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MUSCULAR ACTIVITY AND CARBOHYDRATE METABOLISM[1]

THE PROBLEM: INTRODUCTION

IT has long been discussed whether the breakdown of carbohydrate, rather than of other substances, is primarily responsible for the provision of energy in muscular contraction. It is known and accepted that work may be done, in the general melting-pot of the body, by the use of any kind of foodstuff. We are now concerned, however, specifically with the *primary* process of muscular contraction. In the complete chain of processes involved in long-continued exercise, this primary process may be disguised, or even apparently obliterated, by simultaneous transformations which take place between the different food constituents. Considering the internal combustion engine, it is obvious that petrol and benzole may be used indiscriminately for providing power and driving the machinery. In the same way, however, as we ask whether carbohydrate is the specific fuel of muscle, or whether fat may be used in an identical manner, so we might query whether petrol or coal can be used in an internal combustion engine. The obvious answer is that coal must be prepared beforehand by distillation, before it can be used in the engine, while petrol can be used directly; and that in the preparation of coal to form benzole for use in the engine, a considerable proportion of the energy of the coal is wasted, as regards its work-producing power. Putting our problem in terms of the modern theory of muscular activity and assuming that the initial process in contraction—that which causes the mechanical response—is an entirely non-oxidative one consisting of the formation of lactic acid from glycogen, we are asking now whether the recovery process by which the lactic acid is restored to its precursor can go on at the expense of *any* oxidation, or *only* of that of carbohydrate. *May the recovery mechanism, so to speak, be driven by any kind of combustion, as a steam engine may be, or is it necessary specifically to combust carbohydrate?*

THE RESPIRATORY QUOTIENT

It has long been known that the respiratory quotient during prolonged steady exercise is not unity. It varies with the diet. That, however, does not an-

[1] A lecture delivered at the request of the Mayo Foundation, at Rochester, Minnesota, and at the Universities of Iowa, Nebraska, Minnesota, Wisconsin and Michigan, in October and November, 1924.

swer our question. Carbohydrate may be used exclusively in the muscular process of breakdown and recovery, but as fast, or almost as fast, as it is used up it may be restored, in the general metabolism of the body, by the breakdown of some other substance, *e.g.*, of fat. The combustion of carbohydrate, followed by the reformation of carbohydrate from fat, would affect the respiratory quotient in a manner exactly similar to the direct combustion of fat.

MECHANICAL EFFICIENCY ON DIFFERENT DIETS

The beautiful and very convincing experiments of Krogh and Lindhard (1), published in 1920, showed with little possibility of doubt that the combustion of carbohydrate has some special connection with muscular activity. Employing a method where the respiratory quotient may be determined with an average error of only $\pm$ 0.002, measuring the cost of doing a given amount of work of moderate intensity in a highly trained and carefully observed and calibrated subject, and varying the substances metabolized by varying the diet during and before the experiment, they found the cost of work (*i.e.*, the total amount of energy used in doing a given amount of work) to be a linear function of the respiratory quotient, falling as the respiratory quotient rose. Of the total energy used in any effort, granting that the respiratory quotient be correctly measured, the fraction which is derived from fat may be shown to be a linear function of the respiratory quotient. I say intentionally, "*if the respiratory quotient be correctly measured*": we will discuss later the variations of respiratory quotient produced by lactic acid in the body, during and after severe muscular work. Such variations, however, do not affect Krogh and Lindhard's experiments, where the exercise was moderate, requiring only about one liter of oxygen per minute, and continued for a long time. If now we assume that carbohydrate oxidized is utilized directly for work, or (more accurately) for recovery from work, and fat only after "conversion" involving metabolic processes and loss of energy, the cost of work should be a linear function of the respiratory quotient—as Krogh and Lindhard found. As the mean of a long, careful and carefully weighted series of observations, which give one all the impression of extreme reliability, they found, assuming carbohydrate to be utilized directly for the production of work (or, as I should rather say, for carrying on the recovery process) that fat may be so used only after "conversion" involving a 10 per cent. loss of energy: in modern terms, the recovery process is 10 per cent. less efficient when fat is oxidized than when carbohydrate is oxidized. This suggests strongly that the primary breakdown is of carbohydrate, and that fat is used only in a secondary manner, *e.g.*, to restore the carbohydrate which has disappeared. These experiments of Krogh and Lindhard are particularly valuable since they were made on intact animals, namely, healthy men, and involved the complete process in the whole mechanism.

LACTIC ACID

The most important line of evidence in this connection starts from the work of Fletcher (2) and of Fletcher and Hopkins (3), leading to that of Meyerhof (6), Embden (4), (5), and others. The phenomena of muscular fatigue are known to all, both personally and in the laboratory, as also is the effect of oxygen thereon. An isolated muscle stimulated in nitrogen soon fatigues and never recovers: an isolated muscle stimulated in oxygen may go on contracting for days. These observations of Fletcher's led to the lactic acid story (3). In an isolated muscle at rest and without oxygen the acid accumulates slowly, faster at a higher temperature; with a sufficient supply of oxygen it remains at a low value. Stimulation also will produce lactic acid: in oxygen this lactic acid is removed. According to Embden and his coworkers, the origin of this lactic acid in the muscle is a hexose di-phosphoric ester. They succeeded in isolating an osazone similar to that described by Harden and Young in the case of yeast. This hexose phosphate is presumably a very unstable substance; it has not been isolated from muscle; its amount can be estimated only indirectly and on certain assumptions. Embden regards it as the immediate precursor of the lactic acid which appears, though Meyerhof's experiments make it clear that it is glycogen which bears a quantitative relation to lactic acid. The amount of Embden's "lactacidogen" present in a muscle at any moment must be estimated by measuring the inorganic P_2O_5 immediately after, and one or two hours after, the fine division of the muscle: the increase in the P_2O_5 is supposed to represent the "lactacidogen" which has broken down. The evidence, though indirect, appears to yield results so definite that it is difficult not to believe that hexose phosphate is somehow intimately concerned with muscular activity. After severe muscular work, following a dose of phloridzin in rabbits, and after strychnine convulsions in rabbits and in dogs, there is a marked diminution in the "lactacidogen" present in their muscles. It is interesting too to record that, according to a communication of Robison and Kaye to the British Biochemical Society, the injection of insulin causes an increase in the "lactacidogen" of muscle. It must be admitted, however, that the rôle of the hexose-phosphate is not yet clear.

THE CARBOHYDRATE ORIGIN OF LACTIC ACID

It is very natural to attribute a carbohydrate origin to the lactic acid which is concerned so intimately with muscular contraction. By the fermentation of various types of carbohydrate lactic acid may be formed, and Meyerhof (6) has shown by a series of direct experiments, confirmed by independent methods at Cambridge by Foster and Moyle (7) that when lactic acid appears in muscle, whether from anaerobic conditions or from fatigue, an equivalent amount of glycogen disappears; in the converse process of recovery when the lactic acid is removed, glycogen reappears, not this time in equivalent amount but with a 25 per cent. loss, which is accounted for by the oxygen used and the heat produced in the recovery process. In the isolated muscle, therefore, there can be no doubt that lactic acid has a carbohydrate origin and is restored to carbohydrate in recovery, a fraction of it only being used in the oxidative processes required to drive the recovery mechanism. That this recovery reversal of the glycogen-lactic acid breakdown is, at any rate in isolated muscle, carried out at the expense of energy derived from carbohydrate oxidation, is made the more certain by Meyerhof's observation that *the respiratory quotient of recovery is unity.* Moreover, in the isolated muscle there is no sign of any diminution in the fat contained in the muscle, as was shown by Winfield (8) and confirmed to some degree by later and more severe experiments at Manchester (unpublished). The total amount of glycogen present in a muscle is adequate to account for the whole of the energy used in the most prolonged series of contractions that that muscle is capable of carrying out in oxygen, even under the most favorable conditions (9). It is possible, of course, that no transformation or combustion of fat is possible without the cooperation of other organs (*e.g.,* the liver) or of the body as a whole. We shall see later how far this objection applies. In the isolated muscle, however, we may safely assert that the only processes which are known to occur, the formation of lactic acid from glycogen in the initial phase and the removal of the lactic acid, coupled with the oxidation of a small amount of it in the recovery phase, involve nothing but reactions with, and by, carbohydrate.

PANCREATIC CONTROL

Azuma and Hartree (10) have shown that insulin has no effect whatever on the recovery oxidation in isolated muscle, and Foster and Woodrow (11) that it has no effect on the lactic acid formation in resting surviving muscles. In intact animals under insulin treatment glycogen tends to disappear from the muscles (Dudley and Marrian (12)) possibly partly to form a hexose phosphate, certainly not to form lactic acid. Moreover, Himwich, Loebel and Barr (13) have found that lactic acid formation in the diabetic individual is just as much the basis of muscular contraction as in the normal. This has been confirmed independently by my colleagues Long, Lupton and Hetzel (hitherto unpublished), not only in the case of the formation of lactic acid but in that of its removal in recovery. Apparently lactic acid is just as much involved in the mechanism of contraction in the diabetic as in the normal man. That there is, however, some factor in the pancreas concerned in the carbohydrate metabolism of muscle was shown by preliminary observations of Hopkins and Winfield (14) in 1915, who found that pancreas preparations have an inhibitory action on the formation of lactic acid in minced muscle. Apparently in the pancreas there is a substance, stable at high temperatures, which has a controlling action on the carbohydrate breakdown of muscle. This substance is not a ferment, and may be present in commercial pancreas preparations several years old. Foster and Woodrow (11) followed up this clue and established the fact that there is an inhibitory agent for the anaerobic lactic acid formation in muscle, which may be isolated from the pancreas and produces considerable inhibition even under conditions leading usually to the maximum lactic acid formation. This substance is not insulin, which has no such effect. They suggest that this new unknown substance has a specific controlling function on the carbohydrate metabolism of muscle, and that carbohydrate metabolism may be grouped into two great subdivisions, that of the body as a whole under the control of insulin, and that of muscle, to some degree under the control of this new pancreatic hormone.

ANALOGOUS METABOLISM IN OTHER CELLS

An interesting side-line from Foster and Woodrow's experiments arises when we remember that, according to the modern view of muscle, the basal metabolism of the intact animal is in large part the recovery from the resting lactic acid production of its muscles. This new pancreatic hormone might be expected, therefore, to control the basal metabolism, and possibly we may find in it a means of antagonizing an over-activity of the thyroid—though that is guesswork. Foster and Woodrow, on the basis of these experiments, have put forward the theory of carbohydrate metabolism (just referred to) to which, on quite other grounds, those who have been working on muscular activity have been inevitably reduced, namely, that the carbohydrate metabolism of muscle is a different thing from that of the body as a whole. That this carbohydrate metabolism of muscle, how-

ever, involving lactic acid, is not unique is indicated by many lines of evidence. For example, Stephenson and Whetham (15) have found that *Bacillus Coli,* in a medium containing glucose, uses oxygen if it can get any, and produces CO_2 and lactic acid: in nitrogen, CO_2 and lactic acid are produced up to a certain limit, the fermentation being a self-inhibited one: in oxygen less lactic acid is produced, more CO_2 is liberated and more oxygen is used. Apparently these organisms, in the presence of sufficient oxygen, can break down glucose completely to CO_2 and water. In the absence of sufficient oxygen they break it down, as does muscle, to lactic acid. If suspended in a medium containing no glucose but ammonium lactate, in the absence of oxygen they can do nothing; in the presence of oxygen they can produce CO_2 and use up oxygen, as does a muscle carrying out its recovery process.

Again, Warburg (16), using the delicate gas-manometer method of Barcroft, has measured the CO_2 produced and the oxygen used by various tissues suspended in a glucose-Ringer solution. Some of the CO_2 is produced by combustion of carbohydrate, some is driven out from preformed bicarbonate by acid formation. Expressing as "extra CO_2" the amount of CO_2 produced in excess of that derived from the oxygen used in burning carbohydrate, the "extra CO_2" is a measure of the lactic acid produced by the fermentation of glucose, that is, of the carbohydrate broken down, while the oxygen used is a measure of the carbohydrate oxidized. Normal tissues give a ratio, (extra CO_2)/O_2 of practically zero. Cancerous tissues from a rat, however, give an average ratio of 3.6: human cancerous tissues give a ratio usually from 2 to 4, but varying over wide limits. In normal tissues, therefore, the oxidative process of glucose metabolism is effective and the fermentative process is small: in cancerous tissues the oxidative process is ineffective and the fermentative process is large. If Warburg is correct, the cancerous tissue *is like a muscle in which the recovery mechanism has almost broken down.*

GLYOXALASE

In all tissues of the body except the pancreas Dakin and Dudley (17) found a ferment, glyoxalase, which is capable of transforming methyl glyoxyl $CH_3.CO.CHO$ into lactic acid $CH_3.CHOH.COOH$. This ferment is inhibited by excessive acidity, that is, by an accumulation of the product of its own activity. It is present also in the blood of diabetic persons and in the blood and liver of diabetic dogs. An extract of the pancreas inhibits this reaction, and Dakin and Dudley have called this inhibiting substance *antiglyoxalase.* Antiglyoxalase is destroyed by heat, and on other grounds also it would appear not to be the same as the pancreatic hormone of Hopkins and Winfield, and of Foster and Woodrow. It is conceivable that the normal path of carbohydrate metabolism may lie through the formation of lactic acid by glyoxalase from methyl glyoxal; unfortunately, except for the presence of this potent enzyme glyoxalase, there is little evidence, either for or against this theory.

THE FATE OF LACTIC ACID IN RECOVERY

The fate of lactic acid, which is an undoubted intermediary in the breakdown of carbohydrate in the muscle, was long debated. Its removal during recovery, as established by Fletcher and Hopkins, was naturally credited at first to a simple process of oxidation. There were, however, certain fundamental difficulties about this to which there seemed to be no answer. The heat of combustion of glycogen, from which it is formed, is, according to Slater (18), 3,836 calories per gram, when the glycogen is in its fully hydrated form, as it occurs in solution in the muscle: that of dissolved lactic acid is 3,601 calories (Meyerhof), leaving a total energy for the transformation of the one to the other of only 235 calories. This small quantity then is the total energy available in the initial transformation of glycogen to lactic acid, while in the complete process, if the lactic acid were then oxidized, 3,836 calories would be liberated. The mechanical efficiency, therefore, of muscular contraction, supposing *the whole* of the initial energy were turned into work, could not exceed 6 per cent. Values of 25 per cent. have been found in the case of man. Actually the initial liberation of heat[2] per gram of lactic acid formed in muscle is larger than 235 calories, being about 296 calories. The difference has been attributed by Meyerhof to the neutralization of the acid by buffered alkaline protein salts inside the muscle fiber. There is no doubt that the acid is neutralized as soon as it is formed, since the hydrogen ion concentration does not rise appreciably. Moreover, there is not enough phosphate or bicarbonate present in the muscle to neutralize all the lactic acid formed. Neutralization by phosphate and bicarbonate liberates only a little heat, while that by buffered protein salts liberates a large amount. Even assuming, however, that 296 calories are liberated in the initial phase and that the whole of this energy is turned into work, if the lactic acid were then oxidized the efficiency could still be only 8 per cent. Clearly the lactic acid is not oxidized.

It has proved possible, moreover, to measure the total amount of heat liberated in the recovery process

[2] Total anaerobic (370 cals.) less delayed anaerobic heat (74 cals.)

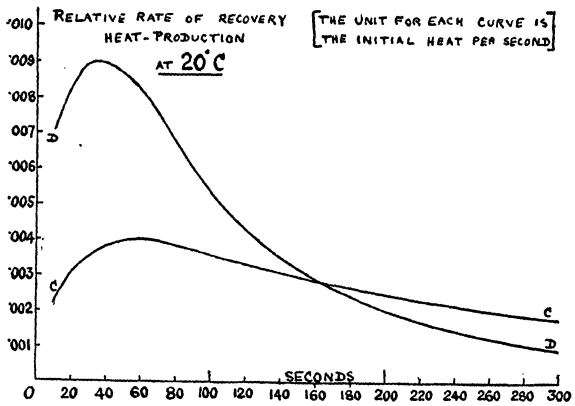

FIG. 1. Delayed heat-production of an isolated muscle in the presence of oxygen: C .03 sec. and D .20 sec. tetanus. (Hartree and Hill, 1922.)

(fig. 1), which in the latest and most careful measurements has come out almost exactly equal to the total heat liberated in the anaerobic phase. Thus, in the formation and the subsequent removal of a gram of lactic acid only 740 calories of heat are found, which is only about one fifth of what would occur if the lactic acid once formed from glycogen were subsequently oxidized *in toto*. Apparently of every 5 molecules of lactic acid removed in the recovery process only one is oxidized; the remaining four are restored to the place, or as the substance, from which they arose. There is no possibility of any error in the general conclusion to be drawn from these heat measurements: the difference to be explained is far too large; probably indeed the heat measurements provide us with the most accurate means of determining the "efficiency of recovery," as we may call it (or, in Meyerhof's term, the "oxidative quotient"), that is, the ratio of the amount of lactic acid removed to that oxidized in its removal. The best value to assume seems to be, in frog's muscle, about 5 to 1, and this is confirmed, as I shall show later, by two independent lines of experiment on man. This conception of the fate of lactic acid has been confirmed by Meyerhof's direct observations of the glycogen restored and the lactic acid lost during the recovery process. All lines of experiment, therefore, on the isolated muscle indicate about the same value for the efficiency of recovery. There is no doubt that one must regard lactic acid in muscle as being not so much the fuel as part of the machinery.

THE RECOVERY PROCESS

Consider now the recovery process in further detail. In the whole animal, without special precautions which we shall discuss later, it is not easy to isolate the recovery process from other events in the animal at large. In the isolated muscle the chemical method of investigation is not sufficiently analogous to what happens during normal existence, since the oxygen supply is cut off from its normal route by the cessation of the circulation, and (having to depend upon diffusion) is necessarily inadequate. *The oxidative removal of lactic acid in isolated muscle stimulated to severe fatigue has to take place under conditions of severe oxygen want, and is a very protracted affair.* The speeds, for example, at different temperatures can not be compared since they depend simply upon the rate at which oxygen can pass in, by diffusion from outside. Fortunately another method is available which, compared with the chemical method, is of surpassing sensitivity, namely, that in which the heat-production is measured (19). Myothermic technique is so sensitive, and so well under control, that it is possible to measure and to analyze the course of the heat production for many minutes after only a single twitch of the muscle, in which case the total amount of energy involved and the total amount of oxygen used are so small that the amount of the latter originally dissolved in the fluid of the muscle is more than adequate to account for the whole of the oxidation carried out. We are independent therefore of the oxygen supply, and can study the speed and magnitude of the recovery process in a muscle provided with an entirely adequate amount of oxygen.

We find, when we stimulate a muscle, that there is initially a large production of heat, which must be attributed to the formation of lactic acid from glycogen and its subsequent neutralization. Then commences a slow process of recovery, in which heat is liberated continuously for many minutes until the muscle has been completely restored to its initial condition. The heat production rises rapidly at first, attains its maximum in a few seconds to half a minute, and then slowly falls to zero again, along a curve which is roughly exponential. This curve of recovery heat production is the thermo-dynamic outline of the recovery process, into which fuller details must be drawn later by biochemical analysis. The speed of the process depends on temperature: it is increased very largely by a rise of temperature, decreased by a fall, so that in a frog at 0° C. complete recovery, even from a few hops, must take an hour or more! Extrapolating the results on frog's muscle to the temperature of the human body, the recovery process from moderate effort should be nearly complete in two to three minutes, given an adequate supply of oxygen: as indeed we find it to be. Its speed depends also on the size of the initial breakdown of which it is the result, not only absolutely

but relatively. Its speed is affected by the hydrogen ion concentration, being diminished by a rise and increased, up to a certain limit, by a fall, beyond which, however, it remains constant. Carbon dioxide, in concentrations of 10 to 15 per cent., produces a considerable fall in the rate of the recovery process, working much more quickly than do other acids, presumably because CO_2 can more easily penetrate the muscle fiber. The effect of hydrogen ion concentration on the speed of the recovery oxidation is analogous to that on the speed of autoxidation of glutathione or cystein. The total extra amount of heat liberated by oxidation in the recovery process is almost exactly equal to that set free in the anaerobic breakdown alone.

THE "ACCUMULATOR FUNCTION" OF MUSCLE

These facts have led us to the conception of the muscular machine as an accumulator of energy, analogous in its way to a lead electrical accumulator. The initial discharge, which may take place at a high rate, depends in no way on the oxygen supply: the final recharge, which is slower, depends directly on oxidation. In voluntary muscle all oxidation must be regarded as recovery oxidation: even though oxidation takes place during continuous exercise, and appears to be contemporary with the exercise, it must really be regarded as recovery from previous elements of the exercise.

It is probably not true to assert that in all organs and tissues oxidation is recovery oxidation. For example, Starling and Verney have recently shown that in a kidney secreting normally the administration of KCN, which abolishes oxidation, produces immediately a change in the secretion, making it in all respects similar to a filtrate from the blood. Apparently "knocking out" oxidation immediately "knocks out" the capacity of the tubule cells to perform their normal function. It is probable that the same immediate dependence upon oxidation exists in other tissues. Possibly those organs, in which sudden and violent activity may be required at a moment's notice and which are stimulated to activity through nerves, tend to act, as does voluntary muscle, like an accumulator: while slower tissues, in which rapid and violent response is not so necessary, may be content to remain dependent for their energy on oxidation, as does an internal combustion engine.

THE RECOVERY PROCESS IN MAN

The conception that all muscular oxidation is really recovery oxidation has produced an extensive change in outlook in regard to respiratory experiments on man. One of the fundamental difficulties of a large animal is the supply of oxygen to his tissues. When muscular exercise starts the oxygen intake rises, attaining a maximum in man in two to three minutes. Respiration and circulation have to be worked up and the recovery process has to get under way. Muscles, however, are required for immediate and violent use, and even the maximum intake of oxygen, which in athletic men is about 4 liters per minute, can provide energy only for comparatively moderate exercise; in order to attain even that maximum a period of two to three minutes is necessary. Actually the human body is capable of exerting itself nearly ten times as violently as it could possibly do were it obliged to obtain all its energy immediately by combustion. Just as a lead storage cell is found to accumulate sulphuric acid in the plates during its activity, so a muscle is found to accumulate lactic acid: just as the storage cell has its sulphuric acid removed from plates to solution during recharging, so the muscle has its lactic acid restored to its precursor in recovery. With this conception it is of interest to study the process of recovery not only in isolated muscles but in man, and in the last few years this study has proceeded a considerable way, especially by the efforts of my colleagues Long and Lupton. Lupton, alas, has not lived to reap the reward of his devoted work, or to realize the full importance of what he did.

LACTIC ACID IN MAN

Lactic acid may be studied directly in man by its estimation in blood removed in the usual way from a vein. During muscular activity the lactic acid in the blood rises, attaining finally, if the exercise be continued long enough, a maximum characteristic

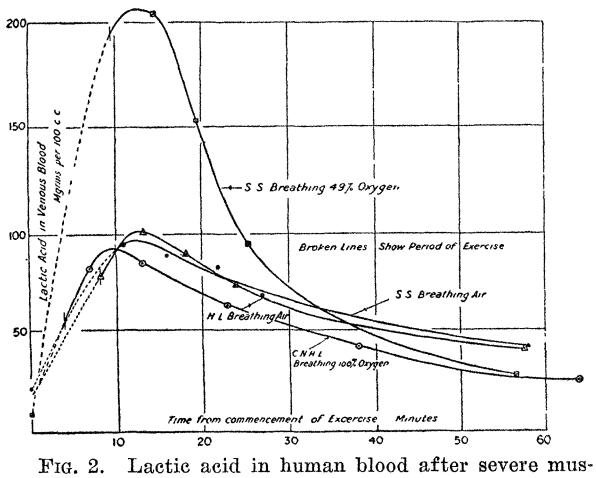

FIG. 2. Lactic acid in human blood after severe muscular exercise; two experiments in air, one in 49 per cent. oxygen, one in 100 per cent. oxygen. Note that the recovery process is not quite complete at the end of the time shown in the diagram. (Hill, Long and Lupton, 1924.)

of the effort made. After awhile the lactic acid distributes itself by diffusion equally in all tissues which are directly in contact with the blood stream. During recovery this lactic acid disappears, in a period depending upon the severity and duration of the preceding exercise but not exceeding, in normal man, about 90 minutes. (Fig. 2). The removal of lactic acid from the blood, which is a sign of its preceding removal from the muscle, is produced by oxidative processes occurring in the latter. These oxidations can be studied by ordinary respiratory methods, employing the Douglas bag technique. The initial phase of the recovery process, which is rapid and is concerned with the oxidative removal of the acid in the muscles where it was formed, can be followed by means of collections in a series of bags. The recovery oxidation falls rapidly, and after moderate exercise reaches zero in a few minutes. If, however, the exercise was severe, the lactic acid will have had time to escape from the muscles into the blood, and into other tissues in contact with the blood, and a second phase of recovery will occur, the removal of lactic acid which has escaped. This second phase may be very protracted and last as long as 80 minutes. The total oxygen used in the recovery process in this way we have named (20) the *"oxygen debt at the end of exercise."* Assuming, what may be shown to be very nearly true, that it is all used in the oxidative removal of lactic acid, and employing a value of 5.2 to 1 for the efficiency of recovery, we may calculate from the oxygen debt the lactic acid present in the body at the end of exercise. We find that *3 grams* or more of lactic acid may be liberated *per second* in the muscles of a powerful man, and that the body is able to tolerate an amount up to a *total of 130 grams*. The oxygen debt may attain a value of 18.7 liters!

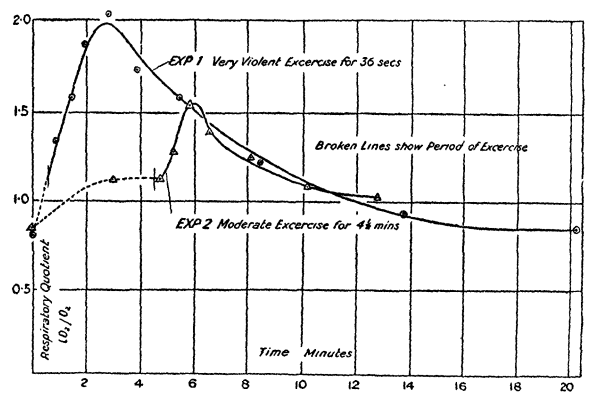

FIG. 3. The respiratory quotient during and after muscular exercise. These figures show the initial phase of recovery only. The final phase is shown in fig 4. (Hill, Long and Lupton, 1924.)

This lactic acid formation, therefore, in the human body is not a small or unimportant factor in muscular exercise; it is the keystone of the whole structure and has a large, indeed a preponderant, effect on the respiratory quotient (21). The respiratory quotient varies in a striking manner, up and down, during the onset of severe exercise and in recovery from it. At first it rises (fig. 3), attaining a value up to 2, during and immediately after the phase of lactic acid liberation, and while the respiratory center is still endeavoring to cope with the increased hydrogen ion concentration of the tissues. Before the hydrogen ion concentration of the body can have returned to its previous resting value an amount of CO_2 must be driven off equivalent to the lactic acid still present. After this previous level of the hydrogen ion concentration has been attained, which happens several minutes after recovery has commenced, the lactic acid continues to decrease and CO_2 has to be retained by the body, since otherwise the latter would become far more alkaline than previously. In the later stages of recovery the CO_2 retained is a measure of the lactic acid removed and very low values of the respir-

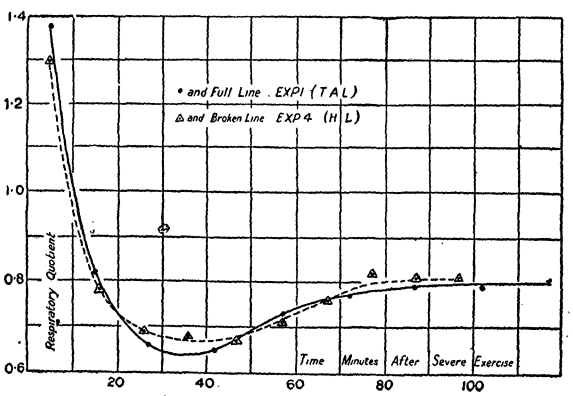

FIG. 4. The respiratory quotient after severe muscular exercise. Note that in the later phases, while carbon dioxide is being retained to compensate for that initially driven off, the respiratory quotient falls to a very low level, returning to its final value at about 80 minutes. (Hill, Long and Lupton, 1924.)

atory quotient may be found, down to 0.6 (fig. 4). Assuming this CO_2 retention to be a measure of the lactic acid removed, and the oxidation in excess of the basal value a measure of the lactic acid oxidized, we may determine in man the efficiency of recovery by respiratory methods, and its value comes to about 5 to 1, the same as in isolated muscle. Another method may be used in estimating the same quantity in man. If the lactic acid found in blood be assumed, in the later stages of recovery, to be uniformly distributed in all the soft tissues of the body which are in immediate contact with the blood stream, we

may calculate by two observations of the blood over any interval the total amount of lactic acid removed, and from the excess oxygen used in that interval we may again determine the ratio of lactic acid removed to lactic acid oxidized. We find as before a value of about 5 to 1, so that in the complete and intact animal the mechanism of recovery appears to be the same as in the simple isolated muscle.

THE USE OF THE RESPIRATORY QUOTIENT

These large variations in the respiratory quotient, during severe exercise and in recovery therefrom, show how necessary it is to exercise the greatest possible precautions if we wish to draw any conclusions from the respiratory quotient as to the substance being oxidized. Such precautions were taken in the experiments of Krogh and Lindhard. The exercise must be moderate and very long continued, and the whole condition of the subject, particularly the hydrogen ion concentration of his tissues, must be "steady." Then only are deductions reliable: *otherwise the value of the respiratory quotient tells us more about the fluctuations of lactic acid in the body than about the nature of the metabolism.*

THE OXYGEN "REQUIREMENT" OF EXERCISE

When muscular exercise commences the oxygen intake rises to a value which is either the equivalent of the exercise, if the latter be moderate, or is the maximum characteristic of the individual subject, if the exercise be severe. In the latter case the exercise can be continued only for a time, the lactic acid accumulates, fatigue comes on, and the muscles finally are incapable of further effort. The oxygen intake is a measure of the severity of the exercise *only* if the latter be (a) sufficiently protracted to enable a steady state to be attained and (b) sufficiently gentle to ensure that there is not a constant accumulation of acid leading to an oxygen debt. Hence by a study of the oxygen intake and the CO_2 output we can never really determine the nature of the primary oxidations of muscular activity, since the exertion must be continued for a long time until the body and all its processes are in a steady state, and the primary reactions of muscular recovery may then be masked by other and secondary effects. The oxidation of carbohydrate required to drive the recovery process may be confused for example with a reformation of carbohydrate from fat.

This fact and others have led us to a study of what we call the "oxygen requirement." The subject of the experiment takes exercise of any character and of any duration, the total organ used during the exercise and in complete recovery from it being measured. An initial and a final estimate of the resting oxygen consumption give us a base line from which the total oxygen consumption resulting from the exercise, during and in recovery from it, may be calculated. The measurement of the oxygen requirement is valuable, since it can be made in the case of any type of exercise, *e.g.*, walking up a single flight of stairs, or in very violent exercise which could not be continued long enough to make a measurement of the oxygen intake possible or useful. It may be a valuable criterion of the mechanical efficiency of work, etc. The oxygen requirement for a short element of exercise is always a measure of the total amount of energy required by the body for that exercise, assuming, as we shall see below, the energy value for oxygen corresponding to the oxidation of carbohydrate.

THE R. Q. OF EXERCISE AND RECOVERY

Much greater interest attaches to the respiratory quotient when we consider, not only exercise, but subsequent recovery. Taking the case of a small element of muscular exercise, such as running slowly for 30 seconds, the resting respiratory exchanges are measured carefully, both before the exercise and after complete recovery. The expired gases are collected both throughout the exercise, and during a recovery interval sufficiently long to ensure that the metabolism has returned absolutely to its initial state. The *excess* oxygen used as a result of the exercise and the *excess* CO_2 given out are then determined by analysis and calculation: *they are found to be precisely equal.* The same is true of fairly violent exercise for a short interval. In the case, however, of very violent exercise, the recovery process may be very protracted and the respiratory quotient of the excess metabolism may be less than unity. If the extra metabolism of a very long period of exercise be measured, it is obvious that the respiratory quotient will not be unity. In such a case nearly all the excess of oxygen used and of CO_2 produced by the exercise occurs during the latter, while the respiratory quotient is say 0.85. Thus, as we should expect, when a bout of exercise is increased in duration from very short to very long, the respiratory quotient of the complete cycle passes gradually, from a value of unity for the very short, to a lower value characteristic, as in the experiments of Krogh and Lindhard, of prolonged steady exercise. These results appeared first incidentally in a study of the oxygen requirement of exercise, carried out for another purpose. We noted, however, that of about twenty experiments practically all gave a respiratory quotient of the excess metabolism of about unity, the mean value being 1.03 (21). The small excess we attributed to the fact that in these experiments recovery was

not quite complete, and the small CO_2 retention of the last phase had not come within our observation. Since then my colleague Dr. Furusawa has examined the matter more carefully. His experiments (see Tables I and II) show that the respiratory quotient of the excess metabolism due to a *short element* of muscular exercise is unity. This is the case, even if the subject, having lived for several days on a diet of fat and protein, has a resting respiratory quotient of little more than 0.71 (Table II). If the exercise be prolonged the stores of carbohydrate are used up and have to be reformed by the transformation of other substances, presumably of fat; such a transformation acts upon the respiratory quotient just as though fat itself were being oxidized, so that the respiratory quotient falls. Given, however, an element of muscular exercise, so moderate in duration and severity as to produce no measurable carbohydrate lack in the muscles and no disturbance of metabolism in the rest of the body, we find that *the whole oxidative cycle of recovery is carried out at the expense of carbohydrate.*

TABLE I.—(*Unpublished experiments by K. Furusawa*)

NORMAL DIET

R. Q. of Excess Metabolism Due to Exercise

Duration or Exercise Mins.	Steps per Min.	Duration of Collection Mins.	Excess Metabolism CO_2/O_2	R. Q.
0.5	92	10	355/350	1.00
0.6	64	10	485/490	0.99
1.0	146	20	2120/2037	1.04
1.0	160	31	4185/4048	1.03
2.0	208	76	11230/10251	1.09
10	120	60	8720/8900	0.98
12	160	85	19860/18620	1.06
15	146	77	25670/25960	0.99
20	146	110	41310/42210	0.98
28	146	63	49520/52900	0.94
30	120	70	20225/20345	0.99
30	146	105	49420/56230	0.88

Not postabsorptive but several hours after a meal.
Average R. Q. resting = 0.85
Average R. Q. excess metabolism = 1.02
(Up to 30 liters O_2.)

TABLE II

(Unpublished experiments by K. Furusawa)

FAT DIET

(Bacon, Butter, Milk, Fat Chops)

R. Q. of Excess Metabolism due to Exercise

Subject	Duration of Exercise Mins.	Steps per Min.	Duration of Collection Mins.	Excess Metabolism CO_2/O_2	R. Q.	Compare R. Q. at Rest
K. F.	0.33	272	22	2733/2570	1.06	0.72
K. F.	1.0	146	20	2400/2260	1.06	0.71
K. F.	2.0	146	30	3020/2964	1.02	0.75
K. F.	4.0	146	43	10525/10822	0.97	0.78
K. F.	7.0	146	50	13730/15145	0.91	0.72
K. F.	9.0	146	100	18910/19940	0.95	0.76
K. F.	9.0	146	88	18835/20420	0.92	0.77
J. L. P.	0.4	216	22	3260/3341	0.98	0.77
J. L. P.	0.5	196	25	2132/1966	1.08	0.77
J. L. P.	1.0	146	26	3300/3345	0.99	0.73
J. L. P.	1.0	162	24	5255/5256	1.00	0.75
J. L. P.	5.0	146	35	12910/13775	0.94	0.75

Fatty diet, K. F. five days, J. L. P. 3 days, before exps.

This confirms and amplifies the experiments of Krogh and Lindhard with which we started this discussion, and makes clear how the experiments on the isolated muscle, with their indication that carbohydrate is the essential fuel of muscle, may be reconciled with the respiratory quotients obtaining in prolonged moderate exercise in man. *The primary fuel of muscle is carbohydrate: the essential element in the machinery is lactic acid, itself derived from carbohydrate.* The breakdown of carbohydrate in muscle is associated with the presence of phosphates, possibly in the form of a hexose diphosphoric ester. What the further details of the process are we do not know, but it is difficult not to believe that the utilization of fat by muscles can occur only after its previous "conversion" somewhere in the body. Even a subject suffering from severe carbohydrate want (Table II) will oxidize carbohydrate, and carbohydrate alone, in the complete cycle of reactions resulting from an "element" of muscular exercise.

A. V. HILL

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GENERAL POLICIES OF THE CARNEGIE CORPORATION[1]

DURING the year comparatively little time has been required for the study of specific new enterprises, for the obvious reason that funds were not available to finance them. As a result, the trustees have been free to devote their energies primarily to the formulation for their own guidance of a tentative body of doctrine as to the general policies of the corporation, and more specifically to a consideration of the fields in which, for the present at least, it should concentrate its efforts. Some discussion of the principles underlying these policies may be of service in making more clearly understood the problem which faces the corporation with reference to any particular grant; for this problem is not a simple one, depending wholly, or even primarily, on the merits of that particular proposal, but a very complex one, involving a number of other factors which must also be taken into account before an intelligent decision can be reached. It should be said at the outset that certain of these factors have already been dealt with in the reports of the acting president for 1922 and 1923, and that the following paragraphs are to be regarded, therefore, as supplementary to the discussions in those reports, rather than as an attempt to cover even the most important elements in this many-sided problem.

[1] From the annual report of the president of the Carnegie Corporation of New York.

It may be of interest at this point to give some indication as to the number of those who in any one year have more than a theoretical interest in these questions. Apart from the projects brought up for consideration by the members of the board itself or presented on behalf of the boards of other Carnegie enterprises, the corporation acted last year on 397 applications. Of the cases in which a budget was submitted with the application, the amount asked for came to more than $40,000,000. In only 68 cases could any grant be made, and of these 33 were renewals of grants made in former years. It would serve no useful purpose to make public a list of the projects declined, but both the applicants and the public may be assured that one and all received consideration by the executive committee, and were brought by it to the official attention of the board, the action taken in each case being made parts of its records.

Turning now to the general questions of policy to which reference has been made, the corporation has given particular attention during the year to the following: the responsibility of educational foundations to the public and to public opinion; the relation between the diffusion of knowledge and the guidance of opinion; factors affecting the limitation of program; and relations with operating agencies.

PUBLIC OPINION

It is now generally recognized that there is no fundamental distinction between the responsibilities of universities supported primarily by public taxation and those of institutions supported primarily by private endowment—both are public institutions. It must also be recognized that educational endowments such as the Carnegie Corporation are essentially public and not private enterprises. Grants made by them are matters of public concern and, other things being equal, they should involve the largest possible degree of public participation in what is recognized on all sides to be a cooperative enterprise. It will not do for those in charge of such endowments to assume that so long as their own motives are completely disinterested, criticism as to their acts and policies should be limited to the wisdom of this or that particular grant. They must recognize that doubts as to the basic social utility of these organizations have long existed in the minds of men and women regarding whose sincerity there can be no question, whatever may be said as to the amount and accuracy of their information. While, for the moment at any rate, the extraordinary results which have been achieved through the grants of these bodies, particularly in the alleviation of human suffering, have operated strongly to increase public confidence,