

## The Effects of Prolonged Muscular Exercise on the Metabolism

By F. C. COURTICE and C. G. DOUGLAS, F.R.S.

(Received October 10, 1935)

### INTRODUCTION

During recent years a great deal of attention has been devoted to the changes in metabolism which result from very hard muscular work, in the main with the idea of correlating the alterations in the respiratory exchange and in the composition of the blood with the chemical changes responsible for the energy of muscular contraction in the isolated muscle under both aerobic and anaerobic conditions. This work, valuable though its results have been, has tended to divert attention away from another aspect of muscular work which is none the less of great practical importance. In everyday life the muscular work which we are called upon to perform is done at a far lower rate than that which is done by the athlete who is pushing himself almost to the limit of his power. It by no means follows that the facts observed during severe exercise, and the deductions made from these, can be applied without alteration when we wish to explain the effects of exercise of far less severity.

It is true that there have been in the past many studies of the physiology of moderate muscular work, but when these are examined in detail they prove to be rather incomplete. As a rule those who have undertaken these investigations have devoted themselves to some limited aspect of the problem, such as the efficiency with which the work is performed under a variety of conditions, the influence of alterations of the diet on the capacity of an individual to do muscular work, or the vexed question of the relative importance of carbohydrate and fat as sources of energy during the performance of the work, and whilst much stress has been laid on events during the actual work too little attention has been given to changes which may result from the work and become apparent during a subsequent period of rest. It therefore seemed to us desirable to study in more detail the effects of prolonged though moderate muscular work, in the hope in particular of throwing further light on the significance of changes of the respiratory quotient, the interpretation of which is admittedly always a very difficult and troublesome problem, as may be gathered from the observations of Cathcart and Markowitz (1927) and

the recent review of Rapport (1930), although it is one that must be faced if we are to gain an insight into the metabolic changes involved.

On consideration we felt that the most profitable course to pursue would be to choose a form of muscular exertion that we could maintain without difficulty for a considerable length of time in the hopes that the total energy expenditure involved would entail a material reduction of what one may call, in general terms, the readily available stores of carbohydrate. If the investigation were not limited to the actual period of the work, but were extended to cover a period of an hour or two of subsequent rest, we anticipated that a review of the whole course of events would assist us in our interpretation of the results. If the observations are restricted to the period of work a difficulty is at once encountered, since, to permit of the observations, the work may have to be done on some form of stationary ergometer, a thing to which the subject may be unaccustomed. Our desire was, however, to study the behaviour of a normal average individual when doing a type of work natural to him. For this reason we decided to abandon the ergometer and substitute walking as the exercise.

Strenuous muscular exercise leads, as is well known, to the appearance of excessive amounts of lactic acid in the blood owing to the fact that the muscular work is in part anaerobic, and as the lactic acid accumulates in the blood during the exercise and is eliminated again in a subsequent period of rest there are resultant variations in the respiratory quotient which are liable to confuse the issue when this quotient is to be used as an index of metabolic changes of a different type. Bock and others (1928) have, however, shown that in a really highly trained athlete a surprising amount of muscular work per minute can be accomplished without the appearance of a significant excess of lactic acid in the blood, whilst Owles (1930) has shown that even in the untrained person a certain critical rate of muscular work must be exceeded before excess lactic acid appears in the blood, a result later confirmed by Cook and Hurst (1933).

Owles's observations were particularly relevant to the present investigation since many of them were made on Douglas, and he found that when walking the critical level corresponded to an oxygen consumption of about 1.8 litres per minute, implying a pace of about 4.5 miles per hour. We felt therefore that so long as we did not exceed this pace we should reduce to a minimum, if not abolish entirely, the effects attributable to lactic acid accumulation and disappearance and in this way simplify the problem.

It was clear that if we were to get any substantial changes as a result of the walk we should have to continue the exercise for a considerable

time. At the same time it was expedient to walk as fast as we dared without running the risk of encountering the lactic acid difficulty so that the whole experiment could be finished in a reasonable time, for it must be remembered that an essential part of our investigation was to continue our observations during a period of several hours' rest after the walk was over. We decided therefore to adopt as our standard exercise a walk on the flat of 10 miles (16 kilometres) at a pace of 4·5 miles (7·25 kilometres) per hour, the walk lasting therefore for just under 2½ hours. In some of the experiments we modified the speed and duration of the walk, and in others we repeated the walk after an interval of rest for a further 6 miles at the standard rate. Many of the experiments were made in the post-absorptive state so as to avoid the influence of food absorbed from the alimentary canal, but as time went on we took food, and in particular carbohydrate, at various times preceding the experiment as this seemed likely to give us additional information of value. In the post-absorptive experiments although no food was taken fluid was allowed. Douglas took two large cups of tea, and Courtice a glass of water, about 20 minutes before the experiment began, and both subjects often drank water at the end of the walk. We did this deliberately so as to ensure a reasonably free secretion of urine throughout the experiment since urine analyses were necessary. This ingestion of fluid explains the fluctuations of urine secretion, and especially the early diuresis, which will be noticed when the results are described.

We ourselves served as the subjects of experiment, differing considerably in age and build; Courtice, aged 24 years with a height of 5 feet 7½ inches, weighing 144 pounds, and Douglas, aged 52 years with a height of 5 feet 10½ inches, weighing 175 pounds, these weights including the clothes in which we walked. We must emphasize the fact that we were in no sense in athletic training; this is certainly true of Douglas, though Courtice was undoubtedly in the better physical condition as he did at intervals play games. As a rule we acted alternately as subjects, and as several days elapsed before the same subject repeated the walk again we do not think that our experiments in themselves led to any material muscular training.

#### METHODS

For the purpose of the walks we used two measured tracks on gravel paths. The larger was 1·39 miles (2,237 metres) in circumference, and roughly square in shape. The east and west sides were level, the south side had a very slight gradient down-hill, the north side a correspondingly slight

gradient up-hill. The smaller track, round the laboratory buildings, was 269 yards (246 metres) in circumference and level. In order to maintain a pace of 4·5 miles per hour the larger track has to be covered in 19 min 30 sec, the smaller in 2 min 2 sec. It was a little difficult to keep the pace quite steady on the large track, but deviations from the required figure were on the average trivial. On the small track, however, there was less difficulty as it was easy to check each circuit against the watch.

The course of a full experiment was as follows. On arriving at the laboratory the subject reclined at rest in a deck chair. Half an hour later his resting respiratory exchange was determined by the bag method over a period of about 10 minutes, and as a rule a second duplicate determination was made in the next 10 minutes. He then started on his walk round the large track. On returning to the laboratory he paused just long enough to allow the bag apparatus to be slipped onto his shoulders and at once continued his walk round the small track. During the third and fourth circuits of this track he collected a sample (80–100 litres) of his expired air, taking the time with a stop watch. On completing the fourth circuit he handed over the bag apparatus to his colleague and set off again round the large track. This procedure was repeated until he had completed five circuits of the large track and  $4 \times 5$  circuits of the small track. He then went back into the laboratory and sat down again in the deck chair until the end of the experiment. During this resting period the total respiratory exchange was determined at half-hourly intervals over a period of 8–10 minutes. In some of the experiments a smaller number of samples of expired air was collected during the walk, but the total distance walked was kept the same. Thus if three samples only were collected the small track was only covered 12 times in all and an extra circuit of the large track was added to make up the 10 miles.

The bladder was emptied just before beginning the walk and just after ending it, and further samples of urine were taken at intervals during the ensuing period of rest. Samples of alveolar air and blood were also collected when required before and at various times after the walk.

#### *Analytical Methods*

(1) The total respiratory exchange was determined in the usual way by the bag method. In order to minimize any error caused by absorption of CO<sub>2</sub> by the rubber the bags were always kept partly filled with expired air in the intervals of use, and we satisfied ourselves that under these conditions a sample of expired air did not change materially in

composition when left in the bag for over half an hour. We always took the precaution of measuring the contents of the bag, and taking a sample for analysis, as soon as possible after the bag had been filled by the subject during an experiment.

(2) The alveolar air was taken during rest by the Haldane-Priestley method. In order to reduce the risk of error without multiplying the number of analyses the mercury with which the gas sampling tube had been filled was allowed to run out in three equal fractions; three samples of alveolar air could thus be collected in a single tube. The figures given in the tables represent the mean of alveolar samples obtained at the end of three normal inspirations and of three normal expirations.

(3) Body temperature was taken in the rectum or mouth with ordinary clinical thermometers.

(4) Blood required for the quantitative determination of  $\text{CO}_2$  combining power, lactic acid, and ketone bodies was taken with a syringe from a vein in the arm after free circulation has been encouraged by immersing the hand and forearm in warm water for 2 or 3 minutes. Coagulation and glycolysis were prevented by the addition of 0·2% potassium oxalate and 0·05% neutral sodium fluoride (in later experiments increased to 0·1%). The blood was immediately put into a tube sunk in melting ice in a Thermos flask and kept here until it was required for use.

The  $\text{CO}_2$  combining power of the blood was determined in duplicate at about 41 mm  $\text{CO}_2$  pressure and 37° C by the method detailed by Douglas and Priestley (1924) using the blood gas apparatus designed by Haldane (1920), the latter being immersed in a water bath maintained at 20° C.

Lactic acid in the blood was determined by the method of Friedemann, Cotonio, and Shaffer (1927), phosphoric acid being substituted for sulphuric acid (Friedemann and Kendal, 1929). In other details we followed Owles's procedure. We wish to thank Dr. R. B. Fisher for the loan of the necessary apparatus. Control analysis made on solutions of lithium lactate in which the concentration of lactate was about the same as that found in the blood of the resting subject gave an average recovery of 97%. Duplicate analyses employing two different sets of apparatus were always made, and the titrations usually agreed within 0·02 cc N/200 iodine, and always within 0·05 cc.

The total ketone bodies in the blood and urine were determined by the gravimetric method of Van Slyke (1917). In this method  $\beta$ -hydroxybutyric acid and aceto-acetic acid are oxidized to acetone and the latter is precipitated in combination with mercuric sulphate (Denigès, 1898). We have expressed our results in terms of  $\beta$ -hydroxybutyric acid: we

made no attempt to estimate the ketone bodies individually. Owing to the quantity of blood or urine required it was only possible to do a few of these analyses in duplicate.

Total nitrogen in the urine was estimated in duplicate by the micro-Kjeldahl method. The urine for these analyses was preserved under toluol.

Blood sugar was estimated in samples of capillary blood obtained from the finger by puncture. The method used was that of Hagedorn and Jensen as given by Peters and Van Slyke (1932), and the analyses were done in duplicate.

All analyses were done by Courtice.

#### RESULTS OBTAINED ON THE POST-ABSORPTIVE SUBJECT WHO HAD PREVIOUSLY BEEN TAKING HIS NORMAL DIET

The results of typical experiments on each of the subjects are shown in Tables I and II. In these five determinations of the respiratory exchange were made during the work and six during the subsequent rest period at half-hourly intervals. It will be seen that Douglas walked at slightly above the standard pace. Figs. 1 and 2 show two further experiments in which the respiratory exchange was followed continuously during the first half-hour after stopping the work by using four bags in succession.

TABLE I—DOUGLAS, POST-ABSORPTIVE. EFFECT OF 10-MILE WALK AT 4·6 MILES PER HOUR

	Respiratory exchange cc/min		R.Q.
	CO <sub>2</sub>	O <sub>2</sub>	
Rest before walking .....	179	236	0·76
End of 2 miles' walk .....	1504	1851	0·81
„ 4 „ .....	1375	1742	0·79
„ 6 „ .....	1476	1832	0·81
„ 8 „ .....	1435	1834	0·78
„ 10 „ .....	1490	1889	0·79
Rest $\frac{1}{2}$ hour after walk .....	181	255	0·71
„ 1 „ .....	177	244	0·72
„ $1\frac{1}{2}$ „ .....	175	237	0·74
„ 2 „ .....	177	238	0·74
„ $2\frac{1}{2}$ „ .....	170	238	0·72
„ 3 „ .....	184	246	0·75

TABLE II—COURTICE, POST-ABSORPTIVE. EFFECT OF 10-MILE WALK AT 4·5 MILES PER HOUR

	Respiratory exchange cc/min		R.Q.
	CO <sub>2</sub>	O <sub>2</sub>	
Rest before walking .....	182	218	0·84
End of 2 miles' walk .....	1399	1645	0·85
„ 4 „ .....	1360	1623	0·84
„ 6 „ .....	1454	1703	0·85
„ 8 „ .....	1404	1697	0·83
„ 10 „ .....	1450	1749	0·83
Rest $\frac{1}{2}$ hour after walk .....	183	237	0·77
„ 1 „ .....	178	237	0·75
„ 1½ „ .....	181	236	0·77
„ 2 „ .....	187	236	0·79
„ 2½ „ .....	178	236	0·76
„ 3 „ .....	184	238	0·77

It should be noted that in fig. 2 the pace maintained by Douglas is 4·75 miles per hour. In our earlier experiments Douglas tended to walk faster than the rate which we later adopted as a standard.

The general course of events can be at once appreciated in these tables and figures. Starting with a normal post-absorptive respiratory exchange and quotient at rest the respiratory exchange rises during the work to a level which is maintained fairly steady so long as the work lasts, while the respiratory quotient tends to rise above the original resting level at the commencement of the work, and, as the work continues, either remains fairly steady at this figure or shows a gradual fall. When the work stops the respiratory exchange falls rapidly and after the first half-hour there is very little further change during the remainder of the experiment. The respiratory quotient, however, falls to a figure definitely below the initial resting value and remains low for the whole 3 hours' rest subsequent to the work.

Individual experiments made on different days naturally showed variation in detail though these variations were not large. As these experiments were made in precisely the same way, and the bag samples were collected at the same intervals of time, a fairer picture of the behaviour of the respiratory exchange can be obtained by averaging a number of experiments on each subject. Owing to the fact that, as will be seen later, we had a number of other observations to make in addition to those on the respiratory exchange we were often obliged to curtail

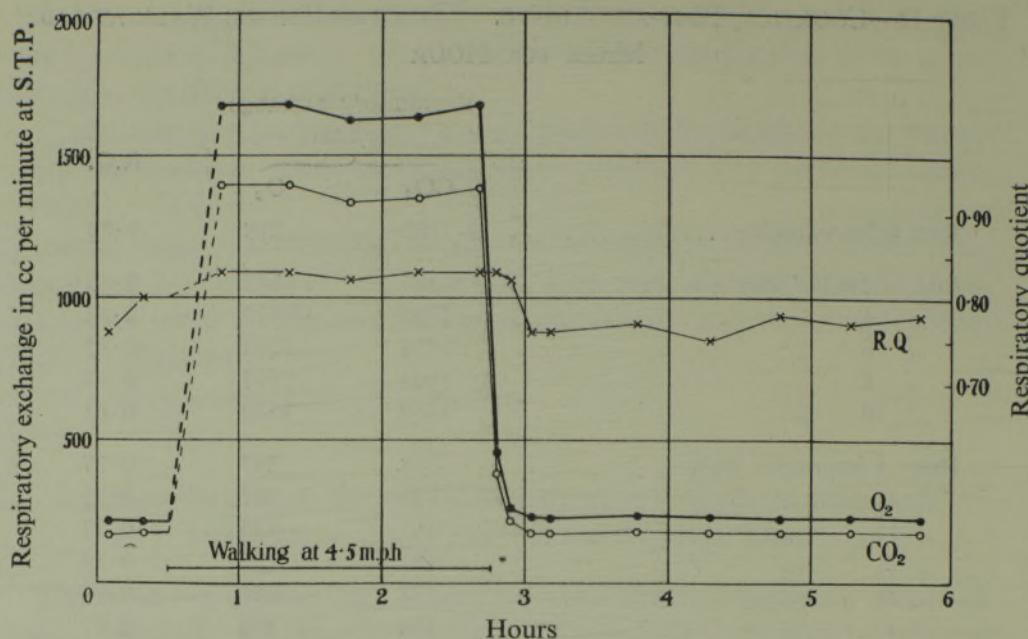


FIG. 1—Courtice, post-absorptive. Effect on respiratory exchange and respiratory quotient of a 10-mile walk at 4.5 miles per hour. × R.Q.; ● O<sub>2</sub>; ○ CO<sub>2</sub>

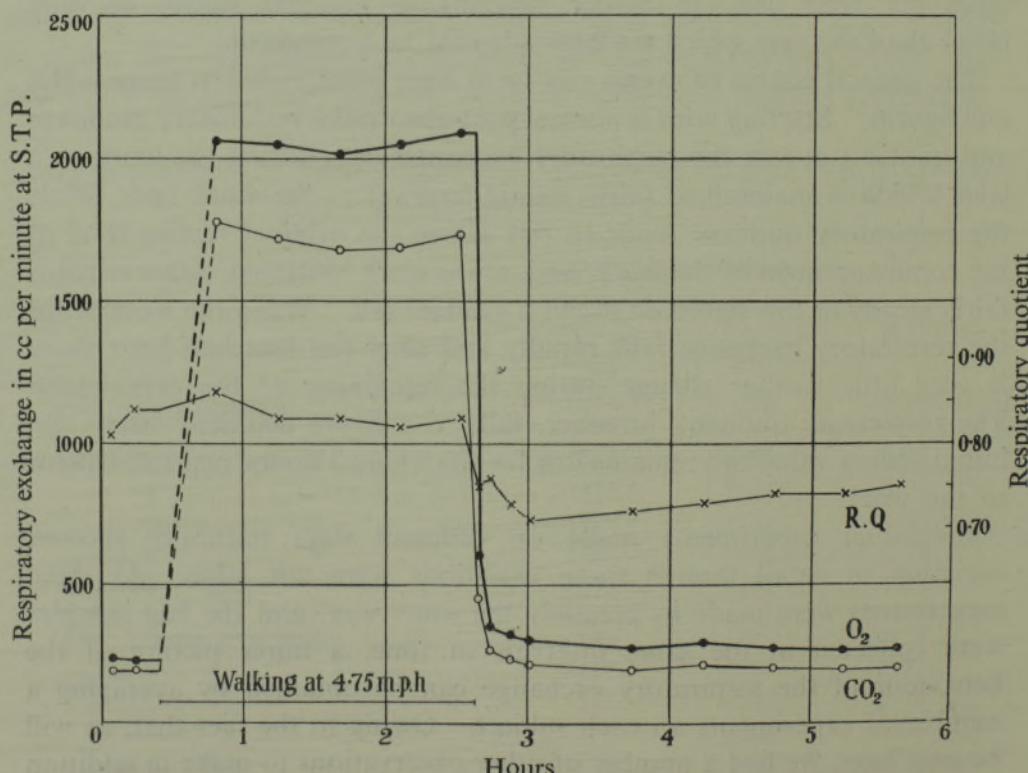


FIG. 2—Douglas, post-absorptive. Effect on respiratory exchange and respiratory quotient of a 10-mile walk at 4.75 miles per hour. × R.Q.; ● O<sub>2</sub>; ○ CO<sub>2</sub>.

the number of bag samples taken either during the work period or during the subsequent rest period. We have therefore only a limited number of experiments in which five determinations of the respiratory exchange were made during the walk and six at intervals of half an hour in the period of rest after the walk. On the other hand there is a far larger number of figures available for determining the average pre-exercise respiratory exchange.

Table III gives the average figures for each subject for the respiratory exchange when resting in the post-absorptive state before beginning the exercise. The values (a) and (b) were obtained during two consecutive

TABLE III—AVERAGE PRE-EXERCISE RESPIRATORY EXCHANGE WHEN SITTING AT REST POST-ABSORPTIVE

	Respiratory exchange		R.Q.	
	CO <sub>2</sub>	O <sub>2</sub>		
<i>Courtice</i>				
Average of 35 experiments from October 24, 1933, to December 10, 1934—				
(a) .....	179	225	0·80	
(b) .....	182	221	0·82	
<i>Douglas</i>				
Average of 17 experiments from October 21, 1933, to November 15, 1934—				
(a) .....	182	232	0·78	
(b) .....	184	229	0·80	

periods of approximately 10 minutes' duration after a preliminary period of half an hour's rest.

It will be seen that Douglas gives slightly higher figures for the respiratory exchange than Courtice, no doubt because of their difference in size, and a slightly lower respiratory quotient. The second of the two determinations gives a slightly higher quotient than the first in each case. Why this should be so we cannot explain, but we satisfied ourselves that further prolongation of the rest does not lead to any sensible alteration in either the respiratory exchange or respiratory quotient. This is shown in Table IV which gives the figures obtained for each subject when the respiratory exchange was determined during rest at half-hourly intervals for a period of 3 hours.

We have seven experiments on Courtice and four on Douglas in which five determinations of the respiratory exchange were made during the

TABLE IV—RESPIRATORY EXCHANGE WITH SUBJECTS AT REST, POST-ABSORPTIVE, WITHOUT EXERCISE. REST STARTED AT 9.00 A.M.

Time	Courtice			Douglas		
	Respiratory exchange		R.Q.	Respiratory exchange		R.Q.
	cc/min			cc/min		
	CO <sub>2</sub>	O <sub>2</sub>		CO <sub>2</sub>	O <sub>2</sub>	
9.30 a.m. ....	191	227	0·84	183	230	0·80
10.00 ,. ....	195	231	0·84	180	231	0·78
10.30 ,. ....	194	230	0·85	177	224	0·79
11.00 ,. ....	184	225	0·82	169	221	0·77
11.30 ,. ....	191	225	0·85	174	222	0·78
12 noon .....	185	224	0·83	181	232	0·78

walk. In the experiments on Courtice the pace was in each instance 4·5 miles per hour. With Douglas two experiments were made at this pace and two at the pace of 4·75 miles per hour.

Table V gives the average figures for each subject in these experiments.

TABLE V—AVERAGE RESPIRATORY EXCHANGE DURING EXERCISE.  
SUBJECTS POST-ABSORPTIVE

Time	Courtice			Douglas		
	Respiratory exchange		R.Q.	Respiratory exchange		R.Q.
	cc/min			cc/min		
	CO <sub>2</sub>	O <sub>2</sub>		CO <sub>2</sub>	O <sub>2</sub>	
Rest before walk	181	225	0·80	189	237	0·80
End of 2 miles..	1359	1638	0·83	1547	1841	0·84
,, 4 ,. ..	1331	1622	0·82	1507	1840	0·82
,, 6 ,. ..	1328	1631	0·81	1525	1863	0·82
,, 8 ,. ..	1310	1632	0·80	1528	1881	0·81
,, 10 ,. ..	1325	1658	0·80	1534	1901	0·81
Rest after walk	181	239	0·76	185	249	0·74

The initial figures for rest agree very closely with the general average figures already given in Table III. The respiratory exchange for Douglas during the walk is higher than for Courtice on account of the slightly faster rate at which he walked and of his greater weight, and the oxygen consumption shows a tendency to rise in the latter half of the walk. The same tendency was shown in other experiments in which fewer determinations were made during the course of the walk. It is difficult to say that Courtice shows a similar phenomenon in the figures given in Table V, but in some individual experiments he, too, had an oxygen

consumption which was somewhat greater at the end of the walk than it had been in the earlier stages. This change, when it occurs, may possibly be due to fatigue.

The respiratory quotient shows a perfectly definite variation. After walking 2 miles the quotient, which at rest previously was 0·80, is 0·83, and 0·84 respectively in the two subjects. It subsequently falls slowly until, at the end of the tenth mile, it has reached the values of 0·80 and 0·81.

For the experiments shown in Table V we have not got a complete series of observations taken at half-hourly intervals during the period of rest after the work, since in some instances only three such observations were made. We give, however, for the sake of comparison, an average figure for such observations as we did make during this 3-hour period, and this will serve to show that the after-effects of the work were of similar character to those that will now be given in greater detail.

In Table VI we give the average figures which were obtained during a period of 3 hours' rest subsequent to a walk of 10 miles at a pace of 4·5 miles per hour in five experiments on Courtice and four on Douglas. In each of these experiments the respiratory exchange was determined at half-hourly intervals beginning half an hour after the work stopped.

TABLE VI—INFLUENCE OF 10-MILE WALK AT 4·5 MILES PER HOUR ON THE RESTING RESPIRATORY EXCHANGE. AVERAGE RESULTS. SUBJECTS POST-ABSORPTIVE

Time	Courtice			Douglas		
	Respiratory exchange cc/min		R.Q.	Respiratory exchange cc/min		R.Q.
	CO <sub>2</sub>	O <sub>2</sub>		CO <sub>2</sub>	O <sub>2</sub>	
Rest before walk....	178	218	0·82	182	232	0·78
½ hour after walk ..	179	232	0·77	178	257	0·69
1    "    "    ..	181	232	0·78	177	244	0·73
1½    "    "    ..	177	229	0·77	173	239	0·73
2    "    "    ..	181	232	0·78	175	243	0·72
2½    "    "    ..	179	231	0·77	173	239	0·73
3    "    "    ..	181	234	0·77	180	241	0·75

In this table the most striking thing is the reduction of the respiratory quotient below the initial resting figure. In the case of Courtice the quotient remains quite steady at a figure 0·05 lower than that shown in the period of rest before the work began. Douglas shows an abnormally low figure for the quotient determined at the end of the first half-hour after the work stopped, but during the next 2½ hours gives figures which

do not show any definite trend but have an average value about 0·05 lower than the initial resting quotient. Apart from the transitory very low quotient shown by Douglas at the end of the first half-hour the change of quotient shown by the two subjects seems to be very similar in type if we take into account the fact that Courtice had a higher quotient than Douglas when resting before the exercise. Courtice's CO<sub>2</sub> production during rest after the work is the same as before the work, and the low quotient corresponds with an increase in the oxygen consumption. Douglas's CO<sub>2</sub> production is somewhat lower, and the oxygen consumption somewhat higher, in the final rest period than they were during the preliminary rest.

It would appear therefore that if we exclude the determination at the end of the first half-hour on Douglas the post-exercise respiratory quotient falls to a level much below that shown before the exercise began, and that this level remains practically unchanged for as long as 3 hours. Courtice's quotient during the post-exercise period invariably remained steady at a low figure, but Douglas's quotient occasionally showed a tendency to creep upwards in the last 2½ hours. An instance of this will be seen in fig. 2, but even in this case the final respiratory quotient is only 0·75 as compared with the pre-exercise figure of about 0·825.

In a number of experiments we made fewer determinations of the respiratory exchange than those on which Table VI is based. An average of the whole of our available data is given in Table VII, excluding determinations made on Douglas at the end of the first half-hour after stopping work. This will serve to give a general idea of the persistent change in the resting respiratory quotient which results from the exercise.

TABLE VII—AVERAGE RESPIRATORY EXCHANGE AT REST, BEFORE, AND AFTER A 10-MILE WALK AT 4·5 MILES PER HOUR. SUBJECTS POST-ABSORPTIVE

	Respiratory exchange cc/min		R.Q.
	CO <sub>2</sub>	O <sub>2</sub>	
Courtice: 23 experiments—			
Before exercise .....	181	223	0·81
After exercise .....	181	237	0·76
Douglas: 15 experiments—			
Before exercise .....	182	229	0·79
After exercise .....	176	240	0·73

In any argument regarding the proportions of carbohydrate and fat being oxidized which is based on the respiratory quotient the influence of

the simultaneous metabolism of protein on this quotient must be taken into account. Strictly speaking, the nitrogen output in the urine can only be taken as an index of protein metabolism if the urine is collected over a long period, e.g., 24 hours. At the same time we know that the protein metabolism of the body is almost uninfluenced by muscular work. We did, however, make some determinations of the total nitrogen excretion in the urine during the course of our experiments in order to get some idea of the order of magnitude of the protein metabolism. Table VIII gives the average results of two experiments on each subject.

TABLE VIII—NITROGEN EXCRETION IN THE URINE. SUBJECTS POST-ABSORPTIVE. WALK OF 10 MILES AT 4·5 MILES PER HOUR

	Courtice		Douglas	
	Urine cc/hour	Nitrogen mg/hour	Urine cc/hour	Nitrogen mg/hour
Rest before walk .....	78	620	167	723
During walk .....	70	499	83	442
Rest 1st hour after walk .....	44	481	39	451
„ 2nd „ .....	35	434	48	569
„ 3rd „ .....	42	465	30	433

The rate of production of urine is obviously high in the earlier part of the experiments, diuresis being particularly marked during the preliminary rest of Douglas. This is due to the fluid deliberately drunk beforehand. The rate of production of urine is considerably reduced after the walk, but it never falls to a very low figure. As we nearly always drank water at the end of the walk this must have compensated in some measure for the loss of water in the sweat during the exercise. The nitrogen output per hour is at its highest during the preliminary rest period: no doubt this is dependent on the diuresis. During the rest of the experiment there is no great variation in the hourly rate of nitrogen output.

The preliminary period during which the urine was collected lasted for 2 hours, the walk for  $2\frac{1}{4}$  hours, and the subsequent rest for 3 hours. Taking this into account the average rate of nitrogen output for the whole experiment is 520 mg per hour for Courtice and 540 mg for Douglas, corresponding to a protein metabolism of about 3.3 gm per hour. Assuming in accordance with Loewi's calculation as given by Lusk (1928) that the oxidation of 1 gm of protein in the body is accompanied by the production of 774 cc CO<sub>2</sub> and the consumption of 966 cc O<sub>2</sub>, the oxidation of 3.3 gm of protein per hour would imply an output of 43 cc CO<sub>2</sub> and consumption of 53 cc O<sub>2</sub> per minute. In Table IX we show how the

average respiratory quotients shown in Table VII will be affected if allowance is made for a protein metabolism at the above rate.

TABLE IX—AVERAGE OBSERVED R.Q. AND CALCULATED  
NON-PROTEIN R.Q.

Subject	Rest before exercise		Rest after exercise	
	Observed R.Q.	Non-protein R.Q.	Observed R.Q.	Non-protein R.Q.
Courtice .....	0·81	0·81	0·76	0·75
Douglas .....	0·79	0·79	0·73	0·71

If it is assumed that the lower nitrogen output during and after the walk gives a fairer representation of the actual protein metabolism at the time the alteration in the respiratory quotients will be even less. In either case the non-protein respiratory quotient only differs sensibly from the observed quotient when the quotient is very low.

It will be clear that any discussion of the metabolic changes during the work must involve a consideration of the period of rest after the work is over, since any considerable alteration in comparison with what we observe during the initial resting period must be largely dependent on what has happened during the work. The figures given in Table IV indicate that there is no material alteration in the resting respiratory exchange and quotient over a period of 3 hours so long as the rest is uninterrupted by muscular exercise.

It has been shown in Table V that the respiratory quotient rises from 0·80 to 0·83 or 0·84 when the work is begun and then falls steadily though slowly to 0·80 or 0·81. Such a change of the respiratory quotient looks at first sight trifling. If we assume, however, that the observed quotient during the work is solely determined by the relative proportions of carbohydrate and fat being oxidized at the time, the part played by protein metabolism being negligible during the work, these proportions can be calculated by means of Zuntz's table (as given by Douglas and Priestley, 1924). Thus in Courtice's case 0·814 gm of carbohydrate and 0·494 gm of fat appear to be oxidized per minute at the end of the first 2 miles' walk, and 0·597 gm of carbohydrate and 0·574 gm of fat at the end of 10 miles. Corresponding figures for Douglas are 0·981 gm of carbohydrate and 0·517 gm of fat at the end of the first 2 miles, and 0·774 gm of carbohydrate and 0·632 gm of fat at the end of 10 miles. Although the change in the quotient may be small, it does imply, by this method of reckoning, that the proportions of carbohydrate to fat metabolized are very substantially altered as the work continues, and that of the

energy liberated during the work the proportion due to the oxidation of carbohydrate to that due to the oxidation of fat is in the ratio of 1:1·2 in the early period of the work, whereas this ratio is 1:2·0 approximately in the final stages of the work.

Taking average values for the whole period of work shown in Table V the total metabolism would be represented by the figures given in Table X. For Douglas it must be remembered that some of the figures on which this table is based are taken from experiments in which he walked at 4·75 miles per hour. Taking only experiments done at a pace of 4·5 miles per hour we found an average consumption by him of 98 gm carbohydrate, 74 gm fat, and 7 gm protein during the work, giving a total energy output of 1121 calories.

TABLE X—AVERAGE TOTAL METABOLISM DURING A 10-MILE WALK AT  
4½ MILES PER HOUR. SUBJECTS POST-ABSORPTIVE

Substance metabolized	Courtice		Douglas	
	Gm	Calories	Gm	Calories
Carbohydrate .....	92	376	109	447
Fat .....	69	644	76	707
Protein .....	7	29	7	29
		1049		1183

Such a calculation of the nature of the substances metabolized is, however, only valid if other factors which are liable to disturb the respiratory quotient can be excluded. Leaving aside for the moment the possible conversion of carbohydrate into fat or fat into carbohydrate, with storage of the product formed, there are a number of other factors which may affect the respiratory quotient, and the presence or absence of such factors can be best gauged not merely by confining our attention to the period of work but by taking into consideration the phenomena shown during subsequent rest. Under this heading we have to take into account the possibility of temporary over- or under-breathing whilst collecting the bag sample, and the influence of change of body temperature, persistent alterations in the alveolar  $\text{CO}_2$  pressure or  $\text{CO}_2$  combining power of the blood, possible accumulation of lactic acid in the blood, and failure to complete the terminal stages of fat metabolism with the consequent accumulation of ketone bodies.

*Over- and under-breathing*—We do not believe that this factor was operative in our experiments. We were both well used to breathing through valves, and we always breathed through them for 5 minutes

before starting to collect a bag sample of expired air so as to give time for any initial disturbance of the breathing to pass off.

*Body temperature*—During the walk the rectal temperature had risen 2° F, or rather more, by the time that the first circuit of the large track had been completed. A further rise of about 1° took place during the second circuit, and thereafter the rectal temperature remained steady. Typical observations on the behaviour of the rectal temperature after stopping the exercise are given in Table XI. It will be seen that Douglas's temperature just after stopping the work is nearly 1° above Courtice's. After half an hour's rest Courtice's temperature has fallen to a level which then remains steady for the rest of the experiment. Douglas's temperature on the other hand takes at least an hour to reach a steady level, and that level is well below that attained by Courtice.

TABLE XI—EFFECT OF A 10-MILE WALK AT 4·5 MILES PER HOUR ON THE RECTAL TEMPERATURE

	Rectal temp. ° F	Rectal temp. ° F	
<i>Courtice</i>			
Before walk .....	98·4	Before walk .....	—
After stopping walk—		After stopping walk—	
2 min. ....	101·0	4 min. ....	101·1
7 „ .....	100·2	36 „ .....	98·2
12 „ .....	99·4	90 „ .....	98·3
17 „ .....	99·2	130 „ .....	98·2
22 „ .....	99·0	170 „ .....	98·3
27 „ .....	98·9	210 „ .....	98·4
32 „ .....	98·6		
37 „ .....	98·5		
42 „ .....	98·5		
47 „ .....	98·5		
52 „ .....	98·5		
57 „ .....	98·6		
<i>Douglas</i>			
Before walk .....	98·6	Before walk .....	98·4
After stopping walk—		After stopping walk—	
7 min. ....	101·8	5 min. ....	101·7
51 „ .....	98·4	54 „ .....	98·1
77 „ .....	97·9	85 „ .....	97·7
113 „ .....	97·7	114 „ .....	97·6
138 „ .....	97·5	145 „ .....	97·6
177 „ .....	97·6	174 „ .....	97·6
202 „ .....	97·6	200 „ .....	97·7

Rise of body temperature increases the activity of the respiratory centre, and will therefore tend to cause over-ventilation and an increase of respiratory quotient whilst it is taking place; when the body temperature is falling again a retention of  $\text{CO}_2$ , with consequent lowering of the respiratory quotient, must occur. But the temperature which affects the respiratory centre cannot be in our experiments the same as the rectal temperature; it must be a good deal lower since in the heart warm blood coming back from the active muscles will get mixed with cool blood returning from the skin. We have no means of measuring the effective temperature of the blood reaching the brain, but we did take

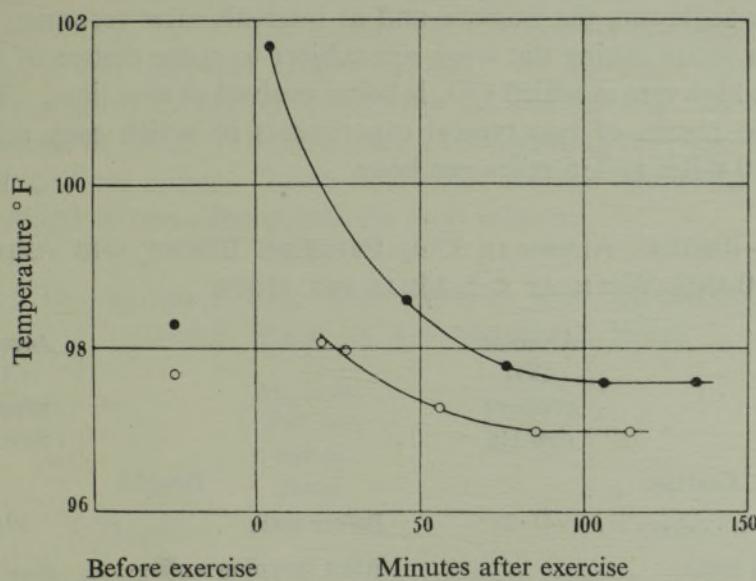


FIG. 3—Effect on rectal and mouth temperatures of a 10-mile walk at 4·5 miles per hour. ● rectal temperature; ○ mouth temperature.

some readings of the mouth temperature as a possible index of this. Owing to the excessive cooling of the mouth by the hyperpnoea during the muscular exercise, and for some time afterwards, we felt that it was no use making the first measurement of mouth temperature until we had been at rest for 20 minutes after stopping the work. A comparison of the rectal and mouth temperatures in the case of Douglas is shown in fig. 3. It looks from this as though the effective temperature of the blood reaching the brain varied in the same sense as the rectal temperature though, of course, to nothing like the same degree.

Any influence which alteration of the body temperature may have on the respiratory quotient is really limited to the period when the temperature

is changing. When once the temperature has become stable the respiration will reach an equilibrium in correspondence and the respiratory quotient will cease to be affected by the temperature. One would expect therefore that in our experiments if change of body temperature has any influence on the respiratory quotient such an effect will be limited to about the first half-hour of exercise when the body temperature is actually rising, and to about the first half-hour after the exercise stops in Courtice, and the first hour in Douglas, when the body temperature is falling. The tendency in the first instance will be to raise the respiratory quotient, in the second instance to lower it.

*Alveolar CO<sub>2</sub> pressure*—We have limited ourselves to observations made before beginning the exercise and at intervals after resuming rest. Observations made during the work are subject to some degree of error owing to the high rate at which CO<sub>2</sub> is being evolved at that time. Table XII gives the results of two typical experiments in which each subject walked for 10 miles at 4·5 miles per hour.

TABLE XII—RESTING ALVEOLAR CO<sub>2</sub> PRESSURE BEFORE AND AFTER A 10-MILE WALK AT 4·5 MILES PER HOUR

	Alveolar CO <sub>2</sub> pressure mm Hg		Alveolar CO <sub>2</sub> pressure mm Hg
<i>Courtice</i>		<i>Douglas</i>	
Before walk .....	41·2	Before walk .....	39·4
After stopping walk—		After stopping walk—	
5 min. ....	41·7	5 min. ....	38·7
15 „ .....	41·4	15 „ .....	38·5
25 „ .....	41·1	25 „ .....	38·5
51 „ .....	40·6	48 „ .....	38·9
106 „ .....	41·6	98 „ .....	38·7
156 „ .....	41·4	143 „ .....	38·6

From these figures it will be seen that the alveolar CO<sub>2</sub> pressure after the exercise remains steady at a level which is practically identical with that shown before the exercise began. With Douglas, if there is a reduction in the alveolar CO<sub>2</sub> pressure, it is less than 1 mm. This result was confirmed in a number of other experiments, but in a few experiments Douglas did exhibit a definite, though slight reduction of the alveolar CO<sub>2</sub> pressure as a result of the exercise, and this reduction persisted for several hours. Instances of this will be referred to later.

*CO<sub>2</sub> combining power of the blood*—Although the resting alveolar CO<sub>2</sub> pressure seemed to be either unaffected by the exercise, or at most affected to but a trifling extent, the CO<sub>2</sub> combining power of the blood was found to be definitely, though slightly, lower than the pre-exercise value, in a sample of blood taken a minute or two after stopping the exercise, and it subsequently continued to fall slowly so that the lowest values were found in the third hour of rest after the exercise.

*Lactic acid in the blood*—A reduction in the CO<sub>2</sub> combining power of the blood naturally raises the suspicion that it may be associated with an increase in blood lactic acid. Although Owles's experiments had rendered it extremely improbable that there could be any significant accumulation of lactic acid during the exercise in our experiments we felt that it was desirable to confirm this. As our main interest in this connexion lay in the period of rest after the exercise was over we took the first sample of blood 3 to 5 minutes after resuming rest, and two further samples at later stages. Table XIII gives average figures for lactic acid in the blood in two experiments on each subject.

TABLE XIII—BLOOD LACTIC ACID DURING REST BEFORE AND AFTER A 10-MILE WALK AT 4·5 MILES PER HOUR

	Mg lactic acid per 100 cc blood		Mg lactic acid per 100 cc blood
<i>Courtice</i>		<i>Douglas</i>	
Before walk .....	8·1	Before walk .....	9·6
5 min. after walk .....	10·3	3 min. after walk .....	11·4
120      "      .....	9·4	48      "      .....	7·9
240      "      .....	8·8	118      "      .....	8·9

In blood samples collected from a vein in the arm 5 minutes after stopping the walk the lactic acid was about 2 mg higher per 100 cc of blood than when resting before the walk began. But this very small increase soon disappeared, and in determinations made at intervals from 45 minutes to 4 hours after the exercise was over values identical with the pre-exercise resting figure were shown in each subject. These observations are therefore in agreement with those made by Owles, and show that the type of work which we employed was insufficient to cause more than the most trivial accumulation of excess lactic acid in the blood. This fact is further corroborated by the absence of appreciable effect on the alveolar CO<sub>2</sub> pressure during the early stages of rest after the exercise.

After resuming rest the respiratory exchange falls very rapidly at first, but it takes about half an hour for Courtice, and an hour for Douglas, before it actually becomes steady. We cannot however take this to imply an oxygen debt in the sense in which this term is used by A. V. Hill. The oxidative removal of the trace of excess lactic acid which we found as a result of the exercise can be at most but a minor contributory cause of the excess oxygen consumption after the work is over. In any case the respiratory exchange cannot reach a steady resting level until the effects of the exercise on the heart and respiration have passed off, and there is one important factor which we must certainly not lose sight of in this connexion, viz., the changes of body temperature, since the metabolism of the body at large should continue to diminish until the body temperature falls to a constant figure, and this constant figure is not reached until half an hour to an hour have elapsed after resuming rest. If we suppose that the oxidative removal of traces of excess lactic acid and the falling body temperature result in a retention of CO<sub>2</sub> in the body, and are thus responsible, at least in some degree, for the maintenance of a low respiratory quotient in the early part of the post-exercise rest period, they cannot account for the persistent low respiratory quotient in the second and third hours of that period. Lactic acid accumulation cannot explain the fall in the CO<sub>2</sub> combining power of the blood, for although this fall is evident directly the work stops it steadily becomes greater during the whole 3 hours of rest long after the trace of excess lactic acid has disappeared from the blood.

*Ketone bodies in the blood and urine*—At an early stage of our experiments we found that urine secreted during the rest period after the exercise was over almost invariably gave a strong reaction with Rothera's nitro-prusside test for ketone bodies. With Courtice the reaction was negative in a few tests, and as a general rule it was less pronounced with him than with Douglas. In no instance did we ever get a positive Rothera reaction with urine secreted either during the preliminary rest or during the walk. This suggested to us the desirability of investigating the production of these ketone bodies in greater detail.

The failure to obtain a positive Rothera reaction in the urine secreted during the walk was not dependent on any decreased urinary output. The figures shown in Table XIV show that during the walk there was a free secretion of urine throughout which failed to give a Rothera reaction, although this reaction was positive in urine secreted during subsequent rest. Figures given later will show that during the 10-mile walk there was no increase in the ketone bodies in the blood. When ketonuria did develop after the exercise the Rothera reaction was always well marked

*Effects of Muscular Exercise on Metabolism*

401

TABLE XIV—DOUGLAS, POST-ABSORPTIVE. WALK AT 4·5 MILES PER HOUR

	Urine cc/hour	Rothera reaction
0 to 2·8 miles' walk .....	185	Negative
2·8 to 6·2 miles' walk .....	56	Negative
6·2 to 10·4 miles' walk.....	57	Negative
Rest during 3 hours after walk .....	33	Positive

in the urine secreted during the first half-hour of rest, and though it might become more pronounced in later specimens of urine the ketosis evidently developed very rapidly after the cessation of exercise.

Courtice, as has been said, occasionally failed to show ketonuria, but if he somewhat restricted the carbohydrate in the diet taken on the day before, eating mainly fatty meat, eggs, etc., and diminishing the amount of bread taken, he always showed marked ketonuria after the exercise. Table XV shows the results of two experiments made on him: in A he had had his normal diet on the previous day whilst in B the carbohydrate

TABLE XV—COURTICE, POST-ABSORPTIVE. WALK OF 9·8 MILES AT 4·5 MILES PER HOUR

*Experiment A*—Normal diet on previous day. Post-exercise R.Q. 0·77. *Experiment B*—Carbohydrate in diet on previous day slightly restricted. Post-exercise R.Q. 0·74.

<i>Experiment A</i>	Ketone bodies in urine mg/hr	<i>Experiment B</i>	Ketone bodies in urine mg/hr
Rest before walk .....	2·9	Rest before walk .....	—
During walk .....	2·3	During walk .....	3·8
0 to 2 hours after walk ....	9·7	0 to 1½ hours after walk ..	21·4
2 to 3       ,,       ....	8·7	1½ to 3       ,,       ..	35·3
3 to 4       ,,       ....	7·9	3 to 4       ,,       ..	41·8

*Note.*—“Ketone bodies” are expressed throughout as  $\beta$ -hydroxybutyric acid.

in the diet had been restricted. Ketonuria occurred in each case after exercise, but to a far greater extent in experiment B. The Rothera reaction was strongly positive in the latter, though it was but faintly shown in experiment A.

Table XVI gives the results obtained on the same subject in which the course of events after the exercise was over was followed for  $9\frac{1}{2}$  hours instead of the usual 3. Several interesting points are shown in this table. The respiratory exchange during the whole of this long period of rest

TABLE XVI—COURTICE, POST-ABSORPTIVE. WALK OF 10 MILES AT 4·5  
MILES PER HOUR

	Respiratory exchange		R.Q.	Alveolar CO <sub>2</sub> pressure mm Hg	Urine cc/hour	Urine ketone bodies mg/hr
	cc/min.	CO <sub>2</sub>				
Preliminary rest	173	215	0·80	41·6		
	171	218	0·79	41·6	40	10
During walk ..	—	—	—	—	37	11
Rest after walk						
for—						
h. min.						
0 12	—	—	—	42·5		
0 35	188	249	0·75	—	29	47
0 52	—	—	—	41·5		
1 20	190	250	0·76	—		
2 5	179	249	0·72	—		
2 20	—	—	—	40·7	24	131
2 50	177	237	0·75	—		
3 35	180	239	0·75	—	24	68
4 20	181	237	0·76	—		
4 34	—	—	—	40·4		
5 5	196	249	0·78	—	55	90
5 50	189	255	0·74	—		
6 35	181	245	0·74	—		
6 49	—	—	—	39·0	58	102
7 20	184	247	0·75	—		
8 5	181	250	0·72	—		
8 50	182	250	0·73	—	48	117
9 4	—	—	—	39·3		
9 35	175	234	0·75	—	29	79

remains very steady. The CO<sub>2</sub> production is on the average 10 cc and the O<sub>2</sub> consumption 28 cc above the initial resting figures, and the respiratory quotient is 0·75 in contrast with the pre-exercise figure of 0·80. Mere prolongation of the resting period beyond the customary 3 hours does not therefore result in the respiratory quotient returning to its original value. In this experiment the alveolar CO<sub>2</sub> pressure shows a slight though progressive decrease during the post-exercise period. Although

*Effects of Muscular Exercise on Metabolism*

403

quantitative analysis showed that the urine secreted during the preliminary rest and during the walk contained ketone bodies equivalent to the excretion of about 10 mg of  $\beta$ -hydroxybutyric acid per hour the Rothera test was negative: possibly this result is to be explained by the nature of the ketone bodies excreted, since acetone and aceto-acetic acid give the Rothera test while  $\beta$ -hydroxybutyric acid does not. During the subsequent rest period when the Rothera test was strongly positive the rate of excretion of ketone bodies, expressed as  $\beta$ -hydroxybutyric acid, is strikingly and persistently increased.

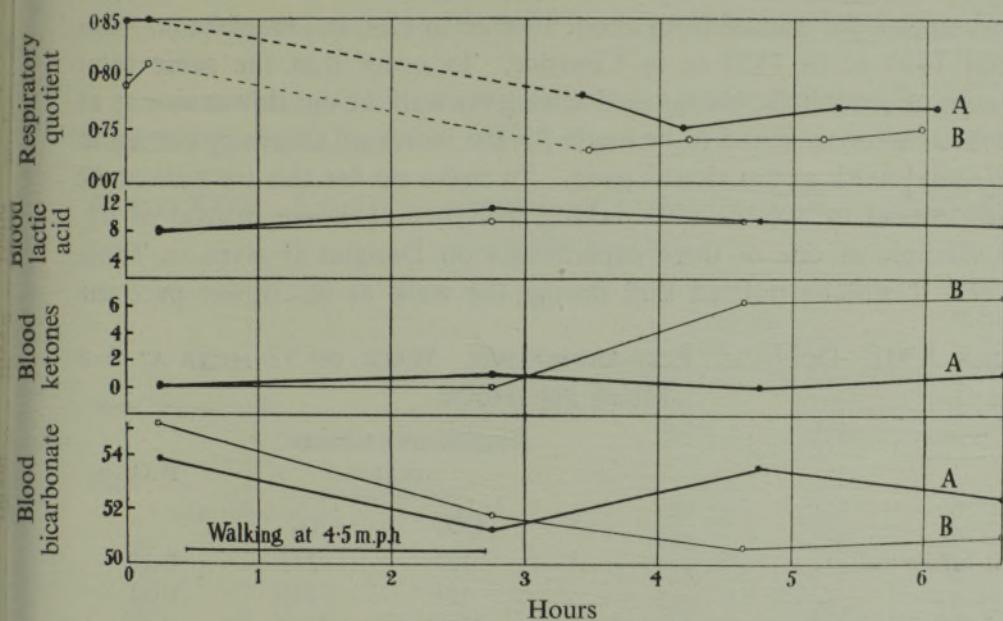


FIG. 4—Courtice. Blood lactic acid in mg %. Blood ketones expressed as mg  $\beta$ -hydroxybutyric acid %. Blood bicarbonate =  $\text{CO}_2$  combining power of blood in volumes %. A, normal diet on previous day; B, carbohydrate in diet on previous day slightly restricted.

Owing to the large variations in the volume and concentration of the urine excreted during an experiment the determination of the ketone bodies excreted in the urine will not give a good indication of the concentration of the ketone bodies in the tissues. We have therefore determined in addition the concentration of ketone bodies in the blood.

In fig. 4 we have plotted additional data obtained in two experiments on Courtice which have already been referred to in Table XV.

In both experiments the change in lactic acid concentration in the blood is insignificant, but in experiment B there is a definite rise of some 6 mg per 100 cc in the ketone bodies of the blood and a fall of about

4 volumes per cent in the CO<sub>2</sub> combining power of the blood in the post-exercise period, whereas in experiment A the change of ketone bodies in the blood is inappreciable and the reduction of CO<sub>2</sub> combining power certainly much less. This suggests that the progressive reduction in the CO<sub>2</sub> combining power of the blood which was so often found in our experiments is connected with the appearance of the ketone bodies.

It might be thought that the readiness with which ketonuria is produced is possibly dependent not so much on the duration of the work as on the rate at which the work is done. In some experiments we reduced the rate of walking from 4·5 to 3·5 miles per hour. This reduced the oxygen consumption per minute from about 1800 cc to 1200 in Douglas and from about 1650 cc to 1150 cc in Courtice. In order that the same total amount of oxygen should be used during the walk at the slower rate as at the faster allowance had to be made for the increased efficiency per kg m horizontal work at the slower pace. To make up for this we walked 12 miles instead of 10, the walk taking therefore 3½ hours instead of 2½. An example of one of these experiments on Douglas is given in Table XVII. It will be noticed that during the walk at the slower pace the

TABLE XVII—DOUGLAS, POST-ABSORPTIVE. WALK OF 12 MILES AT 3·5 MILES PER HOUR

	Respiratory exchange		R.Q.
	CO <sub>2</sub>	O <sub>2</sub>	
Rest before walk .....	197	246	0·80
" .....	191	235	0·81
End of 2 miles' walk .....	1012	1277	0·79
" 4 "	924	1199	0·77
" 6 "	941	1182	0·80
" 8 "	984	1263	0·78
" 10 "	969	1244	0·78
" 12 "	928	1209	0·77
Rest ½ hour after walk .....	164	234	0·70
" 1 "	178	237	0·75
" 1½ "	171	233	0·73
" 2 "	173	231	0·75
" 2½ "	176	232	0·76
" 3 "	178	235	0·76

respiratory quotient does not rise above the initial resting level, and that there is only a slight progressive fall as the exercise continues. This was confirmed in other experiments made in the same way. The respiratory quotient after the work is over behaves in very much the same way as in

*Effects of Muscular Exercise on Metabolism*

405

experiments at the faster pace, save that the level finally reached is perhaps rather higher than in those experiments. The Rothera test was positive in urine secreted after exercise in this and other experiments of the same type. Even after a walk of 10 miles at 3·5 miles per hour the Rothera test was faintly positive, but it was much stronger when the distance was increased to 12 miles, though we thought that the ketonuria was even then rather less pronounced than when we walked at the faster pace. A factor which plays a large part in determining the ketonuria is evidently the absolute amount of work done irrespective of the rate at which it is done, and it looks therefore as though the main result of our experiments was to antedate the ketosis which develops during simple starvation.

The ketonuria resulting from exercise was easily abolished by ingesting sugar as is shown in Table XVIII in an experiment made on Courtice.

TABLE XVIII—COURTICE. EFFECT OF INGESTION OF SUCROSE ON POST-EXERCISE KETOSIS

		Respiratory exchange cc/min		R.Q.
		CO <sub>2</sub>	O <sub>2</sub>	
Rest before walk .....		170	215	0·79
," .....		176	217	0·81
<b>Rest—</b>				
45 min. after walk .....		170	232	0·73
90 " .....		170	228	0·74
150 " .....		184	248	0·74
195 " .....		180	240	0·75
245 " .....		Ingested 100 gm sucrose		
35 min. after sucrose .....		223	268	0·83
80 " .....		248	276	0·90
125 " .....		204	236	0·86
170 " .....		208	250	0·83
<b>Blood</b>				
ketone				
bodies				
mg %				
Before walk .....	0·0	Before walk .....		Urine
4 min. after walk .....	0·0	During walk .....		ketone
116 " .....	6·3	8–103 min. after walk ..		bodies
236 " .....	6·7	103–166 " ..		mg/hr
120 min. after sucrose ....	0·0	166–243 " ..		
		0–2 hours after sucrose ..		
		2–4 " ..		
		.. .. ..		0·0

During 4 hours' rest after a 10-mile walk at the rate of 4·5 miles per hour there was a considerable increase in the ketone bodies in the blood and in the amount of these bodies excreted in the urine. At the end of this time 110 gm of sucrose were ingested with the result that there was a considerable rise in the respiratory quotient and a rapid disappearance of the ketone bodies.

#### THE INFLUENCE OF CARBOHYDRATE FOOD TAKEN BEFORE THE MUSCULAR EXERCISE

It has been pointed out in the preceding section that although Douglas invariably showed a ketosis as a result of the exercise, Courtice in some experiments did not, whilst his respiratory quotient during post-exercise rest was higher than Douglas's. It will also be seen from the average figures given in Table VII that Courtice tends to have a rather higher initial respiratory quotient during rest than Douglas. The diet taken by the two subjects on the days preceding these experiments was their natural one, and it seemed possible that the differences in quotient might depend either on the fact that Courtice naturally selects a diet richer in carbohydrate than Douglas or that he can store carbohydrate in available form more readily.

We therefore tried the effects of increasing considerably the carbohydrate in the diet taken on the day preceding the experiment. Courtice ate principally bread, biscuits, and jam and took a good deal of sucrose in addition: Douglas ate porridge with sugar, bread, jam, and spaghetti. The actual experiments were of course made with the subjects in the post-absorptive state.

The results of two typical experiments are shown in Tables XIX and XX.

The respiratory quotient during preliminary rest, during the walk, and during the subsequent period of rest is higher than in the experiments previously described when the subjects had been taking their normal diet on the previous day. The general picture is much the same save that when the carbohydrate diet had been taken on the previous day the respiratory quotient runs throughout at a higher level. Fig. 5 shows the contrast between the respiratory quotients of the two subjects under different circumstances.

The upper pair of curves shows the changes of the respiratory quotient in Courtice (A) and in Douglas (B) when a normal diet had been taken on the previous day in each case. The curves are drawn from the average figures in all those experiments in which we had a full series of deter-

*Effects of Muscular Exercise on Metabolism*

407

TABLE XIX—COURTICE, POST-ABSORPTIVE. HIGH CARBOHYDRATE DIET ON PRECEDING DAY. WALK OF 10 MILES AT 4·5 MILES PER HOUR

	Respiratory exchange cc/min		R.Q.
	CO <sub>2</sub>	O <sub>2</sub>	
Rest before walk .....	195	210	0·93
,, .....	191	203	0·94
End of 2 miles' walk .....	1309	1468	0·89
,, 4   ,, .....	1365	1507	0·91
,, 6   ,, .....	1355	1509	0·90
,, 8   ,, .....	1325	1497	0·88
,, 10   ,, .....	1296	1485	0·87
Rest $\frac{1}{2}$ hour after walk .....	180	217	0·83
,, $1\frac{1}{4}$ ,, .....	181	217	0·83
,, $1\frac{3}{4}$ ,, .....	180	224	0·80

TABLE XX—DOUGLAS, POST-ABSORPTIVE. HIGH CARBOHYDRATE DIET ON PRECEDING DAY. WALK OF 10 MILES AT 4·5 MILES PER HOUR

	Respiratory exchange cc/min		R.Q.
	CO <sub>2</sub>	O <sub>2</sub>	
Rest before walk .....	185	220	0·84
,, .....	185	213	0·87
End of 4·2 miles' walk .....	1415	1648	0·86
,, 7·9   ,, .....	1446	1694	0·85
Rest $\frac{1}{2}$ hour after walk .....	176	236	0·74
,, 1   ,, .....	172	221	0·78
,, $1\frac{1}{2}$ ,, .....	169	218	0·78
,, 2   ,, .....	172	219	0·78
,, $2\frac{1}{2}$ ,, .....	167	216	0·77
,, 3   ,, .....	164	212	0·77

minations during the work as well as after it. In the middle pair of curves the same curve (A) for Courtice is contrasted with curve C which is based on the average figures shown when he had restricted to some degree the carbohydrate taken on the previous day. It will be seen that this restriction of carbohydrate has the result that his post-exercise respiratory quotient is practically identical with that of Douglas (curve B) who was taking his normal diet. In the lower pair of curves, curve B

for Douglas is contrasted with curve D which gives the result of an experiment in which he had taken a greatly increased amount of carbohydrate on the previous day.

In the three experiments made on Douglas and the three on Courtice in which an increased amount of carbohydrate was taken on the previous day the urine collected at intervals during the post-exercise period failed to give a positive Rothera reaction. Blood samples taken from a vein

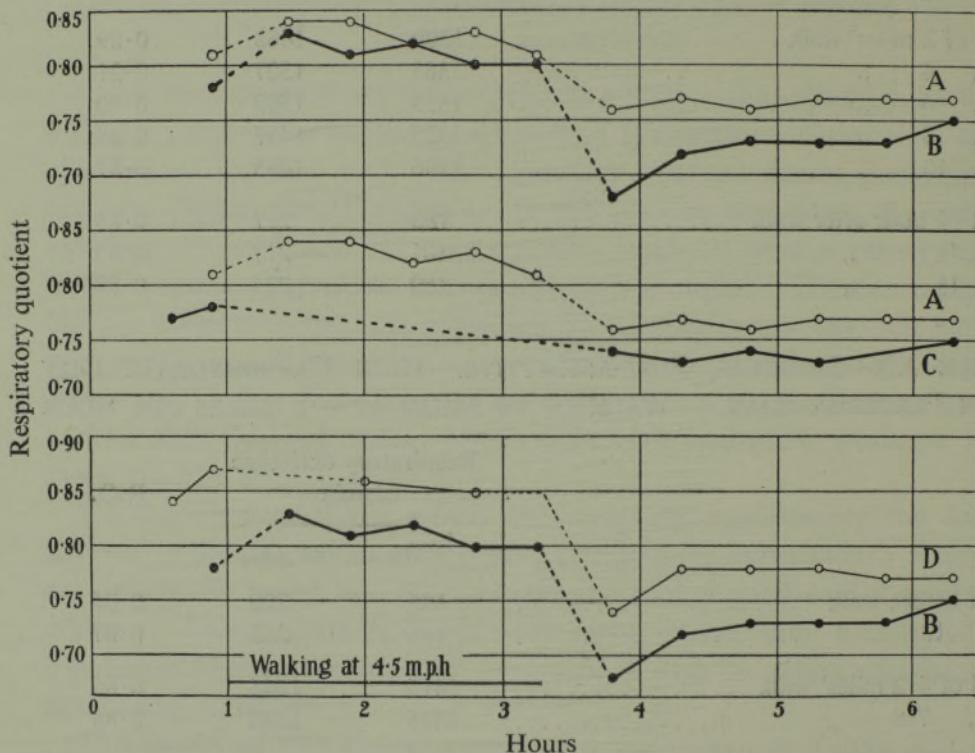


FIG. 5.—Subjects post-absorptive. A, Courtice, normal diet previous day; B, Douglas, normal diet previous day; C, Courtice, carbohydrate somewhat restricted on previous day; D, Douglas, high carbohydrate diet on previous day.

in the arm showed that there was no persistent diminution of the  $\text{CO}_2$  combining power such as has been described in the previous section. This will be clear from the results given in Table XXI which were obtained in two experiments on each subject, in one of which a normal diet had been taken on the day before and in the other a carbohydrate rich diet. On the latter diet the  $\text{CO}_2$  combining power of the blood of each subject, especially of Douglas, shows a slight fall in samples taken just after the exercise, but in further samples taken at the end of the first and second hours' rest the original  $\text{CO}_2$  combining power has been regained, although

TABLE XXI—SUBJECTS POST-ABSORPTIVE. 10-MILE WALK AT 4·5 MILES PER HOUR. EFFECT OF EXERCISE ON THE CO<sub>2</sub> COMBINING POWER OF THE BLOOD. NORMAL DIET TAKEN ON PREVIOUS DAY IN ONE CASE, A HIGH CARBOHYDRATE DIET IN THE OTHER

	Normal diet: ketosis present		High carbohydrate diet: no ketosis	
	CO <sub>2</sub> pressure mm Hg	CO <sub>2</sub> vols. per 100 cc blood	CO <sub>2</sub> pressure mm Hg	CO <sub>2</sub> vols. per 100 cc blood
	<i>Douglas</i>			
Rest before walk .....	41·5	53·4	40·8	53·4
Rest 5 min. after walk .....	41·9	51·4	41·4	51·9
„ 53 „ .....	42·2	50·8	41·5	52·6
„ 130 „ .....	42·1	50·3	41·7	53·3
„ 166 „ .....	41·7	50·5		
<i>Courtice</i>				
Rest before walk .....	41·4	53·2	41·8	53·7
Rest 3 min. after walk .....	41·3	52·5	41·8	52·9
„ 50 „ .....	41·4	52·8	42·1	53·9
„ 120 „ .....	41·3	51·6	42·0	54·0

in the experiments in which a normal diet had been taken beforehand the CO<sub>2</sub> combining power continued, if anything, to drop further. Although the slight fall in the CO<sub>2</sub> combining power just after the exercise may be dependent on the trifling accumulation of excess lactic acid in the blood at this time, it is clear that the further and continued fall must be due to the accumulation of ketone bodies, since it only occurs in those experiments in which there is evidence of ketosis.

Taking our experiments as a whole it can be said that ketonuria was always present when the resting respiratory quotient was 0·76 or lower. With a respiratory quotient of 0·77 ketonuria sometimes occurred, and even with a respiratory quotient of 0·78 we occasionally got a faint positive result with the Rothera test.

Although post-exercise ketonuria on the day of the experiment could apparently be readily prevented by taking plentiful carbohydrate on the day before, the case was different when the subject deliberately took food shortly before the start of the experiment. In these experiments he was, of course, no longer in the post-absorptive condition. Table XXII gives the result of one experiment on each subject in which he had had his

normal breakfast (eggs or cutlets and bacon, toast, jam, and tea) before beginning the experiment. Courtice sat down to rest in the laboratory 40 minutes after breakfast and Douglas 20 minutes, so that the first

TABLE XXII—EFFECT OF A 10-MILE WALK AT 4·5 MILES PER HOUR AFTER A NORMAL BREAKFAST

	Douglas			Courtice		
	Respiratory exchange		R.Q.	Respiratory exchange		R.Q.
	CO <sub>2</sub>	O <sub>2</sub>		CO <sub>2</sub>	O <sub>2</sub>	
Rest before walk ..	237	295	0·80	242	290	0·83
,, ..	242	290	0·84	247	297	0·83
End of—						
2 miles' walk....	1528	1799	0·85	1404	1602	0·88
4    ,,   ....	1495	1818	0·82	1409	1588	0·89
6    ,,   ....	1439	1789	0·80	1404	1612	0·87
8    ,,   ....	1452	1811	0·80	1409	1629	0·86
10   ,,   ....	—	—	—	1386	1633	0·85
Rest—						
½ hour after walk	185	264	0·70	—	—	—
1       ,,	181	256	0·71	200	260	0·77
2       ,,	177	248	0·72	196	254	0·77
2½    ,,	171	242	0·71	—	—	—
3       ,,	170	241	0·71	205	273	0·75
4       ,,	—	—	—	204	272	0·75

respiratory exchange determinations at rest were made roughly 1 hour after breakfast. The respiratory exchange during the initial rest is very much greater than in the post-absorptive experiments, although the respiratory quotient is only slightly above the average for the latter experiments. With Douglas the respiratory quotient during the work is very much the same as that shown in the post-absorptive experiments, but with Courtice it is definitely higher. After the exercise is over Douglas's respiratory quotient falls to the surprisingly low level of 0·71, and it remains steady at this figure until the end of the third hour of rest. This was, in fact, the lowest persistent respiratory quotient which occurred in the whole course of our experiments, and it was accompanied, as would be expected, by an intense Rothera reaction in the urine. On the other hand Courtice's respiratory quotient in the post-exercise period only varies between 0·77 and 0·75, figures similar to those shown in the ordinary post-absorptive experiments. His urine, too, at this time gave a

positive Rothera reaction. Even when Douglas took 60 gm of sucrose with porridge for breakfast ketonuria still developed after the walk though not to a marked degree. During the walk the respiratory quotient was much higher than in the usual post-absorptive experiments. It is however, unnecessary to refer in detail to these experiments since the facts are just as clearly shown when the breakfast is practically limited to sugar.

In this case we took 50 gm of either glucose or fructose (B.D.H. laevulose) and from 20 to 40 gm of bread, which would contain from 10 to 20 gm of starch. The sugar was dissolved as a rule in tea, but sometimes in lemonade, and the bread was eaten in the hopes that it might help to slow down the rate of absorption of sugar from the gut. This carbohydrate meal was taken from 20 to 30 minutes before sitting down for the preliminary rest, and the walk was begun from 80 to 110 minutes after the meal had been taken, by which time the bulk of the sugar should have been absorbed.

Tables XXIII and XXIV give the average results of six experiments on each subject, in three of which glucose had been ingested and in the other three fructose. The individual experiments in any one of these groups of three gave almost identical results.

TABLE XXIII—COURTICE. EFFECT OF WALKING 10 MILES AT 4·5 MILES PER HOUR AFTER INGESTION OF EITHER GLUCOSE OR FRUCTOSE

	After glucose			After fructose		
	Respiratory exchange cc/min		R.Q.	Respiratory exchange cc/min		R.Q.
	CO <sub>2</sub>	O <sub>2</sub>		CO <sub>2</sub>	O <sub>2</sub>	
Rest before walk ..	241	264	0·91	252	259	0·97
,, ..	235	257	0·91	250	262	0·95
End of—						
2 miles' walk ....	1515	1630	0·93	1448	1629	0·89
4    ,, ....	1414	1615	0·88	1410	1628	0·87
6    ,, ....	1372	1620	0·85	1421	1660	0·86
8    ,, ....	1339	1626	0·82	1372	1642	0·84
10   ,, ....	1360	1690	0·80	1379	1700	0·81
Rest—						
½ hour after walk	179	242	0·74	180	235	0·77
1       ,,	187	245	0·76	180	236	0·77
1½   ,,	177	236	0·75	182	238	0·77
2       ,,	181	238	0·76	186	237	0·78
2½   ,,	181	239	0·76	179	232	0·77

The respiratory exchange during the initial rest period is considerably higher than in the post-absorptive experiments, but during the walk and the post-exercise rest period the oxygen consumption is practically the same as in the latter experiments. The respiratory quotient during the initial rest is about 0·91 in the glucose experiments and 0·95 in the fructose

TABLE XXIV—DOUGLAS. EFFECT OF WALKING 10 MILES AT 4·5 MILES PER HOUR AFTER INGESTION OF EITHER GLUCOSE OR FRUCTOSE

	After glucose			After fructose		
	Respiratory exchange cc/min		R.Q.	Respiratory exchange cc/min		R.Q.
	CO <sub>2</sub>	O <sub>2</sub>		CO <sub>2</sub>	O <sub>2</sub>	
Rest before walk . . .	258	291	0·89	268	281	0·95
,,      . . . . .	258	283	0·91	263	279	0·95
End of—						
2 miles' walk . . . . .	1635	1722	0·95	1622	1790	0·91
4    ,,     . . . . .	1540	1744	0·88	1570	1776	0·88
6    ,,     . . . . .	1560	1784	0·87	1520	1759	0·86
8    ,,     . . . . .	1534	1816	0·85	1592	1855	0·86
10   ,,     . . . . .	1522	1837	0·83	1544	1832	0·83
Rest—						
½ hour after walk	179	255	0·70	186	252	0·74
1    ,,	182	244	0·75	182	242	0·74
1½   ,,	182	238	0·76	179	233	0·77
2    ,,	177	233	0·76	180	232	0·78
2½   ,,	178	238	0·75	178	230	0·77

experiments. After walking 2 miles the respiratory quotient has risen to about 0·94 in the glucose experiments but has fallen to about 0·90 in the fructose ones. Thereafter the respiratory quotient falls steadily, the figures being nearly identical for each sugar. At the end of the tenth mile Courtice's quotient is practically the same as in the post-absorptive experiments, while Douglas's is a little higher, *cf.* Table V. In the post-exercise rest period both respiratory exchange and quotient quickly fall to a steady level. Both subjects have practically the same quotient during this period. This is the same as that shown by Courtice in the ordinary post-absorptive experiments, but for Douglas is definitely higher than in the latter, *cf.* Tables VI and VII. The respiratory quotients in these experiments have been plotted in fig. 6. The results are clearly very much the same no matter whether glucose or fructose has been

taken beforehand, but with fructose the respiratory quotient in the post-exercise period tends to be the higher.

In all of these experiments a positive Rothera reaction was given in the urine secreted during the post-exercise rest period, save in one experiment with glucose on Douglas, and in one experiment with fructose on each subject. We got the impression that the Rothera reaction was less marked in the fructose than in the glucose experiments.

The regularity with which ketosis resulted from the muscular work in our normal post-absorptive experiments, and particularly in the experiments in which sugar was ingested shortly before beginning the work,

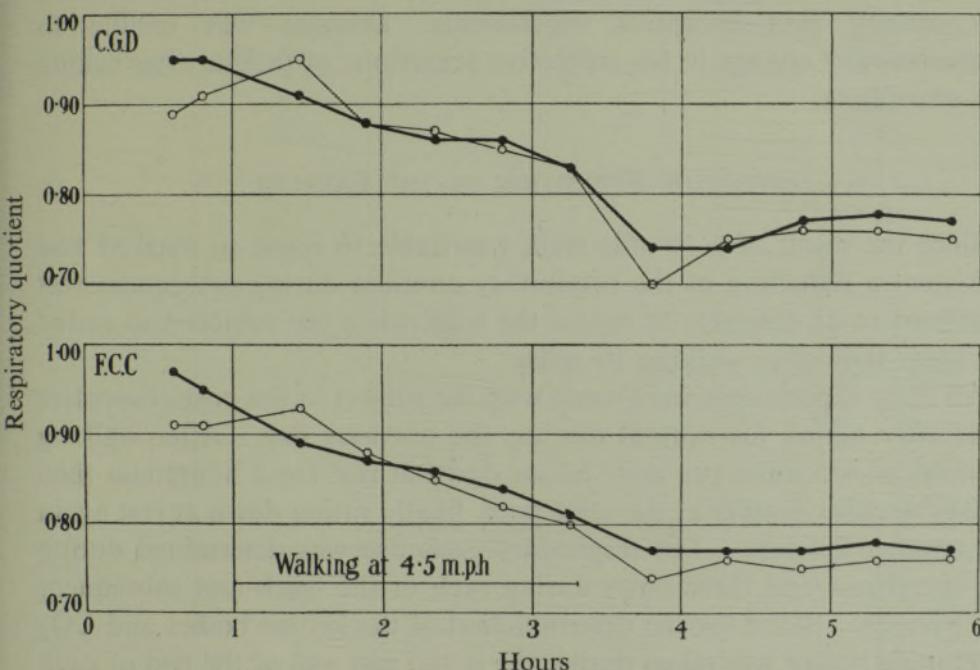


FIG. 6—Effect on the respiratory quotient of a 10-mile walk at 4.5 miles per hour after ingesting either glucose or fructose. ● Fructose; ○ Glucose.

surprised us, for a 10-mile walk cannot be regarded as excessive exercise even if one has had no breakfast before doing it. The ketosis which develops during starvation is well known, as is the fact that comparatively light work may cause some degree of ketosis in subjects who have been taking a diet in which the carbohydrate has been greatly reduced and the fat increased (*cf.* Gemmill, 1934), but our experiments were made under quite different nutritive conditions.

Since phosphate plays so essential a part in the chemical changes associated with muscular contraction and Embden, Grafe, and Schmitz

(1921) have claimed that the muscular efficiency during active exercise may be increased by the ingestion of phosphate, we made two experiments on Douglas in the post-absorptive state when he had had his normal diet on the day before to test the possible influence of phosphate. In the first of these the subject took 2.5 gm of  $\text{NaH}_2\text{PO}_4$  at 11 p.m. on the previous evening and another 2.5 gm 2 hours before beginning the experiment. In the second he took 5 gm at 6.30 p.m. and 5 gm at 11 p.m. on the day before and another 5 gm 2 hours before beginning the experiment. Determinations of the alveolar  $\text{CO}_2$  pressure showed that there was no appreciable acidosis, and we could detect no difference in either the respiratory exchange or the respiratory quotient from what was found in ordinary post-absorptive experiments. Douglas was unable to appreciate any change in his subjective sensations of fatigue after taking the phosphate.

#### EFFECT OF REPETITION OF THE EXERCISE

Since the result of a 10-mile walk was liable to cause so marked and persistent a reduction of the respiratory quotient during subsequent rest it seemed to us desirable to repeat the walk when the subject had rested for some time after walking 10 miles.

All these experiments were made with the subject in the post-absorptive state after taking his normal diet on the previous day. After walking 10 miles at 4.5 miles per hour he sat down at rest for 2 hours and then walked another 6 miles at the same pace, finally sitting down at rest again for another 2 hours. The respiratory exchange was determined during the initial rest and three times during each of the work and subsequent rest periods. Blood for the determination of the ketone bodies and  $\text{CO}_2$  combining power was taken during the initial rest and at the end of each period of work and subsequent rest. The alveolar  $\text{CO}_2$  pressure was determined at intervals during the resting periods, and urine samples were taken for the quantitative estimation of the ketonuria.

Fig. 7 gives the average results obtained on Douglas in three experiments which were in close agreement.

It will be seen that the respiratory exchange and quotient follow quite the usual course during the first walk of 10 miles and the 2-hour period of rest following it. The respiratory quotient during the latter period remains steady at about 0.73 in contrast with the initial pre-exercise figure of 0.80. During the second walk of 6 miles the respiratory exchange mounts to about the same level as in the previous walk and the quotient rises to 0.78, but it does not attain the value of 0.81 shown towards the

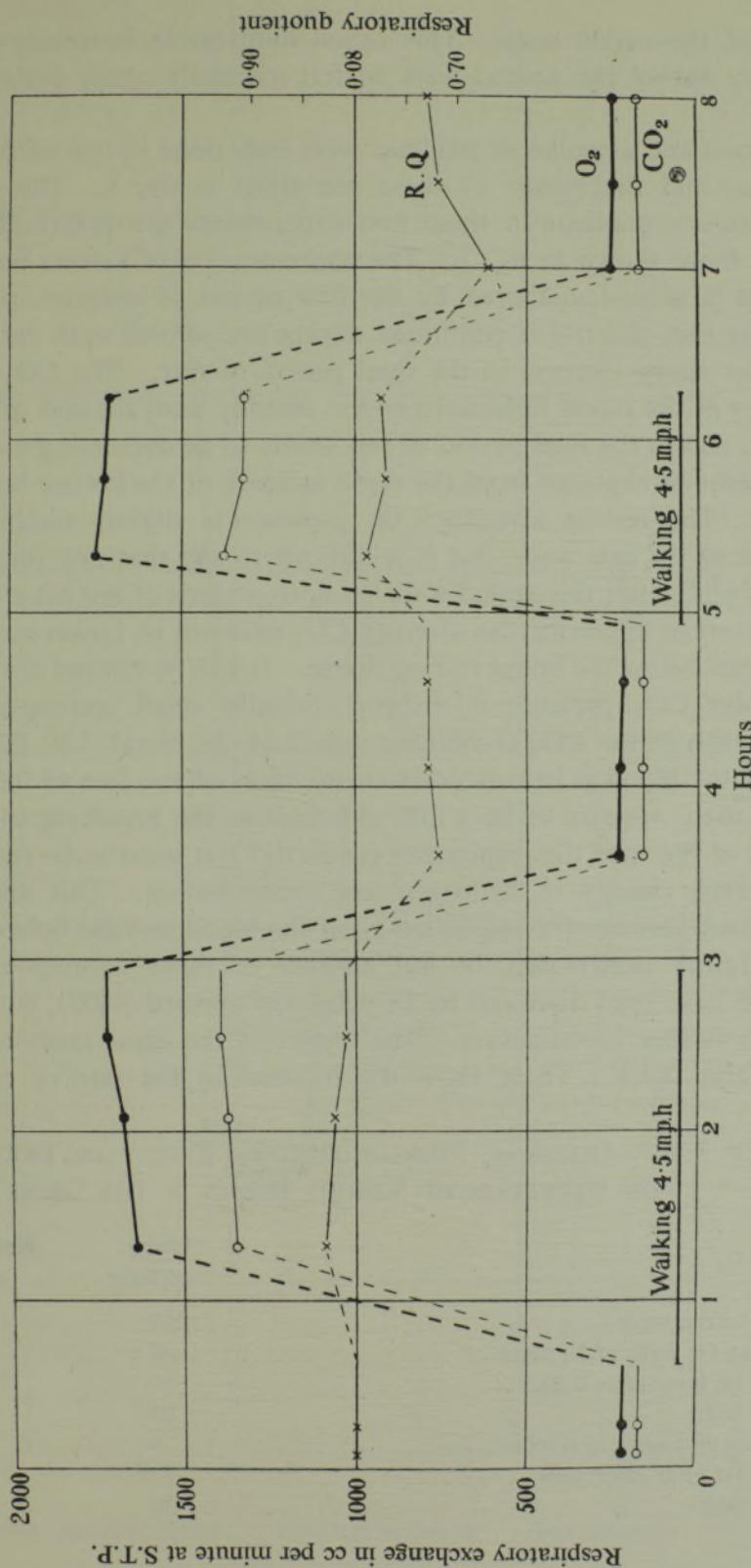


FIG. 7—Douglas, post-absorptive. Effect of walking 10 miles at 4.5 miles per hour followed by a further walk of 6 miles at the same pace after an interval of rest of 2 hours.  $\times$  R.Q.;  $\bullet$   $O_2$ ;  $\circ$   $CO_2$ .

end of the earlier walk. This raised quotient is, however, maintained steady during the second walk to fall markedly again during the final rest.

Blood and alveolar air analyses were only done in two of these experiments, and the results of these are given in fig. 8. The changes of respiratory quotient in these two experiments are practically identical with those shown in fig. 7. The concentration of ketone bodies in the blood is almost unaltered by the first period of exercise, rises slightly during rest, the rise is continued during the second walk and there is a further sharp increase in the final period of rest. The  $\text{CO}_2$  combining power of the blood falls more or less steadily until the end of the second walk, and in the final period of rest seems to be decreasing more rapidly, as might be expected from the rapid increase of the ketone bodies at this time. The resting alveolar  $\text{CO}_2$  pressure is slightly diminished as a result of the first walk, but it is difficult to say that any further change takes place after the second walk: in both periods of rest after the exercise the average figure for the alveolar  $\text{CO}_2$  pressure is, however, only about 1.5 mm below the initial resting figure. It will be noticed that the fall of alveolar  $\text{CO}_2$  pressure is disproportionately small compared with the reduction of the  $\text{CO}_2$  combining power of the blood. If, therefore, the  $p_{\text{H}}$  of the blood is calculated from the ratio of the free to the combined  $\text{CO}_2$  there appears to be a fall, although as the breathing was perfectly quiet at the time the respiratory centre did not seem to be responding to any such change of hydrogen ion concentration. This apparent discrepancy between the calculated  $p_{\text{H}}$  of the blood and the behaviour of the respiratory centre may be but another of those anomalous instances which have been discussed by Douglas and Havard (1932), but the matter needs further investigation. The results of the urine analyses are given in Table XXV. These show the increase in the rate of excretion of

TABLE XXV—DOUGLAS, POST-ABSORPTIVE. EFFECT OF DOUBLE WALK ON EXCRETION OF KETONE BODIES IN THE URINE

	Urine cc/hour	Ketone bodies mg/hour
Rest before walk .....	203	4.3
During 1st walk of 10 miles .....	40	2.7
Rest 1st hour after walk .....	31	9.5
,, 2nd „ .....	85	10.5
During 2nd walk of 6 miles .....	9	2.1
Rest 1st hour after walk .....	22	35.9
,, 2nd „ .....	36	100.3

*Effects of Muscular Exercise on Metabolism*

417

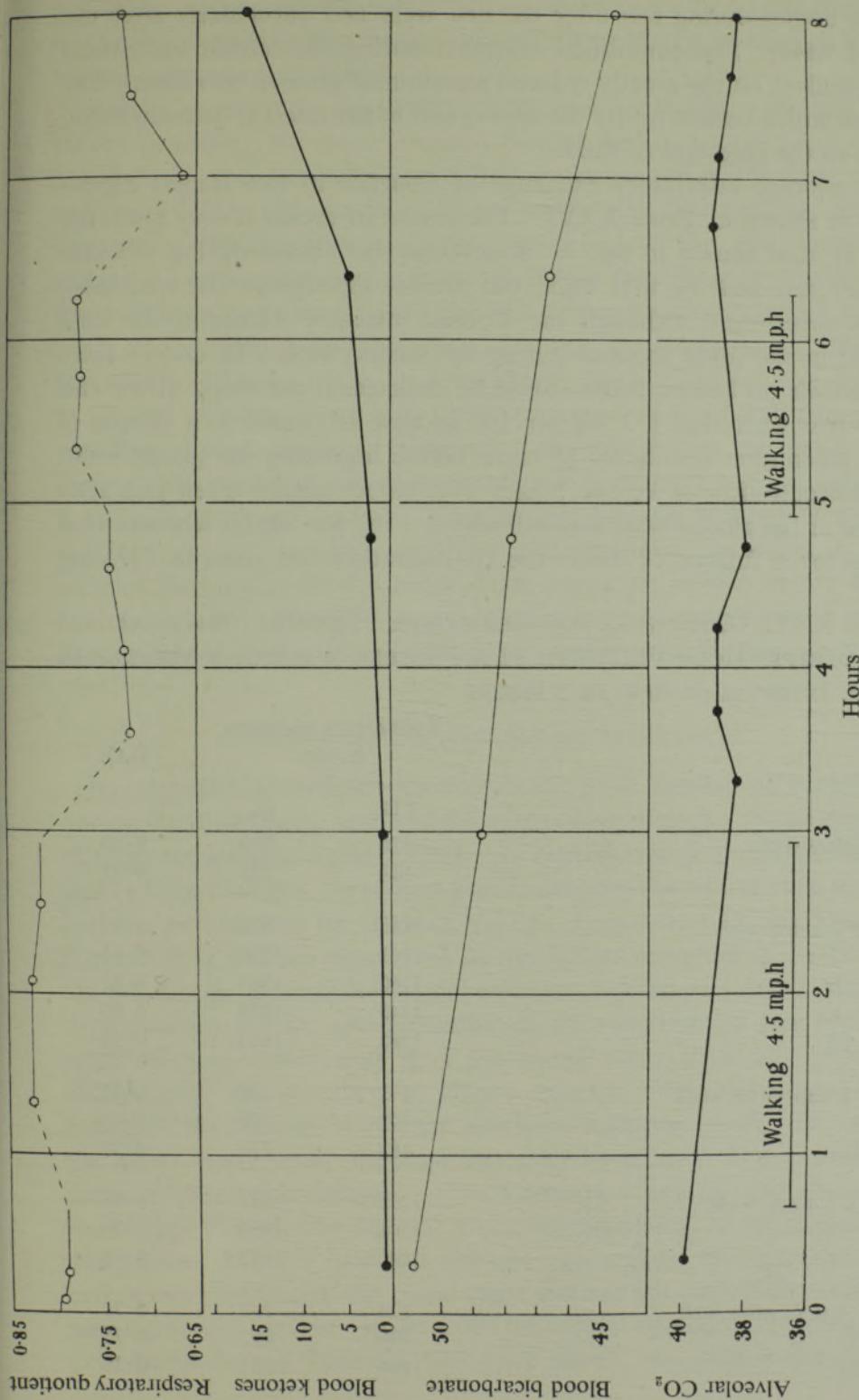


FIG. 8—Douglas, post-absorptive. Effect of walking 10 miles at 4.5 miles per hour followed by a further walk of 6 miles at the same pace after an interval of rest of 2 hours. Blood ketones expressed as mg  $\beta$ -hydroxybutyric acid %. Blood bicarbonate =  $\text{CO}_2$  combining power of blood in volumes %. Alveolar  $\text{CO}_2$  pressure in mm Hg.

ketone bodies during rest after the first walk and particularly after the second walk. The diminished excretion during the second walk must be dependent on the greatly reduced secretion of urine at this time. The diuresis which occurs before the walks, and in the interval between them, is due to the ingestion of fluid.

The average respiratory exchange of Courtice in two similar experiments is shown in Table XXVI. The course of events is very much the same as that shown in fig. 7. Ketonuria was absent during the preliminary rest and the first walk, but present throughout the remainder of the experiment, although the Rothera reaction seemed to be least marked in the urine secreted during the second walk. In one of these experiments no ketone bodies could be detected in the blood at the end of the first walk, but 1.3 mg per 100 cc were recovered in a sample of blood taken after resting for 1½ hours before beginning the second walk. The concentration of ketone bodies in a blood sample taken just after the end of the second walk was still only 1.1 mg per 100 cc, whereas after resting for a further 1½ hours the concentration had risen to 11.5 mg

TABLE XXVI—COURTICE, POST-ABSORPTIVE. TEN-MILE WALK AT 4.5 MILES PER HOUR FOLLOWED BY A FURTHER WALK OF 6 MILES AFTER AN INTERVAL OF REST OF 2 HOURS

	Respiratory exchange cc/min		R.Q.
	CO <sub>2</sub>	O <sub>2</sub>	
Rest before walk .....	176	219	0.80
,, .....	183	223	0.82
End of 2 miles' walk .....	1285	1570	0.82
,, 4     ,, .....	1261	1556	0.81
,, 6     ,, .....	1260	1567	0.81
,, 8     ,, .....	1242	1558	0.80
,, 10    ,, .....	1262	1616	0.78
Rest ½ hour after walk .....	172	230	0.75
,, 1     ,, .....	172	229	0.75
,, 1½    ,, .....	182	234	0.78
End of 2 miles' walk .....	1253	1611	0.78
,, 4     ,, .....	1241	1602	0.78
,, 6     ,, .....	1245	1612	0.78
Rest ½ hour after walk .....	178	243	0.73
,, 1     ,, .....	190	252	0.75
,, 1½    ,, .....	188	251	0.75

per 100 cc. The concentration of ketone bodies in the blood had therefore not been increased during the second walk above the figure reached during the intermediate rest period.

In these experiments the subject rested for 2 hours after a 10-mile walk before beginning the second walk. Ketone bodies accumulated in the blood during this rest period, and their concentration might then remain unaltered during the second walk or increase slightly, but they did not disappear. We therefore tried what would happen if a short interval of rest were interposed at earlier intervals during the course of a walk. We knew that we never developed ketonuria during an uninterrupted 10-mile walk, and we found that this was also true if we increased the length of the walk to 12 miles. On the other hand, if we rested for half an hour at the end of every fourth mile ketonuria appeared much earlier, and this was true of both subjects. Thus urine secreted during the first 4 miles, during a rest period of half an hour and during the next 4 miles' walk gave a negative Rothera reaction. During the ensuing half-hour's rest the Rothera reaction became positive, and continued positive in urine secreted during the third 4 miles' walk, becoming intense during a final resting period. It looked therefore as though ketonuria, when once it had developed during rest, could not be abolished by further exercise.

#### BLOOD SUGAR AND SUGAR TOLERANCE

Blood sugar determinations were made in a number of experiments during the pre-exercise and post-exercise resting periods. Some examples of these are given in Table XXVII. In experiments A and B on Courtice and in C on Douglas the subject was in the post-absorptive state and had had his normal diet on the day before. Experiment D on Douglas is interesting as it is the experiment of which data are given in Table XXII. On this day he had had his normal breakfast but the post-exercise respiratory quotient fell to, and remained at, an exceptionally low level. In none of these experiments does the blood sugar show any significant change after the exercise, but always remains within the normal limits. Evidently the amount of exercise which we took was insufficient to affect the blood sugar level, although this may be affected if the exercise is more severe and prolonged. Thus Edwards, Margaria, and Dill (1934) found that if work was done at a rate corresponding to an oxygen consumption of 2 to 2·5 litres per minute, with a pause of 5 minutes at the end of every half-hour, the blood sugar did not fall until the exercise had been continued for 3 to 4 hours when the subject was becoming exhausted. Dill, Edwards, and Talbott (1933) have shown, too, that in the dog the

TABLE XXVII—EFFECT OF A 10-MILE WALK AT 4·5 MILES PER HOUR ON THE RESTING BLOOD SUGAR. EXPERIMENTS A, B, AND C, SUBJECTS POST-ABSORPTIVE; EXPERIMENT D, NORMAL BREAKFAST BEFORE EXPERIMENT

	<i>Courtice</i>		<i>Douglas</i>	
	Blood sugar mg/100 cc		Blood sugar mg/100 cc	
	Exp. A	Exp. B	Exp. C	Exp. D
Initial rest .....	94	89	Initial rest .....	99
Rest after work for—			Rest after work for—	
1 min. ....	86	83	1 min. ....	92
5 „ .....	89	94	„ .....	91
15 „ .....	95	93	70 „ .....	94
25 „ .....	96	87	101 „ .....	98
55 „ .....	97	—	134 „ .....	—
85 „ .....	—	87	164 „ .....	—
100 „ .....	97	—	194 „ .....	—
118 „ .....	94	101		95
140 „ .....	101	—		
172 „ .....	—	87		
190 „ .....	93	—		
217 „ .....	—	90		

blood sugar does not fall until severe muscular work has been done for a long time.

For Courtice we have also tested the sugar tolerance both before and after exercise. Fifty gm of sucrose were taken in solution in water with a little lemon juice in the post-absorptive state after resting for half an hour, and the blood sugar was determined every quarter of an hour whilst resting for 2 hours. On another day the same amount of sucrose was taken after resting for 2 hours following a walk of 10 miles, and the blood sugar was determined during the ensuing 2½-hour rest. Fig. 9 gives the average results of four experiments before and four experiments after exercise. It will be seen that after exercise the blood sugar concentration rises rather more slowly and falls to a normal level more gradually. In other words there is evidence of a reduced sugar tolerance.

In fig. 10 the influence is shown of the ingestion of 50 gm of either sucrose, glucose, or fructose on the respiratory quotient during rest when these sugars are taken by the post-absorptive subject in the first instance after a preliminary rest period of half an hour, and in the second 1 to 2 hours after he had finished a 10-mile walk.

The respiratory quotient before taking the sugar is considerably lower in the experiments made after exercise than in those when no muscular work had been done. Even if we make allowance for this, the absolute change of respiratory quotient after taking either sucrose or glucose is less in the experiments made after work, and the rate at which the quotient rises is slower. The same effect is less prominently shown after taking fructose. With both sucrose and glucose the highest value of the respiratory quotient is maintained longer in experiments made after work than in those in which no work was done. The lag in the rise of the respiratory quotient which is shown when the sugar is ingested during rest after exercise cannot be due to slow absorption of the sugar, since

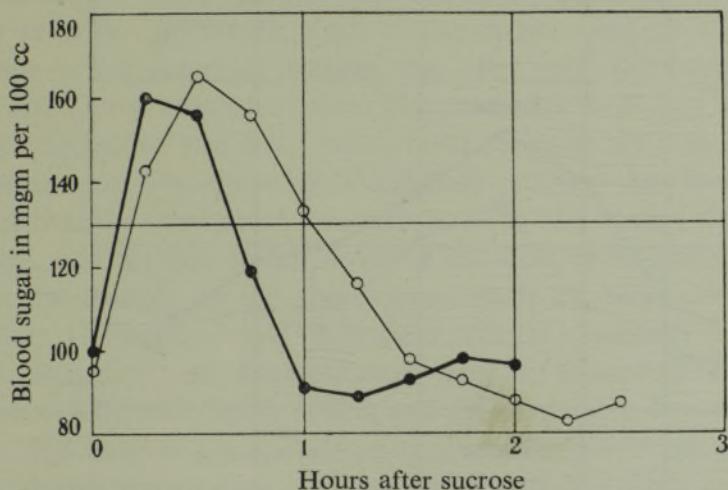


FIG. 9—Courtice. Effect of ingesting 50 gm of sucrose on the blood sugar before and after walking 10 miles at 4·5 miles per hour. ● Before exercise; ○ After exercise.

fig. 9 shows that at the end of half an hour the blood sugar is actually higher when the sugar is ingested after exercise than when no exercise is taken.

#### DISCUSSION OF THE RESULTS

During the work we were evidently in what is termed the "steady state". The walk was done at a reasonably uniform rate throughout. Our own analyses and alveolar  $\text{CO}_2$  estimations, as well as Owles's earlier observations on Douglas, make us confident that changes in the respiratory quotient during the walk in our experiments cannot be attributed to material changes in the lactic acid content of the blood. The period during which the body temperature was actually rising as a result of the exercise was limited to about the first half-hour of the walk, and

thereafter the body temperature remained steady. We began the first determination of the respiratory exchange during the work after we had been walking for about 22 minutes. The body temperature may still have been rising at this time, but the respiratory quotient during the last

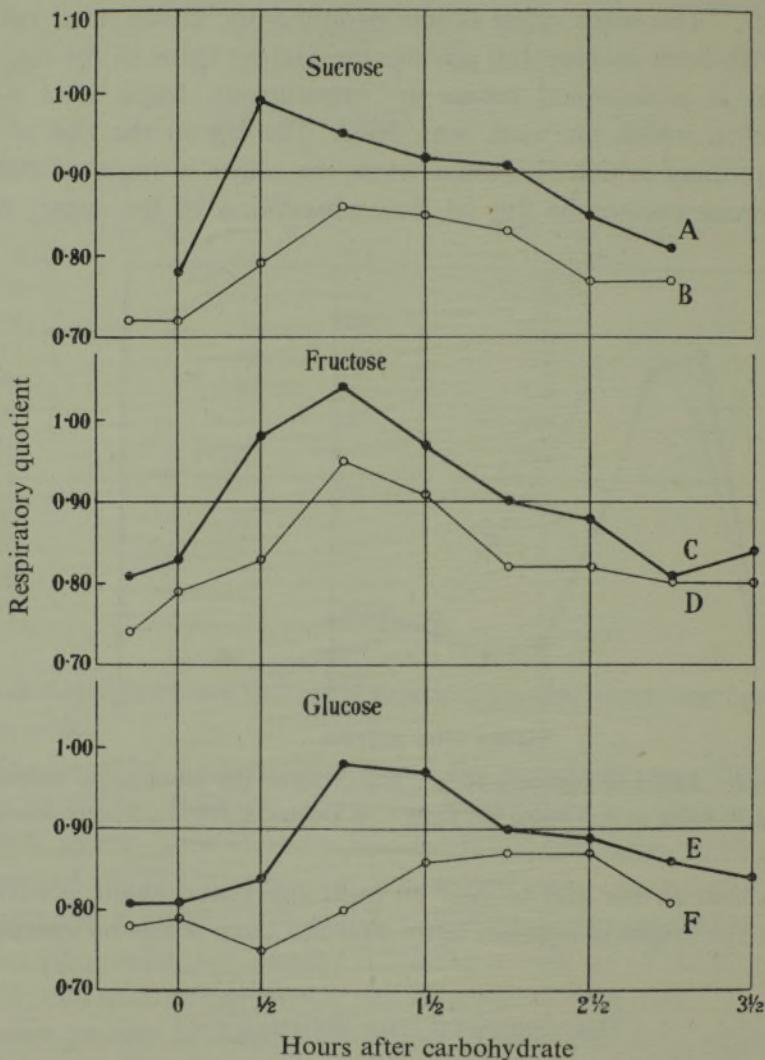


FIG. 10—Courtice. Effect on the respiratory quotient of 50 gm of sucrose, glucose, or fructose before and after walking 10 miles at 4.5 miles per hour. ● Before exercise; ○ after exercise.

1 $\frac{3}{4}$  hours of the walk must have been unaffected by body temperature since this remained steady during this period. We have shown, too, that ketonuria never developed during the walk. Excluding therefore lactic acid, body temperature, and ketosis as factors affecting the respiratory

quotient during the work we are left with the conclusion that this quotient must depend on the ratio of the substances oxidized to supply energy, for it hardly seems likely that at a time when the rate of oxidation is greatly increased the quotient can be affected by the conversion of carbohydrate into stored fat, or vice versa, so long at least as the quotient is in the neighbourhood of 0·8. It has already been pointed out that if we accept the respiratory quotient as a true oxidation quotient it means that during the walk about 100 gm of carbohydrate must have been used in those experiments made on the post-absorptive subject who had been taking his ordinary diet on the previous day.

So far as the actual respiratory exchange during the work is concerned our figures agree with what has been found by other observers in work of similar severity. Although much of the earlier work on the respiratory exchange during muscular exercise, e.g., that published by the schools of Zuntz and Durig, seemed to show that moderate work had little influence on the respiratory quotient, more recent investigations on subjects who were either post-absorptive or taking their ordinary diet have established the fact that the respiratory quotient tends to rise at first during work of this type, and perhaps to fall slowly if the work is long continued. This is true, for instance, of the observations made by Amar (1910), Douglas, Haldane, Henderson, and Schneider (1913), Benedict and Cathcart (1913), Benedict and Murschhauser (1915), Campbell, Douglas, and Hobson (1920), and Smith (1922) and the conclusion has therefore been drawn that there is a preponderating use of carbohydrate as a source of energy during the exercise. Krogh and Lindhard (1920), in their investigation of the relative value of fat and carbohydrate as sources of muscular energy, found that if the respiratory quotient was very high it tended to fall when work was begun, and if it was low it tended to rise, there being little change when the resting quotient was between 0·8 and 0·9.

Our own observations agree with those of Krogh and Lindhard so far as we find that with low initial respiratory quotients the change of quotient during the work is greater than when the initial quotient is higher, but in our experiments even when the initial quotient is somewhat above 0·8 there may still be a distinct rise, at least in the earlier periods of the work. This is shown in fig. 11, which gives the results on both subjects in the post-absorptive state, the higher initial quotients being due to an increase in the carbohydrate taken on the previous day. The upper series of points show the change in respiratory quotient when the initial resting figure is compared with the first determination made during the work; in the lower series of points the initial resting figure is compared with the average respiratory quotient during the whole of the work.

In Krogh and Lindhard's experiments the respiratory quotient during the work varied somewhat irregularly, but on the whole there is a slight tendency towards a fall, and they conclude that the organism maintains a remarkably constant proportion between the amounts of carbohydrate and fat katabolized, this proportion being a function of the available supplies of the two sources of energy. The change in quotient shows that the balance between carbohydrate and fat is very slowly altered as the work progresses in favour of the latter.

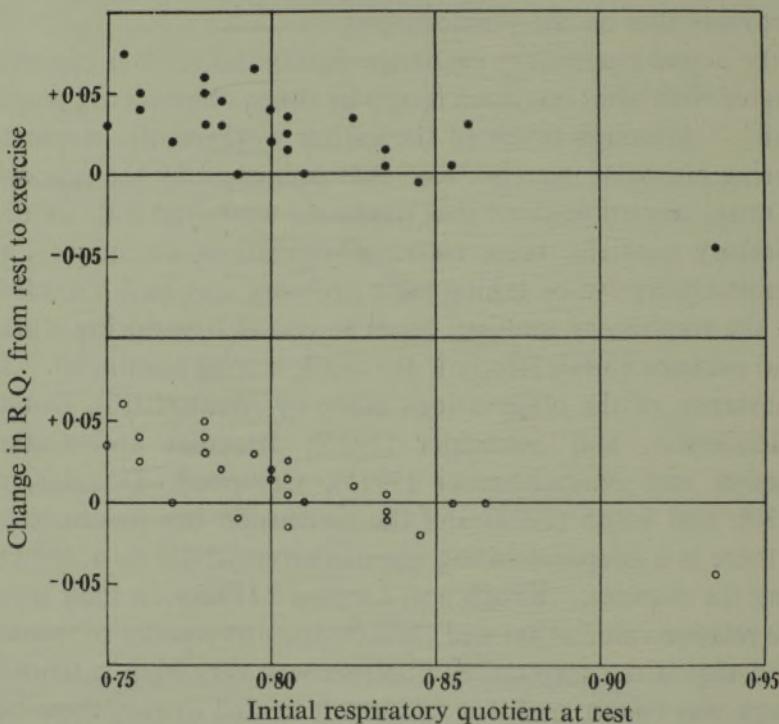


FIG. 11—Alteration in the initial respiratory quotient caused by walking at 4·5 miles per hour. ● Change produced during early period of walk; ○ change produced taking average R.Q., during whole walk of 10 miles.

The work which we did in our experiments was more severe, and lasted longer, than that in Krogh and Lindhard's experiments, and our actual determinations of the respiratory exchange were spread over a longer period of work. It is not surprising therefore that we got more evidence of a fall of respiratory quotient during the course of the work. A similar fall is apparent in the more recent observations of Christensen, Krogh, and Lindhard (1934) on the effect of severe and prolonged athletic exercise. We agree that the respiratory quotient must depend largely on the availability of carbohydrate at the time, and that as the work

continues this availability becomes reduced owing very likely to the gradual depletion of glycogen stores in the liver. In the later stages of work we may expect therefore to have a much smaller proportion of carbohydrate to fat metabolized than in the earlier stages, and we have given on p. 394 figures to show this.

It does not of course follow that all individuals will react in precisely the same way, for "availability" is a general term which must include such factors as the influence of the diet previously taken, as well as individual differences in the capacity for storing and possibly for mobilizing carbohydrate. Another factor which may come into play is the influence of differences in the rate at which the work is done. Even when we restrict ourselves to work which may be regarded as light or moderate in character there is evidence that if the respiratory quotient increases during the work the rise is more evident at the faster rates of work. If the work is definitely hard for the subject there may of course be a considerable rise of the respiratory quotient, but in such a case it is very likely to be due in part to the accumulation of lactic acid. In the experiment detailed in Table XVII in which the pace of the walk was reduced to  $3\frac{1}{2}$  miles per hour there is no rise of the respiratory quotient even in the earlier stages of the walk, and at most but a slight fall as the work continues. The total amount of work done (as judged from the oxygen consumption) is, however, just the same as in the experiments done at the pace of  $4\frac{1}{2}$  miles per hour. Yet the calculated consumption of carbohydrate during the walk in this experiment is only 71 gm as compared with the figure of about 100 gm found in experiments at the faster pace.

A reduction of 100 gm in the available carbohydrate in the body may at first sight appear too small to matter seriously, but the significance of this reduction must depend on the amount of carbohydrate originally available, and it is impossible to determine what this amount is. The old statement that the liver of a well-nourished man may contain 150 gm of glycogen, and that there is about an equal amount in the muscles, cannot be accepted as it stands in view of more recent determinations of the glycogen stores in animals under different conditions. Junkersdorf (1925) fed dogs on a diet similar to Voit's standard diet for man and found an average of 6.1% of glycogen in the liver and 0.55% in the muscles. Schöndorff (1903), feeding dogs on a carbohydrate rich diet, found a glycogen content in the liver of 7.3–18.7%, and in the muscles of 0.7–3.7%, while Junkersdorf (1921, b) showed that the glycogen content of the dog's liver may reach 16.4% with excessive feeding with protein and carbohydrate. Assuming that these figures can be applied to man, and that a man weighing 70 kilos has a liver weighing 1.5 kg and muscles

weighing 21 kg (30% of his body weight), the glycogen content of the liver might vary from 92 gm to 280 gm, and of the muscles from 115 gm to 777 gm. Whatever a reasonable estimate of the glycogen stores of a normal man may be, it seems evident that we may encounter extreme variations according to the amount of carbohydrate taken in the diet.

It has long been known that starvation coupled with muscular work leads to a very rapid reduction of the glycogen in the liver of experimental animals, as well as to a more gradual reduction of muscle glycogen. Junkersdorf (1921, *a*) found that after starving dogs for 11 days the glycogen content of the liver was 0·59% and of the muscles 0·21%. Comparing these figures with those given above for dogs on the Voit standard diet the glycogen content of the muscles has been considerably diminished, but that of the liver has been reduced in much greater proportion. The greater ease with which the glycogen content of the liver can be depleted in comparison with that of the muscles is also shown after the administration of phlorhizin (Junkersdorf, 1922, 1923) or pancreatectomy (Fisher and Lackey, 1925; Chaikoff, 1927). Bollman, Mann, and Magath (1925) have shown that after extirpation of the liver the normal level of blood sugar cannot be maintained at the expense of the glycogen in the muscles, while Best, Hoet, and Marks (1926) have shown that an insulin hypoglycaemia does not appreciably lower the glycogen content of the skeletal muscles of the spinal animal unless insulin convulsions are caused.

All these facts seem to show that although glycogen may be readily given up by the liver to supply the needs of the body the muscles tend to maintain their glycogen content, presumably because its presence is intimately associated with their normal activity. If therefore in our experiments the brunt of the supply of carbohydrate demanded by the active muscles has to be borne by the liver, assuming that the form of exercise which we have adopted was not sufficiently strenuous or prolonged to cause a significant diminution of muscle glycogen, the loss of something like 100 gm of liver glycogen may well have been material, especially if the liver at the start had a glycogen content well below the maximum. We can therefore understand that as the work continues an increasing call must be made upon fat to supply the energy required.

When we took our normal diet on the day preceding the experiment our initial respiratory quotients were about 0·81 and 0·79, but when we had deliberately taken a diet rich in carbohydrate on the preceding day the initial quotients were 0·93 and 0·86. In one of the latter experiments on Courtice, Table XIX, the calculated consumption of carbohydrate during the walk was 153 gm and in another on Douglas 141 gm, *i.e.*,

greatly in excess of the average figure of about 100 gm obtained when the subjects had been living previously on their normal diet, whilst the resting respiratory quotients after exercise did not fall below the figures found during pre-exercise rest when the diet taken previously had been normal in character. This suggests to us that when taking his normal diet neither subject had made anything like full use of the storage capacity of his liver for glycogen.

The calculated consumption of carbohydrate may reach far higher figures for good athletes when the exercise is much more severe and prolonged than in our experiments. Thus Benedict and Cathcart's post-absorptive subject M. A. M. consumed 368 gm of glycogen during work on the bicycle ergometer lasting for 4 hours 22 minutes, which he regarded as equivalent to cycling 100 miles on the road. It may be noted that the average respiratory quotient during pre-exercise rest in the post-absorptive state was about 0.85 in this subject, so he very likely had a larger initial supply of available carbohydrate than we had on our normal diets. Christensen, Krogh, and Lindhard (1934) record that a subject on a diet extremely rich in carbohydrate can consume 400 gm of carbohydrate during work on the bicycle ergometer for 4 hours at a rate of 1080 kg m per minute, which would involve an oxygen consumption of about 2800 cc per minute, whilst his respiratory quotient fell during the course of the work from 0.91 to 0.82. In this case the subject apparently worked to exhaustion, and there is nothing, of course, to show the degree to which the glycogen stores of the muscles were implicated as well as those of the liver. The important part played by carbohydrate in maintaining the capacity of a dog to do very severe muscular work for many hours has been strikingly shown by Dill, Edwards, and Talbott (1933).

Turning now to the period of rest after the work we have to consider the significance of the persistent low respiratory quotient. The excess lactic acid found in the blood at the end of the work is so insignificant in amount that its elimination can hardly play any part as a cause of the low quotient in the early stages of rest. We are inclined to attribute the abnormally low quotient seen in Douglas at the end of the first half-hour's rest to the influence of falling body temperature. The main cause of the lowering of the respiratory quotient must depend on a genuine difference of the metabolism from that which characterized the pre-exercise period. A natural suggestion to make is that, if we are right in supposing that the work did result under the conditions of our experiments in a substantial depletion of the available carbohydrate, when the metabolism falls to its resting level again a far greater proportion of fat to carbohydrate will be used than in the pre-exercise period. This explanation is strongly

supported by the ketosis which develops very quickly after the work stops and slowly increases as time goes on. Ketosis is generally believed to occur when the ratio of carbohydrate to fat metabolized sinks below a certain level. It seems to be agreed that when the metabolism of fat to carbohydrate (*i.e.*, ketogenic to anti-ketogenic substances) is in the molecular ratio of 1:1 there is little or no ketosis, though the ketosis becomes marked if this ratio rises to 2:1. In Table VII it was shown that Courtice has an average respiratory exchange of 181 cc of CO<sub>2</sub> and 237 cc of oxygen, with a respiratory quotient of 0.76, during the post-exercise rest period. Allowing for a protein metabolism of 3.3 gm per hour it can be calculated by the methods of either Woodyatt (1921) or Shaffer (1921, 1923) that there would be a ratio of ketogenic to anti-ketogenic substances of about 1.1:1. A post-exercise respiratory quotient of 0.76 was the highest with which we invariably had a ketosis, though, as has been pointed out earlier, we sometimes got ketonuria with a quotient of 0.77 and occasionally we could detect a faint positive Rothera reaction with a quotient as high as 0.78.

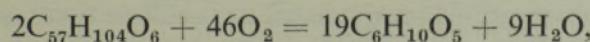
Another question which obviously needs consideration is whether the persistent low respiratory quotient during post-exercise rest is influenced by the conversion of either protein or fat to carbohydrate, and the storage of the latter in the liver and possibly the muscles. If the respiratory quotient were to remain at so low a level that it could not be explained by the simultaneous oxidation of protein and fat this might be regarded as evidence in favour of this conversion, provided that the incomplete combustion of fat with the production of ketone bodies were insufficient to account for the facts. If, for example, one molecule of β-hydroxybutyric acid is formed from one molecule of oleic acid while the remainder of the latter molecule is oxidized to CO<sub>2</sub> and water the respiratory quotient of the reaction will be 0.667, whereas if the oleic acid molecule were completely oxidized to CO<sub>2</sub> and water the quotient would be 0.707.

Unfortunately, as is so common in experiments of this type, our figures do not afford indubitable evidence of this transformation of fat into carbohydrate. Thus in Table IX it is shown that Douglas's average post-exercise respiratory quotient is 0.73, and that if we make what seems a fair maximum allowance for the protein metabolized the quotient sinks to 0.71, and we must admit that this could be explained simply by the complete oxidation of fat even if we do not regard such an explanation as probable. In one experiment on Douglas given in Table XXII we record a persistent post-exercise respiratory quotient of 0.71, which, if allowance is made as before for the protein metabolism, might be reduced to 0.68,

but this is the only instance in which we got a persistent quotient below 0·7.

In those experiments in which we measured the amount of ketone bodies excreted in the urine the average output did not exceed 100 mg per hour, cf. for instance Table XVI. The formation of 1 gm of  $\beta$ -hydroxybutyric acid requires an uptake of 108 cc of oxygen without corresponding liberation of  $\text{CO}_2$ , and consequently the formation of 100 mg of this acid per hour would require an oxygen uptake of 10·8 cc or 0·18 cc per minute. Admittedly these estimations of the rate of excretion of ketone bodies were made in experiments in which the respiratory quotient was a good deal higher than in the exceptional instance given above, and we ought to take into account the fact that the rate of excretion of ketone bodies in the urine does not necessarily show the rate of their accumulation in the body, but so far as we can judge we need not consider the formation of ketone bodies seriously as a cause of the low respiratory quotients in our experiments.

As it is difficult to get conclusive evidence by this line of argument we have tried to arrive at a figure which would represent the maximal rate of conversion of fat into carbohydrate which is compatible with the observed respiratory exchange and quotient during post-exercise rest in our experiments. In order to do this we have assumed that the energy liberated by the subject during rest is the same, no matter whether work has or has not preceded the rest, and is derived from the oxidation of precisely the same mixture of protein, carbohydrate, and fat, and that if the observed respiratory quotient falls during the post-exercise period this is due merely to a concurrent conversion of fat into carbohydrate with storage of the latter. If we take the figures for Courtice given in Table VII we see that his  $\text{CO}_2$  output is the same during rest after exercise as it was before, but that his oxygen consumption is 14 cc higher, so that his respiratory quotient has fallen from 0·81 to 0·76. Let us take it for the moment that this constant output of  $\text{CO}_2$  represents the rate at which energy is being liberated. Assuming for argument that the whole of the carbon in the fat molecule can be converted into carbohydrate by the uptake of oxygen (though we admit, of course, the weakness of any such empirical equation) we should get for triolein



and an uptake of 1 litre of oxygen would convert 1·7 gm of fat into 3 gm of carbohydrate. By this method of reckoning the extra 14 cc of oxygen consumed by Courtice per minute during the post-exercise period above the quantity necessary to give the same respiratory quotient as during the

pre-exercise rest, viz., 0·81, would represent the conversion of 1·5 gm of fat into 2·6 gm of glycogen per hour.

It is less easy to make a similar calculation for Douglas since, as will be seen from the average figures given in Table VII, not only is the post-exercise consumption of oxygen higher than during the pre-exercise period, but, in addition, the post-exercise output of  $\text{CO}_2$  is less than the pre-exercise. The simplest thing to do is to assume as above that the  $\text{CO}_2$  output indicates the rate of energy liberation, and that the lower value during rest after work is due merely to the fact that the degree of rest was more complete after the exercise than before it. If during the post-exercise period the respiratory quotient had been the same as in the pre-exercise period, viz., 0·79, the  $\text{CO}_2$  output of 176 cc would have corresponded with an oxygen consumption of 221 cc and the oxygen consumption actually observed would have been 19 cc greater than this figure. This would correspond to the conversion of 2·0 gm of fat into 3·5 gm of glycogen per hour. Even if we take the exceptional instance shown in Table XXII it would only require the conversion of 2·8 gm of fat into 4·9 gm of carbohydrate per hour to change a quotient of 0·79 into the observed figure of 0·71.

Of course a calculation of this type must not be pressed too far. In making it we have deliberately discounted any alteration of the ratio of fat and carbohydrate burned, nor have we considered the possibility of the conversion of protein into carbohydrate, although the more there is of this the less will be the conversion of fat. But the point that we wish to make is really this, that so far as we can see any conversion of fat or protein into carbohydrate with storage of the latter must have been at a very slow rate. We do not mean to imply that such a conversion cannot take place, but that if it does the rate is insufficient to lead to a material replenishment of the stores of available carbohydrate in the liver or elsewhere. We feel that this is supported by the fact that the low respiratory quotient was maintained steady in the last 2 hours of post-exercise rest while the ketosis was increasing, and that even when the post-exercise rest period was prolonged to 9½ hours there was no indication that the quotient was rising towards its normal value.

Poulton (1933) has recently drawn attention to the fact that in many of the published observations on the basal metabolism there is a discrepancy between the heat output directly determined in the calorimeter and that estimated from the respiratory exchange at low and high respiratory quotients, agreement being only reached with a respiratory quotient of about 0·785. This might be regarded as evidence in favour of the conversion of carbohydrate to fat at high quotients and of fat to carbohydrate

at low. If we calculate the calorie output by means of the Zuntz-Schumburg table in our experiments, Courtice has on the average a somewhat higher calorie output during rest after exercise than in the initial rest period, viz., 1.13 calories per minute as opposed to 1.07. Douglas on the other hand gives a post-exercise figure of 1.13 calories and a pre-exercise of 1.10. These differences are hardly large enough to be significant. If we plot out, as we have in fig. 12, the results of individual experiments it will be seen that for Courtice there does seem to be a definite tendency for the calculated calorie output to be higher at the low quotients which prevail after exercise, these low quotients being dependent on an increase in oxygen consumption without any definite variation in the CO<sub>2</sub> output. The scatter of the individual points for Douglas is too great to justify any definite conclusion. Again, therefore, evidence in favour of a transformation of fat into carbohydrate must be regarded as inconclusive.

Occasionally we felt chilled when sitting still for a long time after the exercise was over, and this may have prevented the metabolism from falling as low as at other times, but apart from this we can see no reason why the metabolism after the work should not be as low as during the pre-exercise period, if not lower: at all events we were apt almost to fall asleep during the long rest after the exercise.

In view of the occurrence of ketosis and of the behaviour of the respiratory quotient during a second period of exercise in our double walk experiments, which will be discussed below, we are inclined to attribute the cause of the low post-exercise respiratory quotients far more to an increase in the ratio of fat to carbohydrate oxidized than to the conversion of fat into glycogen.

In our experiments on the effects of the ingestion of carbohydrate before doing the work we have clearly met the same phenomenon as that described by Christensen, Krogh, and Lindhard (1934) in their investigations on severe and prolonged athletic exercise, viz., that a diet rich in carbohydrate taken on the day preceding the exercise may in certain respects have a greater influence than the ingestion of a quantity of easily assimilable carbohydrate either during, or shortly before beginning, the work. They conclude that "when long continued, severe work is to be performed the preceding diet must provide ample energy, mainly in the form of carbohydrate, to fill up the stores of glycogen. When the absolute maximum of work is to be attained . . . about 2 days' rest is required to secure a complete filling up of the glycogen stores, and it appears that this cannot be done by taking large amounts of carbohydrate just prior to the work".

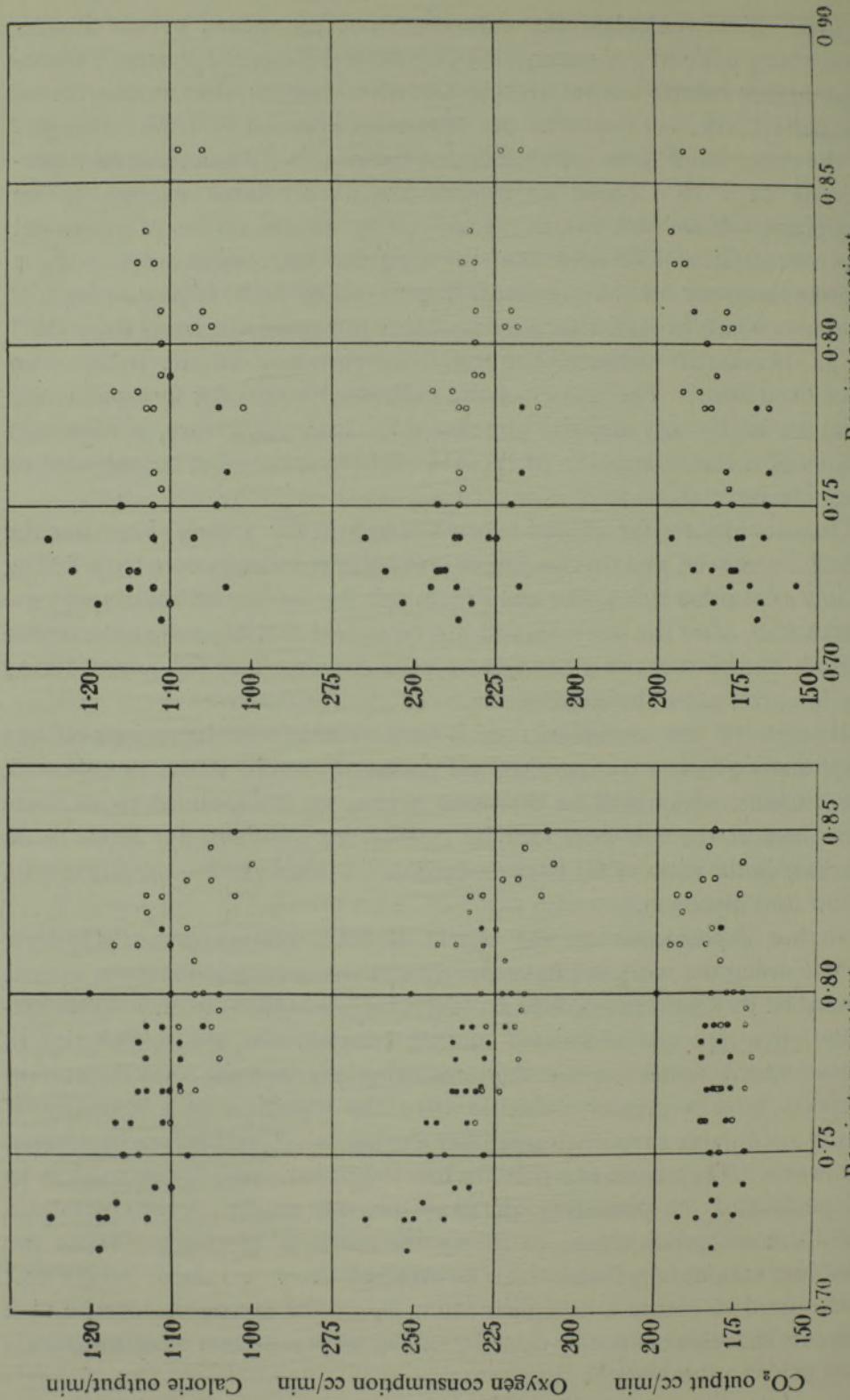


FIG. 12.—The relation between the R.Q. and the CO<sub>2</sub> output, oxygen consumption, and calculated calorie output with the subject resting. O Before exercise; ● after exercise. The left-hand side of the figure refers to Courtice, the right-hand side to Douglas.

In our own experiments, when we took a predominantly carbohydrate diet on the day preceding the experiment, the experiment itself being made on the post-absorptive subject, the general behaviour of the respiratory exchange was very much the same as when the subject had been previously taking his normal diet, save that the respiratory quotient ran throughout at a higher level and ketonuria failed to appear during the period of rest succeeding the exercise. On the other hand when we took carbohydrate, mainly in the form of glucose or fructose, shortly before beginning the experiment post-exercise ketonuria developed in 9 out of 12 experiments. We only took 60–70 gm of carbohydrate in these experiments, but, assuming that in the normal post-absorptive experiments about 100 gm of glycogen was used up during the exercise, we felt that the ingestion of this moderate amount of carbohydrate might possibly so far compensate for this loss of glycogen as to make a substantial difference during the post-exercise rest. What actually happened was that the respiratory quotient, which was very high at the beginning of the work, fell rapidly and steadily so that as the work neared its end it was not very different from the figure found in the normal post-absorptive experiments. If we make a straightforward calculation of the carbohydrate used up during the work it would appear that the only result of the ingestion of the carbohydrate just before beginning the experiment is to exaggerate the use of carbohydrate during the work to such a degree that when the work stops we have much the same condition as in the normal post-absorptive experiments, and as a result we still find a post-exercise ketonuria. Such a calculation neglects the possibility of the transformation of carbohydrate into stored fat, and though we may feel that such a transformation is improbable when the respiratory quotient is in the neighbourhood of 0·8 we cannot disregard this as a possibility when the quotient approaches and even exceeds 0·9, for it may be that when there is a sufficient surplus of carbohydrate available some of this may be converted into fat, even though the metabolism of the muscles is greatly increased at the time. Attention has also been drawn to the accentuation of carbohydrate metabolism during muscular work when glucose or fructose has been ingested beforehand by Carpenter and Fox (1931), although the exercise in their experiments was less severe and of shorter duration than in ours.

When the carbohydrate was ingested shortly before the beginning of the experiment the work must, we feel, still have resulted in a very material depletion of the body's stores of "readily available" carbohydrate if we are to explain the low quotient and the ketosis which persist after the exercise is over—a depletion which is not nearly so apparent when we

took a carbohydrate diet on the previous day, presumably because this gave a better opportunity for increasing the stores of available carbohydrate, very likely in the form of glycogen in the liver.

Depleted though the stores of available carbohydrate may have been in our normal post-absorptive experiments, and even in those in which we ingested carbohydrate just before beginning the experiments, they were by no means exhausted. This, we think, is clearly shown by the results of the double walk experiments. We know that a single 10-mile walk always resulted in a low respiratory quotient which persisted for hours and was accompanied by an increasing ketosis. If, however, after 2 hours' rest we walked for a further 6 miles the quotient at once rose considerably, and remained steady at this higher level until the end of the walk when it dropped abruptly again to a low level. It is noteworthy, too, that though a ketosis developed in the interval between the two walks this ketosis either showed no further change, or but a slight increase, during the second walk, although in the final period of rest it became very marked.

We have not made any determinations of the lactic acid in the blood at the end of the second walk, but since there was hardly a perceptible increase at the end of a single 10-mile walk it seems unlikely that a further walk at the same pace after an interval of 2 hours' rest would have given a different result. Using the arguments which have already been developed about the significance of the respiratory quotient during a single 10-mile walk we feel that the steady respiratory quotient during the second walk gives an index of the proportions of substances being oxidized at the time, and that during this period a larger proportion of carbohydrate to fat is being used than in either the intermediate or the final rest periods. Taking the data for Douglas which are shown in fig. 7 the oxygen consumption during the second walk was about 1730 cc per minute and the respiratory quotient 0.78. Neglecting the protein metabolism during the walk these figures would correspond to an oxidation of 0.486 gm of carbohydrate and 0.667 gm of fat per minute, and the total amount of carbohydrate used up during the 80 minutes' walk would be 39 gm and of fat 53 gm. The amount of carbohydrate used is substantial, but the proportion of energy derived from carbohydrate to that derived from fat is now only about 1:3.

If this is so, a pertinent question at once suggests itself. Why is it that the predominantly fatty metabolism which characterizes the intermediate period of rest should so abruptly change with the onset of the second period of work into a type in which carbohydrate plays a more prominent part, and that there should be an equally abrupt reverse change in the final

period of rest? It is not easy to answer this question, but there are certain facts which seem suggestive.

In the experiments made on Courtice there is evidence of a reduced sugar tolerance during the post-exercise rest period. The sugar tolerance curve has been frequently used as an index of the power of the tissues to use glucose, either by storing it as glycogen or fat, or by burning it, and the curves shown in the experiments on Courtice closely resemble the tolerance curves obtained after starvation or high fat diets by previous workers. Staub (1922) found that the sugar tolerance curve was lower on a fat diet than on a carbohydrate diet, and to account for this postulated a reduced output of insulin from the pancreas on the former diet. Sweeney (1927) studied the effects of starvation and of fat, protein, and carbohydrate diets, and concluded that the higher sugar tolerance on a carbohydrate diet was due to a greater sensitization of the insulin secreting mechanism, with a resultant increase in the secretion of insulin, an explanation with which Macleod (1930) agreed. On the other hand Dann and Chambers (1930) have shown that in dogs which have fasted from 15 to 30 days the administration of glucose causes little rise of the respiratory quotient, and that when insulin is injected at the same time as the administration of glucose very little more glucose is oxidized, showing apparently that the reduced sugar tolerance in these conditions is not merely due to lack of insulin. More recently Himsworth (1934) has suggested that fat diets cause a decreased susceptibility of an animal to insulin, and carbohydrate diets the reverse, possibly because insulin is secreted in an inactive state and has to be activated in the body by some unknown substance which is increased by a carbohydrate diet and decreased by a fat diet. We have clearly much to learn before we shall understand the mode of action of insulin.

It is quite likely that an increased secretion of insulin plays a part in causing the greater use of carbohydrate during the performance of the work when that work is done soon after ingesting carbohydrate, but though a mere surplus of carbohydrate gaining access to the body may be effective in causing increased insulin production, or in bringing about an enhanced effect of that substance, there may well be some other factor at work in addition. If, for instance, the activity of the islets of Langerhans—and, no doubt we ought to add, of the other endocrine organs associated with the general metabolism of carbohydrate in the body—were closely correlated with the varying activity of the muscles, an explanation might be found of the variations of the use of carbohydrate which appear to occur in our experiments. We could in this way account for the fact that in our double walk experiments an increase in carbohydrate

utilization occurs as soon as the second walk begins and is maintained as long as the walk lasts. Tempting though such an hypothesis may be no precision can be given to it until we have far more information as to the exact part played by insulin and other endocrine secretions in carbohydrate metabolism, but we feel that the possible influence of these secretions during muscular activity may well repay further investigation.

#### SUMMARY

The effects of a long walk on the general metabolism of two subjects who were not in athletic training have been studied in detail, observations being made not only during the walk but also during a subsequent period of rest lasting 3 hours. The standard exercise in most of the experiments was a walk of 10 miles at a rate of 4·5 miles per hour.

In the post-absorptive subject who had previously been living on his normal diet it is shown that the respiratory quotient during the work rises somewhat above the preliminary resting value in the early stages and falls gradually as the work continues, and that these changes cannot be ascribed to the accumulation of excess lactic acid in the blood, to rise of body temperature, to a material degree of change in the CO<sub>2</sub> combining power of the blood, or to a developing ketosis. It is therefore concluded that the respiratory quotient under the conditions of the experiments can be taken as an index of the materials oxidized in the body, implying that during the course of the work about 100 gm of carbohydrate were used and that as the work continues there is a substantial alteration in the ratio of carbohydrate to fat metabolized.

When walking at the slower rate of 3·5 miles per hour the respiratory quotient during the walk may alter but little from that during preliminary rest.

During rest after the exercise in these post-absorptive experiments there is a fall of the respiratory quotient to the average figures of 0·76 and 0·73 in the two subjects, which is due to the fact that the oxygen consumption is higher and the CO<sub>2</sub> production either the same as, or somewhat lower than, the pre-exercise values, and this fall persists unchanged for 3 hours, and even in one experiment for as long as 9½ hours. This persistent fall in quotient was accompanied by a definite excess of ketone bodies in the blood and ketonuria, and by a progressive fall in the CO<sub>2</sub> combining power of the blood, although the alveolar CO<sub>2</sub> pressure fell only slightly, if at all, below the pre-exercise level. Only a trifling excess of lactic acid could be detected in blood samples taken just after stopping the walk; in later samples the lactic acid concentration was the same as during preliminary

rest. An abnormally low quotient shown by one of the subjects half an hour after stopping work seemed to owe its explanation rather to the fall of body temperature than to the oxidative removal of lactic acid.

Ketosis never developed during an uninterrupted 10- or even 12-mile walk, but appeared very soon after resuming rest. The onset of ketosis seemed to be associated rather with the total amount of muscular work done previously than with the rate at which that work was done. Thus walking at 3·5 miles per hour for a length of time that implied the same total oxygen consumption as a 10-mile walk at 4·5 miles per hour produced much the same after-effects as the walk at the faster rate, although the actual carbohydrate consumption during the walk appeared to be less.

In the post-absorptive subject who had taken a high carbohydrate diet on the previous day the general course of the respiratory exchange was much the same, save that the respiratory quotient ran throughout at a higher level. No ketosis developed after the exercise, nor did the progressive fall of the  $\text{CO}_2$  combining power of the blood occur. Experiments of this type suggested that under normal dietetic conditions neither subject had made anything like full use of his capacity for storing glycogen, and that consequently the use of so moderate a quantity as 100 gm of carbohydrate during work under normal post-absorptive conditions might imply a really significant depletion of available carbohydrate in the body.

If, however, after taking a normal diet on the previous day, a normal breakfast was taken, or 50 gm of either glucose or fructose with 20–40 gm of bread were ingested shortly before beginning the experiment, post-exercise ketonuria developed in the majority of the experiments and the respiratory quotient fell nearly as low as in the normal post-absorptive experiments. The main result of such ingestion of sugar seemed to be so to enhance the use of carbohydrate (though some carbohydrate may possibly have been converted into stored fat) during the work that at the end of exercise the general condition was almost the same as in the ordinary post-absorptive experiments.

Confirmation has therefore been obtained of the view that a diet rich in carbohydrate taken on the day preceding the exercise may in certain respects have a greater influence than the ingestion of a quantity of easily assimilable carbohydrate shortly before beginning the work.

The previous ingestion of  $\text{NaH}_2\text{PO}_4$  was not found to have any appreciable influence on the course of events in the normal post-absorptive experiments.

The non-protein respiratory quotient never fell to so low a figure during rest after exercise, save possibly on one occasion, as to afford indubitable evidence of the conversion of fat into stored carbohydrate. Reasons are

given for supposing that such a conversion must have been limited in extent and insufficient to cause a material replenishment of the stores of available carbohydrate in the body. The main factor which is responsible for the persistent low quotient and ketosis appears to be the low ratio of carbohydrate to fat oxidized.

Although the stores of available carbohydrate may have been depleted at the end of a 10-mile walk they were not exhausted, since repetition of the walk for a further 6 miles at the standard rate after an interval of rest resulted in a rise of the respiratory quotient which was maintained throughout the exercise to fall abruptly again as soon as the exercise stopped.

The second walk was accompanied by no further change, or only a relatively slight increase, in the concentration of ketone bodies found in the blood during the intermediate rest period, although the ketosis became pronounced in the final rest period.

During the post-exercise rest period the blood sugar concentration never fell below the normal limits. Ingestion of sucrose, glucose, or fructose gave, however, distinct evidence of a reduced sugar tolerance. On this basis the possibility is discussed that the function of the endocrine organs associated with carbohydrate metabolism may be correlated with the varying activity of the muscles, and so afford at least a partial explanation of the changes in carbohydrate metabolism which result from muscular exercise.

#### REFERENCES

- Amar, J. (1910). "Le Rendement de la Machine humaine," Paris.
- Benedict, F. G., and Cathcart, E. P. (1913). 'Publ. Carnegie Inst.', No. 187.
- Benedict, F. G., and Murschhauser, H. (1915). 'Publ. Carnegie Inst.', No. 231.
- Best, C. H., Hoet, J. P., and Marks, H. P. (1926). 'Proc. Roy. Soc.,' B, vol. 100, p. 32.
- Bock, A. V., Vancaulaert, C., Dill, D. B., Fölling, A., and Hurxthal, L. M. (1928). 'J. Physiol.,' vol. 66, p. 136.
- Bollman, J. L., Mann, F. C., and Magath, T. B. (1925). 'Amer. J. Physiol.,' vol. 74, p. 238.
- Campbell, J. M. H., Douglas, C. G., and Hobson, F. G. (1920). 'Phil. Trans.,' B, vol. 210, p. 1.
- Carpenter, T. M., and Fox, E. L. (1931). 'Arbeitsphysiologie,' vol. 4, pp. 532, 570.
- Cathcart, E. P., and Markowitz, J. (1927). 'J. Physiol.,' vol. 63, p. 309.
- Chaikoff, I. L. (1927). 'J. biol. Chem.,' vol. 74, p. 203.
- Christensen, E. H., Krogh, A., and Lindhard, J. (1934). 'Quart. Bull. Health Organization of the League of Nations,' vol. 3, extract No. 13.
- Cook, L. C., and Hurst, R. H. (1933). 'J. Physiol.,' vol. 79, p. 443.
- Dann, M., and Chambers, W. H. (1930). 'J. biol. Chem.,' vol. 89, p. 675.

- Denigès, C. (1898). 'C.R. Acad. Sci. Paris,' vol. 126, p. 1868.
- Dill, D. B., Edwards, H. T., and Talbott, J. H. (1933). 'J. Physiol.,' vol. 77, p. 49.
- Douglas, C. G., Haldane, J. S., Henderson, J., and Schneider, E. C. (1913). 'Phil. Trans.,' B, vol. 203, p. 185.
- Douglas, C. G., and Havard, R. E. (1932). 'J. Physiol.,' vol. 74, p. 471.
- Douglas, C. G., and Priestley, J. G. (1924). "Human Physiology," Oxford Univ. Press.
- Edwards, H. T., Margaria, R., and Dill, D. B. (1934). 'Amer. J. Physiol.,' vol. 108, p. 203.
- Embden, G., Grafe, E., and Schmitz, E. (1921). 'Z. physiol. Chem.,' vol. 113, p. 67.
- Fisher, N. F., and Lackey, R. W. (1925). 'Amer. J. Physiol.,' vol. 72, p. 43.
- Friedemann, T. E., Cotonio, M., and Shaffer, P. A. (1927). 'J. biol. Chem.,' vol. 73, p. 335.
- Friedemann, T. E., and Kendall, A. I. (1929). 'J. biol. Chem.,' vol. 82, p. 23.
- Gemmill, C. L. (1934). 'Amer. J. Physiol.,' vol. 108, p. 55.
- Haldane, J. S. (1920). 'J. Path. Bact. Lond.,' vol. 23, p. 443.
- Himsworth, H. P. (1934). 'J. Physiol.,' vol. 81, p. 29.
- Junkersdorf, P. (1921, a). 'Pflügers Arch.,' vol. 186, p. 238.
- (1921, b). *Ibid.*, vol. 187, p. 269.
- (1922). *Ibid.*, vol. 197, p. 500.
- (1923). *Ibid.*, vol. 200, p. 443.
- (1925). *Ibid.*, vol. 210, p. 351.
- Krogh, A., and Lindhard, J. (1920). 'Biochem. J.,' vol. 14, p. 290.
- Lusk, G. (1928). "Science of Nutrition," Philadelphia.
- Macleod, J. J. R. (1930). 'Lancet,' vol. 2, p. 512.
- Owles, W. H. (1930). 'J. Physiol.,' vol. 69, p. 214.
- Peters, J. P., and van Slyke, D. D. (1932). "Quantitative Clinical Chemistry," vol. 2, London.
- Poulton, E. P. (1933). 'Proc. R. Soc. Med.,' vol. 26, p. 1591.
- Rapport, D. (1930). 'Physiol. Rev.,' vol. 10, p. 349.
- Schöndorff, B. (1903). 'Pflügers Arch.,' vol. 99, p. 191.
- Shaffer, P. A. (1921). 'J. biol. Chem.,' vol. 47, p. 433.
- (1923). 'Medicine,' vol. 2, p. 375.
- Smith, H. M. (1922). 'Publ. Carnegie Instn.,' No. 309.
- Staub, H. (1922). 'Z. klin. Med.,' vol. 93, pp. 89, 123.
- Sweeney, J. S. (1927). 'Arch. int. Med.,' vol. 40, p. 818.
- van Slyke, D. D. (1917). 'J. biol. Chem.,' vol. 32, pp. 455, 495.
- Woodyatt, R. T. (1921). 'Arch. int. Med.,' vol. 28, p. 125.