually administered about 1\(\frac{1}{2}\) hr. after the exercise stopped.

Blood sugar was estimated in samples of capillary blood taken from the finger by puncture, after the hand had been warmed in water at about 45°C, by the method of Hagedorn and Jensen as given by Peters and Van Slyke (1932), except for the use of Whatman no. 44 filter papers in place of cotton-wool for filtration.
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Blood lactic acid was determined in duplicate analyses by the method described by Friedemann, Cotonio and Shaffer (1927) and Friedemann and Kendall (1929). Blood was taken for this purpose from a vein in the forearm, coagulation and glycolysis being prevented by the addition of 0·2% potassium oxalate and 0·1% sodium fluoride. The blood was kept on ice from the time of withdrawal until required for use.

The CO₂ combining power of the same blood was determined by the blood-gas apparatus designed by Haldane (1920) which was completely immersed in a water bath, the blood being first equilibrated at 37°C with air containing CO₂ at a partial pressure of approximately 40 mm. Hg.

It should be noted that the curves given in the figures frequently represent the average results of two or more experiments. As the samples for analysis were always taken at the same time intervals in such cases, and the individual curves resembled one another very closely, such a method of representing the results can be safely used.

The effect of exercise on glucose tolerance

We have confirmed the reduction of sugar tolerance observed in the original experiments of Courtice and Douglas as well as in those of Mills. Fig. 1 shows the effect on the blood-sugar concentration and respiratory quotient after the ingestion of 50 g. of glucose without preliminary exercise and after prolonged moderate exercise. Both subjects reacted similarly.

The rate at which the blood-sugar concentration rises is practically the same, no matter whether or not exercise has preceded the test, but after exercise the curve rises for a longer period and reaches a higher level, so that the area enclosed is greater than in experiments without preliminary exercise. Once the blood-sugar concentration begins to fall, it falls rapidly and in both cases shows a negative phase between the 100th and 150th minutes. This figure shows the average results of three experiments on Courtice and two on Douglas both without and after exercise, but in individual instances blood-sugar concentrations as low as 65 mg./100 c.c. have been found during this negative phase. We occasionally had a slight glycosuria in experiments after exercise. Mills found that in some of his experiments the blood-sugar concentration rose more slowly after exercise than when there was no preceding exercise, and attributed this to delayed rate of absorption from the gut, but in our present series of experiments there is little or no evidence of this.

There is a definite delay while the blood-sugar concentration is increasing after the ingestion of glucose before the respiratory quotient begins to rise.
Fig. 1. Effect of ingestion of 50 g. of glucose on the blood-sugar concentration and respiratory quotient. ○ without preceding exercise; ● after exercise. Courtice: average of three experiments in each case. Douglas: average of two experiments in each case.
Indeed, as will be seen in fig. 1, there may be a fall of quotient at this time. Attention has been drawn to this fall by Tögel, Brezina and Durig (1913), and it is also apparent in a figure given by Higgins (1916) and is suggested in some of the experiments of Cathcart and Markowitz (1927). Tögel, Brezina and Durig state that the fall of quotient is due to a rise in the oxygen consumption without alteration of CO₂ output and is not caused by mere modification of the breathing, and our own results are in general agreement with this. A clear rise of the respiratory quotient above its preliminary resting value does not become evident until the blood-sugar concentration has attained its maximum. This is more clearly shown in fig. 2, and the matter will be discussed in relation to this figure. The rise of respiratory quotient and its subsequent fall follow the same course in the experiments with and without preceding exercise if allowance is made for the lower initial level in the latter case, and are accompanied by the usual increase and decrease of the total respiratory exchange which result from the ingestion of sugar.

It is well known that the glucose tolerance is affected by the amount of carbohydrate in the preceding diet, being increased by a diet rich in carbohydrate and poor in fat, and decreased by a diet poor in carbohydrate and rich in fat. As Courtice and Douglas have brought forward evidence that the persistent low respiratory quotient after prolonged exercise is largely determined by a reduction in the proportion of carbohydrate to fat oxidized in the body, we decided to test the effect of changes of diet in our own case to see how a change of tolerance brought about in this way would compare with the change resulting from prolonged exercise. Mills has shown in Douglas's case that if a diet rich in carbohydrate is taken the sugar tolerance is increased both in experiments made without exercise and after exercise. We have now tested in Courtice's case the effect on the glucose tolerance of a high-carbohydrate, low-fat diet and of a low-carbohydrate, high-fat diet. In the case of the high-carbohydrate diet the amount of fat taken was cut down so far as possible and the subject lived mainly on foods rich in carbohydrate such as bread, potatoes, jam and sucrose for 6 days, with the result that the initial post-absorptive respiratory quotient was 0.94–0.96. A diet closely approximating to the diet no. 7 of Himsworth (1935) was chosen for the low-carbohydrate, high-fat diet, giving a daily intake of 55 g. of carbohydrate, 94 g. of protein and 220 g. of fat, with a total energy value of about 2576 kcal. This diet caused a marked and continuous ketonuria and an initial post-absorptive respiratory quotient of 0.74–0.75: it was maintained for 9 days. In fig. 2 the influence of these diets on the glucose tolerance is contrasted with the results obtained both without
exercise and after a 15-mile walk at 4 1/2 m.p.h. when the subject was taking his normal diet.

In this instance the high-carbohydrate diet makes little or no difference to the glucose tolerance, although during the test the respiratory quotient remains at a much higher level throughout than in tests made when the subject was taking his normal diet. On the other hand the decrease of sugar tolerance after 9 days of the low-carbohydrate, high-fat diet is

Fig. 2. Subject Courtice. Effect of ingestion of 50 g. of glucose on the blood-sugar concentration and respiratory quotient. ○ Normal diet, without exercise (average of three experiments); ◦ high carbohydrate diet, without exercise (average of two experiments); ● low-carbohydrate, high-fat diet, without exercise; × normal diet, after 15-mile walk.
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striking. The sugar tolerance curve after the 15-mile walk bears a close
general resemblance to the tolerance curve on this diet, though the actual
decrease of tolerance is not quite so great. There was marked ketonuria
after the exercise.

Fig. 2 shows, even more clearly than fig. 1, the delay which occurs after
the ingestion of glucose before there is any sensible increase in the respiratory
quotient. This delay, which is about \( \frac{1}{2} \) hr. in the experiments without
exercise with normal and high carbohydrate diets, is of the order of
1 hr. in the experiments with a low-carbohydrate, high-fat diet and after
exercise with a normal diet. While the blood-sugar concentration is rising
the respiratory quotient actually falls, and it only begins to rise as the
blood-sugar concentration passes its maximum, and attains its highest
value after the blood-sugar concentration has begun to fall. It looks
therefore as though the rise of blood-sugar concentration per se does not
cause the rise of respiratory quotient, but this depends on the effective
development of the processes for the disposal of excess sugar which shows
itself in the rapid fall and final negative phase of the blood-sugar concen-
tration.

Whether these processes, including, no doubt, increased insulin secretion,
are gradually developing whilst the blood-sugar concentration is rising,
or only begin when the blood-sugar concentration has risen to some definite
level (an argument which might be supported by the linear rise of sugar
concentration), we do not know. But in this connexion it is interesting
to note that whilst the glucose tolerance is reduced, and sometimes greatly
reduced, when determinations are made an hour and a half after the cessa-
tion of exercise, the tolerance may be but little altered from normal if
glucose is ingested immediately after stopping the exercise, as is shown in
fig. 3. Nevertheless, in this case, although urine secreted during the exercise
never gave a positive Rothera reaction, urine passed at the end of 30 min.
after taking the glucose always showed a strongly positive Rothera reaction,
the ketonuria disappearing gradually during the next hour. As the
ketonuria developed whilst the blood-sugar concentration was rising to
its maximum this suggests that there can be no great increase in the
oxidation of carbohydrate in the body during this period, which is thus
in correspondence with the behaviour of the respiratory quotient.

The reaction to insulin and adrenaline

Mills has tested on Douglas the effect of the intravenous injection of
3 units of insulin both without preceding exercise and after exercise, and
found no appreciable difference in the response save that in the latter case the return of the blood sugar to normal seemed to be a little delayed. In these experiments the blood sugar fell in about 20 min. to 45 mg./100 c.c. while a dose of 5 units scarcely caused any greater fall. We therefore decided in the present series of experiments to reduce the dose of insulin to 2 units,

![Blood sugar concentration graph](image)

**Fig. 3.** Subject Courtice. Effect of ingestion of 50 g. of glucose on the blood-sugar concentration. O Without preceding exercise; x immediately after exercise; ● 1½ hr. after exercise. Each curve shows the average of three experiments.

so that the full effect could be followed without the risk that the blood sugar would reach a level below which it could not be depressed. This dose never caused any appreciable symptoms in Douglas when he was reclining at rest, but Courtice always showed characteristic symptoms of perspiration, slight faintness, and a trifling disturbance of vision. As he appeared to be more sensitive than Douglas to insulin (he is 28 years younger) we reduced the dose to one unit in his case, and with this dose symptoms were barely appreciable while he was at rest.

Fig. 4 shows the results obtained on the two subjects, in the one case without any preceding exercise and in the other an hour and a half after exercise. After the injection of insulin the blood sugar remains constant for about 4 min. and then falls to its lowest level, of 50–55 mg./100 c.c. in Courtice and 55–60 mg./100 c.c. in Douglas, in about 25 min., to rise rapidly in the next 15–20 min. and then remain moderately steady up to the
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60th minute at a level slightly below the initial value. On the whole the behaviour of the blood sugar after insulin is practically identical, no matter whether the experiment is made without preliminary exercise or an hour and a half after exercise, although there is a little delay in the return to normal in the latter case with Courtice.

In control experiments in which no insulin was injected, but samples for blood-sugar determinations were taken at the usual intervals, the

![Graph](http://rspb.royalsocietypublishing.org/)

Fig. 4. Effect of the intravenous injection of insulin on the blood-sugar concentration and respiratory quotient. Dose of insulin, 2 units for Douglas, 1 unit for Courtice. □ Without preceding exercise; ● after exercise. Each curve shows the average of two experiments.

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respiratory exchange hardly differed appreciably from that found in normal post-absorptive observations on the same subject, except that sometimes there was a slight temporary increase immediately after puncturing a vein to represent the insulin injection. The respiratory quotient, too, remained unaltered.

After insulin injection Courtice's oxygen consumption in some cases showed a distinct, though inconsiderable, increase lasting for about 40 min., but in other cases no material alteration. Douglas showed much the same

**Table I. Average oxygen consumption c.c./min. in consecutive periods of 10 min.**

<table>
<thead>
<tr>
<th></th>
<th>Insulin experiments</th>
<th>Control</th>
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<tr>
<td><strong>Courtice</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before insulin</td>
<td>226 222 205 226</td>
<td>220 —</td>
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<tr>
<td></td>
<td>224 223 202 228</td>
<td>220 206</td>
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<tr>
<td>After insulin</td>
<td>269 265 225 222</td>
<td>224 226</td>
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<td></td>
<td>269 250 218 237</td>
<td>235 224</td>
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<td>260 233 213 226</td>
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<td>218 239 221 229</td>
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<td></td>
<td>217 240 218 230</td>
<td>228 234</td>
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<tr>
<td><strong>Douglas</strong></td>
<td></td>
<td></td>
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<tr>
<td>Before insulin</td>
<td>234 234 238 237</td>
<td>238 227</td>
</tr>
<tr>
<td></td>
<td>228 233 228 242</td>
<td>239 230</td>
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<tr>
<td>After insulin</td>
<td>245 256 246 243</td>
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<td>237 231 249 236</td>
<td>248 225</td>
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reaction. The results of one control and five insulin experiments on each subject are shown in Table I. Notwithstanding the slight or negligible alteration in oxygen consumption the respiratory quotient always showed a clear increase lasting for some time, an increase that was more evident in Courtice than in Douglas. This increase was a little greater in experiments without preliminary exercise than in those after exercise: in other respects the behaviour of the quotient is the same in the two cases. The quotient begins to rise about 15 min. after the injection of insulin in Courtice's case and reaches its maximum about the time that the blood sugar is at its lowest; in Douglas's case it begins about the 8th minute and is still evident at the 60th minute.
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Himsworth (1933, 1935), in his experiments on the influence of different diets on the reaction to insulin, has suggested that on a low-carbohydrate, high-fat diet there is evidence of reduced sensitivity to insulin since after the intravenous injection of insulin there is a longer delay before the blood sugar begins to fall, and the fall is slower and does not reach so low a level as in the case when the subject is living on a high-carbohydrate diet.

![Graph showing blood sugar and respiratory quotient over time](image)

**Fig. 5.** Subject Courtice. Effect of 1 unit of insulin intravenously on the blood-sugar concentration and respiratory quotient. No preceding exercise. ○ Carbohydrate diet; ● low-carbohydrate, high-fat diet.

As our experiments, as well as those of Mills, on the effect of insulin after prolonged exercise, gave no evidence of such decreased sensitivity, we have tested on Courtice the influence of alteration of his diet. Fig. 5 shows the effect of insulin injection in one case when he had been living on a high-carbohydrate diet for 6 days, and in the other case when he had been living on a low-carbohydrate, high-fat diet, as described previously, for 9 days. It will be seen that in each case the blood-sugar concentration remains steady for the first 4 min. and then falls at a similar rate to about the same degree, making allowance for the slightly different initial values in the two cases, although the subsequent rise of blood-sugar concentration is slower in the case of the low-carbohydrate, high-fat diet. There is therefore in this instance no evidence of decreased sensitivity.
such as Himsworth found. The respiratory quotient again shows a temporary rise as a result of the insulin injection, although of course the quotient in experiments on a low-carbohydrate, high-fat diet is throughout at a much lower level than on a high-carbohydrate diet.

The rise of respiratory quotient that occurs after the injection of insulin seems to us to imply an increased metabolism of carbohydrate, no matter whether it is an oxidation of carbohydrate or conversion of carbohydrate to fat. At all events it is not due to the formation of excess lactic acid with a resultant hyperpnoea, for in fig. 6 it will be seen that both the lactic acid content and CO$_2$ combining power of the blood remain practically unchanged while the blood-sugar concentration falls and the respiratory

<table>
<thead>
<tr>
<th>Minutes after insulin</th>
<th>Alveolar CO$_2$ pressure mm. Hg</th>
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<tbody>
<tr>
<td>Before insulin</td>
<td>42.5</td>
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<tr>
<td></td>
<td>41.2</td>
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<tr>
<td>10</td>
<td>42.1</td>
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<tr>
<td>20</td>
<td>41.3</td>
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<tr>
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<td>41.0</td>
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<td>41.7</td>
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<td>60</td>
<td>40.8</td>
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quotient rises. Nor have we been able to find any change in the alveolar CO$_2$ pressure suggesting that the change in the respiratory quotient may be due to a temporary disturbance of the breathing resulting from such a cause as the uneasiness due to slight symptoms of hypoglycaemia. Mills tested this on Douglas, and Table II shows the average results obtained with Courtice in two experiments, the alveolar samples being taken at intervals of 10 min. for the hour succeeding the injection intravenously of one unit of insulin. In both these experiments he experienced distinct, though slight, symptoms of hypoglycaemia between the 24th and 40th minutes, but his alveolar CO$_2$ pressure remains unchanged.

Insulin is but one of the endocrine secretions concerned with carbohydrate metabolism, and for comparison we have tested on ourselves the effects of adrenaline given subcutaneously, and of simultaneous subcutaneous injection of adrenaline and intravenous injection of insulin. The general effects of adrenaline in this connexion, e.g. rise of blood
Fig. 6. Effect of the intravenous injection of insulin on the blood-sugar concentration, respiratory quotient, blood lactic acid (in mg./100 c.c.), and CO₂ combining power of the blood at 40 mm. CO₂ pressure (in c.c. CO₂/100 c.c.). Dose of insulin, 2 units for Douglas, 1 unit for Courtice.
sugar and formation of excess lactic acid are of course well known (cp. for instance, Cori, 1931).

The results of our experiments are shown in figs. 7 and 8. After the injection of 0·5 mg. adrenaline the blood-sugar concentration rises to a maximum of over 150 mg./100 c.c. between the 30th and 60th minute, and does not regain its normal level until the lapse of 2–2½ hr. The respiratory exchange rises in both subjects and gradually falls again during the course of the experiment. As we found that the disturbance caused by the

![Graph](image-url)

**Fig. 7. Subject Douglas. Effect of adrenaline, and of adrenaline + insulin, on the blood sugar, blood lactic acid (mg./100 c.c.), CO₂ combining power of the blood at 40 mm. CO₂ pressure (in c.c. CO₂/100 c.c.), and respiratory quotient. • Adrenaline 0·5 mg. subcutaneously; ○ ditto + 2 units of insulin intravenously.**
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withdrawal of blood from a vein in the arm for lactic acid analyses etc. caused an obvious temporary increase in the respiratory exchange, we have in these experiments never collected expired air samples during the 10 min. immediately following the venepuncture so as to allow time for this disturbance to subside. The results of a typical experiment on each subject are shown in Table III.

The respiratory quotient shows a sharp initial rise which may reach

Fig. 8. Subject Courtie. Effect of adrenaline, and of adrenaline + insulin, on the blood sugar, blood lactic acid (mg./100 c.c.), CO₂ combining power of the blood at 40 mm. CO₂ pressure (in c.c. CO₂/100 c.c.), and respiratory quotient. • Adrenaline 0.5 mg. subcutaneously; ○ ditto + 1 unit of insulin intravenously.
unity: this is succeeded by a fall to a level distinctly below the initial value, reaching a minimum in 1–1½ hr., followed by a gradual rise so that the initial value is often regained at the end of 2½ hr.

The lactic acid content of the blood rises considerably during the first half hour and subsequently decreases slowly to regain its initial value in 2½ hr.

The CO₂ combining power of the blood behaves as would be expected from the variation of lactic acid content, falling at first and then gradually rising again until it reaches, or nearly reaches, its initial level.

Figs. 7 and 8 also show the effect of the simultaneous injection of insulin intravenously and of adrenaline subcutaneously, the doses employed being 0·5 mg. adrenaline with 2 units of insulin for Douglas and 1 unit of insulin for Courtice. In fig. 7 (Douglas) the blood-sugar concentration shows an initial fall and recovery similar in time relations to the effect caused by the injection of insulin unaccompanied by adrenaline, save that the blood-sugar concentration falls to a minimum of only 80 mg./100 c.c. instead of 60. After this transitory depression the blood-sugar concentration remains practically unchanged at its initial level for the remainder of the experiment. In spite of the fact that there is no material increase in the blood-sugar concentration, the changes in the lactic acid concentration and the
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CO₂ combining power of the blood, and in the respiratory quotient are practically the same as when adrenaline alone was injected, nor was there any difference in the behaviour of the oxygen consumption in the two cases. In fig. 8 (Courtice) there is the same transitory depression of the blood-sugar concentration, the lowest value reached being 70 mg./100 c.c. instead of 50–55 mg. which was found with insulin alone, and this is succeeded by a rise of the blood-sugar concentration to a level well below that found with adrenaline alone which slowly subsides. Here again there is no material difference in the behaviour of the lactic acid concentration, the CO₂ combining power of the blood or the respiratory quotient from that found when adrenaline was unaccompanied by insulin.

If 0·25 mg. adrenaline instead of 0·5 mg. were injected the results were of the same type as with the larger dose, the changes being merely on a smaller scale.

Discussion

In these experiments the point that we had in view was the possible association of the changes of respiratory quotient during and after prolonged, though moderate, muscular work, which seem to be due to variations of carbohydrate metabolism, with alterations in the activity of the endocrine organs that can influence carbohydrate metabolism.

Taking the glucose tolerance tests as a whole it seems to us that the reduced tolerance which develops after prolonged exercise differs in no way from the reduced tolerance resulting from a diet poor in carbohydrate and rich in fat, and is due to similar causes. It is accompanied in both cases by a low respiratory quotient and ketonuria. Our present series of experiments therefore supports the conclusion, reached by Courtice and Douglas previously, that while it is impossible to exclude the conversion of fat to carbohydrate as a contributory cause of the persistent low respiratory quotient observed after prolonged exercise, by far the more important factor appears to be the diminution in the ratio of carbohydrate to fat oxidized, and the same factor may be expected when the proportion of carbohydrate to fat in the diet is reduced.

We cannot at present offer any explanation of the fact that if Courtice’s glucose tolerance is tested immediately after muscular exercise the curve is almost the same as the normal one when there has been no preceding exercise, and there is clearly a delay before the characteristic reduction becomes evident. It may be due to the persistence of endocrine activity promoting carbohydrate metabolism during muscular work, but this is
hardly compatible with the fact that ketonuria develops during the first half-hour of the test. The matter seems to need more detailed investigation of the conditions during transition from work to rest.

The experiments described in this paper have been made on but two subjects, and we must emphasize the fact that the results are bound to vary with the individual. Mills has shown that he has quite a different type of tolerance curve, and that an amount of muscular exercise which is invariably followed by ketonuria in Courtice and Douglas causes none in him, nor does it cause any sensible alteration in his tolerance curve. These differences he ascribed, probably rightly, to the fact that his normal diet is rich in carbohydrate.

In spite of the reduction of glucose tolerance there was no evidence that the tissues were rendered less sensitive to an intravenous injection of insulin either by preceding exercise or, in Courtice's case, by a low-carbohydrate, high-fat diet, since the blood-sugar concentration fell at the same rate and to the same degree as in normal tolerance tests although its subsequent rise was slightly slowed.

Cori and Cori (1928) state that insulin causes no change in Calorie output but the isodynamic replacement of fat by carbohydrate oxidation. In following the respiratory exchange in detail we found but slight and inconstant effects on the oxygen consumption after small doses of insulin, on which we lay no stress, but there was invariably an increase in the respiratory quotient, more obvious in Courtice than in Douglas. Such an increase is only to be expected from the work of previous observers. In our own case we have argued above that this rise of quotient is probably determined by an increased metabolism of carbohydrate, and, tempting though it may be to suggest that the slight but maintained rise of quotient so often noted during continued muscular work of moderate severity may be dependent on a correlated increase in the secretion of insulin, there are difficulties to be faced before this view can be maintained. These difficulties involve not so much the actual magnitude of the change of quotient after a single intravenous injection of insulin as the time relations of this change and the fact that it is accompanied by a great fall in the blood-sugar concentration.

The latter difficulty must not however be overstressed for during muscular work other factors may help to combat the fall in blood-sugar concentration which would otherwise ensue from an increased secretion of insulin, and it may be relevant to point out that Christensen (1931) and Boje (1936) have found that the untrained subject may show a fall in blood-sugar concentration in the earlier stages of continuous, though moderate, muscular
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work before there is any question of fatigue, and that in Bøje’s experiments this fall is accompanied by a rise in the respiratory quotient.

If a single intravenous injection of insulin is given to Courtice and Douglas whilst at rest the respiratory quotient does not begin to rise for some 15 and 8 min. respectively; it reaches a level which is maintained for a short time and then falls rather slowly. It may be thought that these changes are too slow in development and subsidence to explain the normal changes of quotient during moderate muscular work. Just after the beginning and cessation of muscular exercise it is difficult to assess the influence of an alteration in the proportion of carbohydrate to fat oxidized on the respiratory quotient since other factors are operative which themselves affect the quotient. We need only mention two of these, firstly the rise of body temperature that takes place when muscular work begins and the fall that ensues when work stops, and secondly the fact recently demonstrated so clearly by Bang (1936) that even in moderate muscular work excess lactic acid is formed in the first few minutes, presumably during the time required for the circulation and respiration to reach an equilibrium with the new condition of raised metabolism, but that if the muscular work is continued this excess may disappear so that a little later on we may find no more lactic acid in the blood than during normal rest.

An injection of insulin during actual muscular work shows, however, that the resultant effects develop more rapidly and to a greater degree than during rest, possibly because of the increase in the circulation rate and the alteration in the distribution of blood to the tissues. The effect on Courtice’s blood-sugar concentration of an intravenous injection of one unit of insulin while he was doing steady work on the bicycle ergometer at the rate of 430 kg.m./min., involving an oxygen consumption of about 1000 c.c./min., is compared in fig. 9 with those of a normal experiment at rest (taken from fig. 4). The contrast between these two experiments is striking. After the same initial lag in the two cases the blood-sugar concentration falls far more sharply, and rises again much more rapidly, in the work than in the rest experiment. In the work experiment the blood-sugar concentration fell to 39 mg./100 c.c. at the 12th minute, and to 34 mg. at the 16th minute, as compared with the figure of 50 mg./100 c.c. at the 24th minute in the rest experiment. Hypoglycaemic symptoms were hardly appreciable at rest, but in the work experiment they were very severe in the form of profuse perspiration, faintness, disturbance of vision and diminution of hearing, which passed off fairly rapidly as the blood-sugar concentration rose again. Lawrence (1926) and Bürger and
Kramer (1928) drew attention to the fact that the fall of blood sugar after the subcutaneous injection of insulin in the diabetic is enhanced by muscular exercise, and this has been confirmed by general clinical experience. In the course of our experiments we gained a clear impression that a dose of insulin which causes no symptoms, or practically none, when the subject is at rest may cause quite perceptible symptoms if the subject moves about a little even though he does no active exercise.

Other endocrine secretions besides insulin influence carbohydrate metabolism, and adrenaline, with its power of mobilizing liver glycogen, is generally supposed to be an important factor during muscular work. We might therefore expect that insulin would have a more effective action on the respiratory quotient in the presence of increased adrenaline secretion.

Our own results are in complete agreement with the well established fact that adrenaline injection results in hyperglycaemia and excess lactic acid formation, as well as with the demonstration by Cori and others (1929, 1930) that if insulin is given simultaneously with adrenaline the rise of blood-sugar concentration that would occur with adrenaline alone may be greatly reduced, if not prevented entirely, without any significant change in the accumulation of excess lactic acid. Most other observers have found that adrenaline increases the metabolism. In our experiments the subcutaneous injection of adrenaline is constantly followed by an increased oxygen consumption which is evident for 2 hr. or longer, and is unaffected by the simultaneous injection of insulin. It is quite different from the inconstant results which we found with insulin alone. It is however the behaviour of the respiratory quotient that has principally interested us.
Carbohydrate metabolism and muscular exercise

The changes in the respiratory quotient shown in our experiments after the injection of adrenaline alone—the quick rise, the succeeding fall to a level below the resting normal, the final slow recovery—are characteristic, and entirely different from the change found after insulin injection. It is the classical picture which we have learnt to associate with the accumulation of excess lactic, or other non-volatile, acid in the blood, and the subsequent disappearance of this excess. It corresponds with the changes in lactic acid concentration and in the CO₂ combining power of the blood, and a sufficient explanation can thus be offered to account for the facts.

When the subcutaneous injection of adrenaline is accompanied by the intravenous injection of insulin the changes of lactic acid concentration in the blood and of the respiratory quotient appear to be precisely the same as when adrenaline is injected alone, in spite of the fact that the rise of blood-sugar concentration is considerably reduced if not prevented, and the explanation of the change of quotient might well be the same in the two cases and depend merely on the formation and disappearance of excess lactic acid.

Calculation of the average respiratory quotient as shown in Table IV for the whole period of \(2\frac{1}{2}\) hr. after the injection of adrenaline or of

<p>| Table IV |
|---------------------------------|-------------------|
| Average respiratory exchange c.c./min. before injection | Average respiratory exchange c.c./min. for entire period of (2\frac{1}{2}) hr. after injection |</p>
<table>
<thead>
<tr>
<th>CO₂</th>
<th>O₂</th>
<th>R.Q.</th>
<th>CO₂</th>
<th>O₂</th>
<th>R.Q.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Courtice</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0·5 mg. adrenaline</td>
<td>177</td>
<td>210</td>
<td>0·84</td>
<td>209</td>
<td>257</td>
</tr>
<tr>
<td>0·5 mg. adrenaline</td>
<td>169</td>
<td>201</td>
<td>0·84</td>
<td>197</td>
<td>239</td>
</tr>
<tr>
<td>0·5 mg. adrenaline + 1 unit insulin</td>
<td>176</td>
<td>204</td>
<td>0·86</td>
<td>212</td>
<td>252</td>
</tr>
<tr>
<td>Douglas</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0·5 mg. adrenaline</td>
<td>185</td>
<td>232</td>
<td>0·80</td>
<td>202</td>
<td>254</td>
</tr>
<tr>
<td>0·5 mg. adrenaline</td>
<td>182</td>
<td>227</td>
<td>0·80</td>
<td>210</td>
<td>267</td>
</tr>
<tr>
<td>0·5 mg. adrenaline + 2 units insulin</td>
<td>180</td>
<td>215</td>
<td>0·84</td>
<td>208</td>
<td>252</td>
</tr>
</tbody>
</table>

adrenaline + insulin shows that this, in Douglas's case, is practically identical in each instance with the preliminary quotient, and it looks as though the initial rise of quotient is exactly compensated by the subsequent fall. With Courtice the average quotient after the injection is rather lower than the preliminary figure. This might suggest that in these circumstances
there is no evidence from the changes of quotient of an increased oxidation of carbohydrate attributable to insulin, but that the variation of quotient depends solely on a lactic acid effect, and even that adrenaline exercises an inhibitory effect on carbohydrate oxidation which is otherwise promoted by insulin.

The experimental results do not however warrant so definite an attitude. When insulin is injected alone the rise of respiratory quotient is neither considerable nor long lasting. If an effect on the quotient of the same order as that shown in figs. 4–6 were also present in the earlier period of the experiments with adrenaline + insulin, it would be masked by the lactic acid effect on the quotient if this were calculated over so long a period as 2½ hr., since it might cause a change of no more than 0·01 in this average quotient. In spite of the striking similarity in the behaviour of the respiratory quotient after adrenaline alone and after adrenaline + insulin which suggests a common explanation, the possibility that insulin may contribute in minor degree to the rise of quotient cannot be excluded, although there is no indication that the adrenaline has substantially increased the effect of insulin on carbohydrate oxidation.

The hyperglycaemia and excess lactic acid formation seem to be two independent factors in the sense that insulin checks the former without materially affecting the latter. It might be thought that the advantage gained during muscular work by the mobilization of liver glycogen would be offset by the concurrent formation of excess lactic acid, but though lactic acid formation is the invariable accompaniment of such doses of adrenaline as we have used Cori, Cori and Buchwald (1930) have found that if the dose of adrenaline is small enough there may be a slight rise in the blood-sugar concentration without a detectable change in the lactic-acid content of the blood. While therefore the mobilization of liver glycogen by adrenaline may be an important factor during muscular work, we have been unable to find any indication in our experiments during rest that the mere fact of such mobilization causes any significant increase in the ratio of carbohydrate to fat oxidized even when insulin is given at the same time.

Dill, Edwards and de Meio (1935) have found that a subcutaneous injection of 0·5–1·0 mg. of adrenaline during muscular work increases the respiratory quotient and the concentration of glucose and lactic acid in the blood. They conclude that the rise of quotient is mainly due to an increase in the proportion of carbohydrate oxidized, but in view of our own work we feel that a far more detailed analysis of the whole of the circumstances is required before such a conclusion can carry conviction.
Carbohydrate metabolism and muscular exercise

SUMMARY

1. Detailed observations have been made on two human subjects.
2. During rest after prolonged muscular work of moderate severity, when there was a persistent low respiratory quotient and ketonuria, there was a reduction of glucose tolerance which seems to be the same as that found without preceding exercise simply as a result of living on a low-carbohydrate, high-fat diet. This supports the conclusion that the main cause of the persistent low quotient after prolonged work is the low ratio of carbohydrate to fat oxidized.
3. The reduced glucose tolerance resulting from a low-carbohydrate, high-fat diet, as well as that shown after prolonged muscular work, was not accompanied by any significant difference in the response to insulin injected intravenously.
4. In the resting subject the temporary fall of blood-sugar concentration caused by intravenous injection of insulin was accompanied by a rise of the respiratory quotient which appeared to signify an increase of carbohydrate metabolism. There was no accumulation of excess lactic acid in the blood, and the effects on the oxygen consumption were slight and inconstant.
5. Subcutaneous injection of adrenaline caused an increase in the oxygen consumption. The respiratory quotient showed a characteristic change which could be explained by the accumulation and disappearance of excess lactic acid which accompanies the hyperglycaemia, without postulating any alteration in the oxidation of carbohydrate.
6. After the simultaneous injection of insulin and adrenaline the changes in blood-sugar concentration were diminished, but the changes of lactic acid concentration in the blood and of the respiratory quotient were practically identical with those after adrenaline alone.
7. The bearing of these experiments on the question of the possible significance of insulin and adrenaline secretion during muscular work is discussed.

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The directional sensitivity of the retina and the spectral sensitivities of the rods and cones

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1. Introduction

It is now well established that light rays of the same spectral character and physical intensity entering the eye through different points of the pupil may produce visual impressions which differ in brightness and colour even though the patch of retina stimulated (the fovea) is kept the same.* Rays entering the eye through different points of the pupil and terminating on the same point of the retina are incident on the retina in different directions. Also, they have traversed different paths in the refractive media of the eye and may have suffered different losses by absorption, scattering or reflexion. It has been shown, however, that differences in the light losses in the refractive media do not account for the observed variations in visual response, which must therefore be attributed to variations in the reaction of the retina to light incident on it in different directions or, briefly, to a

* See Stiles and Crawford (1933), Dziobek (1934), Wright and Nelson (1934), Goodeve (1936), Stiles (1937) and Crawford (1937).