MUSCULAR EXERCISE, LACTIC ACID, AND THE SUPPLY AND UTILIZATION OF OXYGEN

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Contents.

Introduction.

Modern progress in knowledge of the behaviour of muscle started from the researches of Fletcher (11, 12, 13) on the respiration of muscular tissue, and has been guided since by that landmark in exact physiology, the investigation by Fletcher and Hopkins (14) of lactic acid in surviving muscle. Hence arose a long series of investigations by many workers on the heat-production, the gaseous exchange, and the lactic acid and glycogen content of muscle; these have been summarized elsewhere (21, 23, 24). The insight thus acquired of the intimate physical and chemical mechanisms of the living muscle exceeds that of any other cell or process. In muscle we have several independent but convergent lines of progress, chemical, physical, and mechanical, and it is possible already to see, often not too dimly, from one to the other. Our knowledge is not, of course, in any single direction complete: it seemed sufficient,

however, to warrant an attempt to press to their logical conclusion, in the case of man, the principles established in working on isolated muscles, while it was to be hoped that such an attempt would throw further light, and suggest further lines of attack, on the more academic problems of the pure physiology of muscle. Hitherto, apart from an occasional reference to lactic acid in connexion with respiration, dyspnoea, or fatigue, there has been little realization of the extraordinary vigour of the chemical processes which occur in muscle, or of the clearness of the principles which govern them. With the generous help of the Medical Research Council the attempt has been made, and the following is a summarized account of some aspects of it, which we believe perhaps may be pertinent to medicine. During the course of our work it has been a continual surprise and incentive to find how precisely the principles established in the case of isolated frog's muscle are verified in the case of muscular exercise in normal man: and we have been encouraged thereby to hope that perhaps these same principles may be found already to bear some tentative application to the case of muscular exercise in the abnormal, and (among other things) to the phenomena of breathlessness.

We have adopted throughout the standpoint reached in modern investigation of the isolated muscle, and have attempted to show, by experiment and deduction, how application may be made to normal man. We have avoided more than an occasional reference to the possible clinical aspects of the facts and principles discussed.

A. *The Function of Oxidation in the Body.*

Oxygen is used in the combustion of food-stuffs to supply the energy required for bodily processes. Even in a state of complete rest the living cell requires oxygen in order to maintain its dynamic state of molecular organization, of readiness and power to respond to a stimulus. It is well known that a nerve deprived of oxygen gradually fails to conduct an impulse, though the amount of oxygen used is exceedingly small (1). In muscle the resting rate of oxygen consumption is much larger, but it has long been known that, especially at relatively low temperatures, a muscle will maintain its excitability for considerable periods in the complete absence of oxygen. This was believed to be due to the supposed fact that oxygen is taken in and stored in the living protoplasm for use in later need ('intramolecular oxygen'). There is no truth in this belief. The most rigorous exclusion of oxygen, even the entire prohibition of oxidation by poisoning with cyanide (46), still leaves the muscle active for a considerable period. Moreover, the magnitude of the 'initial' heat production[1] in a muscle twitch (45), and its time-relations (15), are totally unaffected by the presence or absence of oxygen. *Oxygen is not used in the primary break-down processes of rest or activity,* which proceed uninfluenced

[1] i. e. the heat liberated in the phases of contraction and relaxation, as distinguished from recovery.

for a time by its complete absence: *it is used only in what, strictly speaking, may be called recovery processes.*

If a living, resting, isolated muscle be deprived of oxygen it survives for a while; if the process be not pushed too far, and oxygen be restored to the muscle before it is too late, it then proceeds to make good its previous deficit in oxygen intake by a rise above its earlier resting value. If an isolated muscle be stimulated in oxygen there is a prolonged rise in its oxygen consumption, lasting for some time after the stimulus: if the muscle be stimulated in a chamber free from oxygen, and then, later on, oxygen be admitted, the rate of oxygen consumption rises above normal, and the total oxygen used in a long survival period is the same as if oxygen had been present throughout. The same phenomena, within limits, can be demonstrated in man. It is not practicable to deprive a man, as a whole, of oxygen: the brain is too sensitive to oxygen want. It is practicable, however, to deprive the human muscle of oxygen, in the sense that it is possible for a healthy man to take muscular exercise requiring far more oxygen than can conceivably be supplied through the circulation during the exercise itself, and to establish a heavy 'oxygen debt': indeed, as the result of 24 secs. only of severe exercise in a powerful man, we have found a total oxygen intake during the following 30 minutes of about $8\frac{3}{4}$ litres in excess of the resting value: 24 secs. of exercise led to a delayed consumption of oxygen sufficient to keep the subject comfortable in bed for more than half an hour. In another experiment more prolonged violent effort led to an oxygen deficit of $13\frac{1}{4}$ litres. Were it not for the fact that the body is able thus to meet its liabilities for oxygen considerably *in arrears*, it would not be possible for man to make anything but the most moderate muscular effort. We will consider this more fully later. It is obvious, however, that we must regard the muscle as capable of 'going into debt' for oxygen, of *committing itself to future oxidations on the security of lactic acid liberated in activity.*

We must distinguish therefore between three different quantities—oxygen 'intake', oxygen 'consumption', and oxygen 'requirement'. The first two may differ slightly, in so far as oxygen may (*a*) be taken in, in excess of consumption, to saturate blood previously reduced; and (*b*) be used in excess of intake at the expense of blood previously saturated: the difference is small. The third, however, may differ widely from the others, to the extent that 'expenditure' may largely exceed 'income', so long as the 'security' remains adequate. In the body the 'security' reaches its limit at the lactic acid maximum, and any further expenditure must be made out of 'income' of oxygen through the lungs and circulation. The 'security' given, lactic acid then forces the body later to pay off its debt out of income, in oxidative recovery.

B. *The Rôle of Lactic Acid in the Muscle.*

Lactic acid holds a very special position in the economy of the muscle. Like gas in the internal combustion engine its oxidation provides the power

required to do external work: like the gas, also, it is intimately concerned in the mechanism by which the work is done. It appears to be derived from the glycogen stored within the muscle, either directly or through the intermediation of a hexose diphosphate. In activity, or in prolonged rest without oxygen, lactic acid appears in the muscle (14): in recovery it reverts to glycogen, a small portion only being oxidized (35) (36). If an isolated muscle be kept at rest in oxygen, no lactic acid appears; it finally becomes inexcitable, but does not show the phenomena of *rigor mortis*. If the muscle be deprived of oxygen at rest, or if it be stimulated, lactic acid accumulates within it and corresponding glycogen disappears (36). Deprival of oxygen pushed to its limit means *rigor mortis* and a lactic acid maximum of about 0·5 per cent. to 0·65 per cent.: stimulation, pushed to its limit, means inexcitability and a 'stimulation maximum' of lactic acid of about 0·24 per cent. to 0·4 per cent. Continued lack of oxygen, in a muscle stimulated to a standstill, leads to further lactic acid production and death. The introduction of oxygen to a muscle fatigued by stimulation, or by prolonged lack of oxygen, leads to an oxygen consumption and a heat-production far above the normal resting values, to a disappearance of lactic acid, and to a restoration of the glycogen: the muscle regains its previous excitability, recovery has occurred, and a subsequent stimulus will release lactic acid again. Moreover, Meyerhof has shown: (*a*) that the excess oxygen[2] and the excess CO_2 are equal, that the recovery process therefore has a respiratory quotient of unity, and involves the oxidation only of carbohydrate (or lactic acid); (*b*) that the oxygen and the CO_2 correspond to the total carbohydrate lost by oxidation in the complete cycle; (*c*) that when lactic acid appears glycogen always disappears in exactly corresponding amount; (*d*) that when lactic acid disappears in recovery, glycogen always reappears in corresponding amount, *less a quantity which, calculated from the oxygen consumption, has been lost by oxidation*; (*e*) that only about one-fourth of the lactic acid removed in recovery is oxidized: three-fourths has reappeared as glycogen.

Moreover, Meyerhof has shown (37) that the same phenomena occur, in an exaggerated degree, in muscle which has been finely chopped. Here, in the absence of oxygen, there is a rapid production of lactic acid: in the presence of oxygen the production of lactic acid is less, there is still a recovery process: the lactic acid, however, which has failed to appear has *not* been oxidized, since the total oxygen absorbed is only about one-fifth of the quantity which would have been required to complete the oxidation of that amount.

It is probable, from the work of the Embden School (9), that a hexose diphosphate $[C_6H_{10}O_4(H_2PO_4)_2]$ is an intermediary between glycogen and lactic acid, that it may indeed be the immediate precursor of lactic acid, the 'lact-acidogen' whose explosive transformation into lactic acid, on stimulation of the muscle, initiates the contractile process. Embden showed that, in muscle extract, glucose cannot be broken down into lactic acid, while hexose diphos-

[2] 'Excess oxygen' and 'excess CO_2' are used throughout this paper to express the amount of gas used, or produced, in excess of the resting value, in any given time.

phate can. Moreover, Meyerhof (37) has shown that only in the presence of phosphate can minced muscle transform all its preformed glycogen into lactic acid. Apart from these observations, the chemistry of the break-down and restoration of glycogen in the muscle remains at present a mystery. That phosphoric acid, however, has some special rôle in the process is shown by Embden's work, and it is of unusual interest that Embden, Grafe, and Schmitz (10) found the maximum muscular output of trained men to be considerably increased by the ingestion of phosphates.

C. *Heat-production.*

The contraction of a muscle has long been known to be accompanied by a production of heat: this heat appears more or less simultaneously with the mechanical response. Recent experiments, however, by A. V. Hill (20) and by Hartree and Hill (17) have shown that there is a further extensive production of heat, long delayed after the stimulus which caused it. In an isolated muscle stimulated in oxygen there is a prolonged evolution of heat, lasting for several minutes, which all evidence tends to connect with the oxidative removal of lactic acid in recovery (see Section N below). This recovery heat-production has told us much about the time-relations and other characteristics of the restoration process, following muscular activity. Other experiments by A. V. Hill (19), by Peters (40), and by Meyerhof (38), have shown that the total heat liberated in the anaerobic production of 1 grm. of lactic acid in muscle is about 370 calories. In its later oxidative removal (17) there is a further liberation of about 340 calories. In the complete cycle, therefore, in which 1 grm. of lactic acid is liberated and removed, and the muscle finally restored to its original state, there is a total evolution of 710 calories. But the heat of oxidation of 1 grm. of lactic acid is about 3,788 calories. Hence only a small fraction of the lactic acid can have been oxidized in recovery: in a muscle lightly stimulated, and with an adequate supply of oxygen, only about one molecule in five or six of the lactic acid is oxidized, the remainder being restored as glycogen during the recovery process.

Further experiments by Hartree and Hill (15) have shown that, in addition to this recovery process, there is an evolution of heat—(*a*) during the onset, (*b*) during the maintenance, of a contraction, and (*c*) during relaxation, and the analysis of these has led to the following picture of the mechanism involved. The muscle is to be regarded as an accumulator of energy, energy available for rapid non-oxidative discharge, stored during previous oxidations. In this respect it is similar to an electrical accumulator. The transformation of glycogen into lactic acid, the action of the lactic acid on the muscle proteins, and the neutralization of the lactic acid by the alkaline buffers of the muscle, are the vehicle by which this stored energy is made manifest: during recovery the process is reversed at the expense of a portion of lactic acid oxidized. The accumulator has been recharged, at the expense of oxidations required to run the dynamo.

We must regard the muscle therefore as possessing two mechanisms: (*a*) the anaerobic one of discharge, and (*b*) the oxidative one of recovery. These two mechanisms are probably distinct from one another; the first may certainly act without the second, the second without the first, and their efficiencies may vary independently. The speed, vigour, and efficiency of contraction and the speed of relaxation depend upon the first one: the speed and efficiency of recovery depend upon the second.

The production of lactic acid during contraction, which is probably the ultimate cause of the mechanical response, must be regarded as being very sharply localized within the muscle fibre. Its sudden appearance probably changes the electrical and colloidal state of certain sensitive protein interfaces in the muscle, producing a rise of tension and the phenomena of contraction. During relaxation, a process just as important as contraction though largely neglected by physiologists, the acid is removed from its place of action through neutralization by the alkaline buffers of the muscle. The physical problem of how the acid produces the contraction has not yet been solved, but whatever be the mechanism, its reversal in relaxation would appear to be due simply to the withdrawal and neutralization of the acid whose presence locally in high concentration evoked the response. This affords a simple explanation of the delayed relaxation associated with fatigue: the neutralization of lactic acid has rendered the muscle less alkaline, and further neutralization is slower and less effective.

D. *The Efficiency and Speed of the Recovery Process*

(which will be referred to further in Section N below) appear to depend upon the condition of the muscle. The 'efficiency' may be measured by the ratio (total lactic acid removed) : (portion of lactic acid oxidized), as found in oxidative recovery. In the experiments of Hartree and A. V. Hill (17) this ratio appeared to vary from 4·9 : 1 to 6 : 1, with a mean of about 5·5 : 1; in Meyerhof's experiments (35, 36) it was about 4 : 1; in the former experiments the supply of oxygen was adequate, the muscles were never fatigued, and recovery was rapid; in the latter the contrary was the case and recovery was correspondingly less efficient. It would seem probable that the efficiency of recovery in a healthy trained man is at least as high as in an isolated frog's muscle; we shall assume therefore in what follows a figure of 6 : 1 for the ratio

(total lactic acid removed) : (lactic acid oxidized)

in the recovery process of a healthy normal man.

In the isolated muscle the 'speed' of recovery is best measured by experiments on the recovery heat production (17). Like that of all chemical reactions it depends on the temperature, increasing 2 to 3 times for a rise of 10° C. It increases rapidly with the oxygen pressure. It increases with the magnitude of the effort from which recovery is necessary. It depends presumably upon the katalytic oxidative activity of surfaces inside the living cell. The oxygen pressure in the muscle increases in man with the vigour of the circulation and

the efficiency of the lungs. Moreover, the oxidative activity of a cell may be changed in various artificial ways, e.g. it may be diminished by narcotics or cyanides (Warburg (44)). It is natural therefore to assume that the velocity of oxidative recovery in human subjects may vary similarly—not only in accordance with the oxygen supply, but with the more intimate physico-chemical characteristics of their muscle cells.

E. *The Production of Lactic Acid in Man.*

After severe exercise lactic acid appears in the urine (Ryffel (42)). The amount however is small, and is no measure whatever of the quantity which has appeared in the body. The most obvious tokens of the latter are (*a*) the magnitude of the oxygen debt, and (*b*) the increased respiratory quotient, following severe exercise. It would seem probable that carbohydrate alone provides the energy for the excess metabolism of exercise: this certainly appears to be the case in isolated muscle (33). In moderate, prolonged, steady exercise therefore, in which the concentration of lactic acid attains a steady value in the muscle, the respiratory quotient approximates to unity. As soon, however, as the exercise reaches a severity greater than can be maintained on a contemporary supply of oxygen—as soon as the level of exercise is reached at which lactic acid must continue to accumulate throughout it—the respiratory quotient rises above unity, CO_2 is turned out by lactic acid, sodium (or potassium) lactate being formed from the bicarbonate of blood and tissue fluids. In our observations the extreme upper value of the apparent respiratory quotient (R.Q.) of the excess metabolism, after exercise, has been 2·6: assuming a real respiratory quotient of 1, this means that for every gramme-molecule of O_2 being used, and for every gramme-molecule of CO_2 being produced, 1·6 gramme-molecules of CO_2 were being turned out by lactic acid from bicarbonate.

Now in moderate exercise the main part of the lactic acid liberated in the muscle does not combine with bicarbonate. This is clearly shown in Section M below, and can be substantiated on the isolated muscle. The heat produced in the process of relaxation (as found by Hartree and Hill (15)) is far larger than that corresponding to the neutralization of lactic acid by bicarbonate, and Meyerhof (38) has suggested that the neutralization associated with relaxation is effected by the buffered alkaline proteins of the muscle tissue itself, according to the scheme, (lactic acid) + (sodium protein salt) → (sodium lactate) + (acid protein). This corresponds exactly to what we believe to be the mechanism by which acid is neutralized (and CO_2 carried) in blood (39), *and is capable moreover of providing adequate heat.* Thus, in moderate exercise, the protein buffers of the muscle should be capable of neutralizing all the acid formed, little CO_2 should be driven out, no dyspnoea should occur, and the R.Q. of the excess metabolism should remain at unity. In severe exercise, on the other hand, an excess of lactic acid is produced for which the supply of protein buffers is inadequate, the hydrogen-ion concentration rises, the respiratory effort increases,

and CO_2 is turned out of bicarbonate in muscle and blood. Hence the R.Q. rises above unity, its rise being an index of the amount of acid combining with bicarbonate. On the qualitative side therefore—by the examination of the urine after severe exercise—we know that lactic acid is produced in man and escapes in small quantities into the blood: on the quantitative side, the very great rise of the R.Q., during and after violent effort, is a sign that the acid production is considerable. In the next section we shall show how the 'oxygen debt' may be used as an indicator of the absolute amount of lactic acid present in the body at the end of exercise.

F. *Lactic Acid and Oxygen Debt.*

The 'oxygen debt' is defined as the total amount of oxygen used, after cessation of exercise, in recovery therefrom. It may be measured in man in the following simple manner. Firstly, the resting rate of oxygen intake of the subject is determined by the Douglas bag method in some standard position (standing, sitting, or lying). The exercise is then taken. Immediately on its cessation the subject begins to breathe from the air into a large Douglas bag, remaining at rest in the standard position throughout recovery. We have used bags of capacities *400*, *300* and *200* litres. If one bag be not sufficient, a second one may be used and two analyses made. In experiments described in Section H, on the time-course of recovery, a series of bags was employed, in fairly rapid succession throughout the recovery period, and such experiments have told us how long it is necessary in general to collect the expired gases. After moderate exercise the oxygen intake will return to its resting level in about 6 to 8 min.: after very severe or exhausting exercise it may remain high for a much longer time. The total oxygen used in the selected recovery period is then determined by analysis and measurement in the usual manner. From this is subtracted the oxygen which the body would have used in the same time at rest. The difference represents the oxygen debt at the end of the exercise.

There are four possible objections to this method: (*a*) At the end of exercise a certain amount of oxygen is lacking, which at rest is dissolved or combined in blood or tissues, and this quantity is included in the figure determined as above. It can be calculated, however, that this error is almost negligibly small, at any rate in the case of oxygen debts of several litres. (*b*) One cannot be sure that the oxygen intake has returned to normal, after a selected period of recovery, unless special observations be made to prove that it has. This objection is admitted. The error, however, is always in the same direction, viz. in that of making our observed oxygen debt too small: we have endeavoured always to allow an adequate recovery period, and in some observations (see Section H below) we have followed the rate of oxygen intake throughout. We can claim anyhow that our observations are certainly not too large. (*c*) The oxidations of recovery may replace in part the normal resting oxidative processes: e.g. if part of the resting metabolism be due to the necessity of producing heat to keep the body warm, this part could safely be omitted by the body during recovery from exercise, when loss of heat, rather than its

production, may be important. This objection also is valid. The error however cannot be very large, and in any case it will cause our observations again to be too low, so that again we may claim them as minimum values. (*d*) Part of the oxygen debt observed may be due to the excessive movements of heart and respiratory muscles occurring during recovery: these movements, however, rapidly slacken, and cannot in any case account for more than a small fraction of the considerable oxygen debts found, especially after they have slackened. On the whole, therefore, we may regard our results as reasonably accurate statements of the oxygen required in the metabolic processes of oxidative recovery.

No process is known to occur in muscular exercise in man which is not apparent in isolated muscle, and we shall now assume that the recovery oxygen, measured as above, is used entirely in the oxidative removal of lactic acid. The oxidation is as follows: $C_3H_6O_3 + 3\,O_2 \rightarrow 3\,CO_2 + 3\,H_2O$. Now, if the 'efficiency' of recovery be assumed to be six in the sense defined above, i.e. if a total of six molecules of lactic acid disappear in recovery for every one oxidized, then six molecules of lactic acid will be removed for every three molecules of oxygen used, or two gramme-molecules of lactic acid (i. e. 180 grm.) for every gramme-molecule of oxygen (i.e. 22·2 litres). This means that *an oxygen debt of 1 litre betokens the presence in the body, at the end of exercise, of about 8·1 grm. of lactic acid.* The following table gives the magnitude of the oxygen debt, at the end of various types of exercise, in several different individuals, together with the total lactic acid content of the body calculated therefrom:

TABLE I.

Subject.	Weight Kilos.	Exercise.	Oxygen Debt. c.c.	Total Lactic Acid. grm.
H	73	Flat running at speed of 191 metres per min., for 5 min. 8 secs.	1668	13·5
H.	—	Flat running at speed of 201 metres per min., for 4 min. 18 secs.	2485	20·1
H.	—	10 secs. violent jumping with skipping movement	2510	20·3
H.	—	20 secs. violent jumping with skipping movement	5504	44·6
H.	—	Flat running for 3 min. 23 secs. at a speed of 239 metres per min., i. e. at a speed causing an increasing debt of oxygen	2870	23·3
H.	—	Flat running for 33 min. at a speed of 239 metres per min. Practical exhaustion	7890	64·0
L.	65	36 secs. violent jumping with skipping movement	5700	46·2
L.	—	Flat running at speed of 261 metres per min. for $4\frac{1}{4}$ mins.	7160	58·0
L.	—	Jumping over stool 14 inches high for 2 min. 7 secs.	10499	85·0
W. M. H.	72·5	Violent gymnastic exercises for 30 secs. involving rapid contractions of all the muscles, leading to exhaustion	7670	62·1
		Ditto preceded by a rapid $\frac{1}{4}$ mile run	13250	107·2
S.	68·55	Ditto for 30 secs.	6455	52·3
M. W.	79·9	Ditto for 32 secs.	7810	63·3
W.	—	Flat running, 225 yds. in 23·4 secs.	8745	71·0

We see therefore that large quantities of lactic acid may be produced in the body, certainly up to 1·5 grm. per kilo of body weight. The extreme rapidity with which it can be produced is notable, as is shown by the last entry in the table, where over 3 grm. per sec. were being liberated by a powerful individual running 225 yds. at top speed. Even moderate exercise, such as running at about 7 miles per hour, leads to the production of about 13 grm. of acid in the body. It must not be supposed that this lactic acid occurs only in the absence of oxygen. There is a balance, even at rest, between lactic acid being produced and lactic acid being removed, as will be shown in Section I, dealing with the 'steady state'. The more vigorous the exercise the higher the level of the lactic acid at which the balance occurs, and the greater the oxygen debt at the end of exercise. If, however, the severity of the exercise be too great the supply of oxygen cannot cope with the production of lactic acid, no balance is attained, and exhaustion rapidly sets in.

G. *The Lactic Acid Maximum and the Limit of Muscular Exertion.*

Stimulation of the isolated muscle leads to a so-called 'stimulation' or 'fatigue' maximum of the lactic acid content, which was supposed at one time (14, 21) to depend upon a limit in the amount of the lactic acid precursor. This, however, is not the case. Meyerhof has shown (37) that the immersion of the muscle in a solution of alkaline phosphate buffers may considerably increase the stimulation maximum of lactic acid. Apparently the limit is set by the rise in the hydrogen-ion concentration (cH) effected by the presence of the lactic acid itself, and may be increased if the rise of cH be hindered by the presence of extra alkali. This is a very important observation, as we shall see below, in explaining the differences in maximum effort between different human subjects. It was found also by Meyerhof that the stimulation maximum is practically the same for indirect as for direct excitation: his values range from 0·24 per cent. to 0·43 per cent. Let us assume that a human subject, as the result of a supreme effort, can produce some 0·3 per cent. of lactic acid in all the active muscles involved in violent running, jumping, or skipping. These muscles, in an active 70-kilo man, might weigh about 25 kilos: this figure of course is necessarily a matter of estimation. The total acid present therefore would amount to 75 grm. Hence, if the recovery removal of 8·1 grm. of lactic acid be secured by the intake of 1 litre of oxygen, the oxygen debt in this case of extreme effort should amount to $75/8{\cdot}1 = 9{\cdot}3$ litres. Table I above contains several observations on the oxygen debt found in cases of severe and exhausting exercise. Thus H. running for 33 min. at a rate at which the oxygen requirement exceeded the maximum oxygen intake produced a debt of 7,890 c.c.; M. W. performing violent rapid gymnastic exercises produced in 32 secs. a debt of 7,810 c.c.; W. as the result of a rapid sprint of 225 yds. in 23·4 secs. produced a debt of 8,745 c.c.; L. by violent jumping for 2 min. 7 secs. caused a debt of 10,499 c.c.; W. M. H. by an extreme effort a debt of about $13\frac{1}{4}$ litres. The

prediction therefore is verified; the oxygen debt in these cases attains a value corresponding reasonably well to that calculated from the fatigue maximum of lactic acid in the muscles. It is clear that in such efforts the limit is not placed at an early stage by fatigue occurring in the nervous system, but rather by the presence of acid in the muscles themselves.

Different individuals, even those apparently of similar muscular development, differ enormously from one another in the vigour and duration of their maximum efforts. There are two types of effort: (*a*) the violent and short-lived type not depending on concurrent oxidation, and (*b*) the more moderate, longer lasting type, depending on the supply and utilization of oxygen, i.e. made possible by contemporary and adequate recovery. All possible stages intermediate between these may occur. These individual differences, important in everyday life, in athletics, and probably in medicine, are of a complex nature. The withdrawal of protective nervous inhibitions, the mental and moral factors ('guts') which make one individual inevitably a better man than another, are clearly of importance; the excitability of the respiratory centre, and of the nervous system as a whole, the size and capacity of lungs and heart, the fitness of various organs to stand the strain of violent effort, have all clearly to be taken into account. There remains, however, one simple chemical factor, the efficiency of buffering of the muscles, which determines the fatigue maximum of lactic acid, the maximum oxygen debt, and therewith the extent and duration of a short-lived violent effort. This factor is fully considered in Section M below.

H. *The Rate of Oxidative Recovery from Exercise in Man.*

There are only a few investigations recorded in physiological literature of the rate of return of the oxygen intake to its resting value on the cessation of exercise. Campbell, Douglas, and Hobson (5) followed the return to the normal resting value for periods of 80 and 90 min. following different rates of exercise on a bicycle ergometer. Krogh and Lindhard (26) performed similar experiments using similar apparatus.

Our experiments, which have been concerned with the influence of varying the type and severity of the exercise on the time relations of recovery, have confirmed the earlier observations, and have brought out certain other points of interest. Many types of exercise have been employed, of which the following may be regarded as typical: (*a*) flat running at a speed of 211 metres per min. (8 miles an hour), the time relations of recovery being determined (i) after a short period of exercise (4 min.), and (ii) after a long period (22 min.); (*b*) flat running at a speed of 250 metres per min. (9·3 miles an hour), continued for 6 min.; (*c*) rapid violent jumping with a skipping movement, continued for 36 secs.

Previous to the exercise the resting respiratory exchange was determined in some standard position (usually sitting). The subject finished the exercise

in front of a stand carrying a wide pipe with nine projecting tubes. To one of these tubes the valves and mouthpiece were fixed: to the others were attached rubber bags through single-way stop-cocks. All the tubes were of $\frac{3}{4}$ inch bore, the apparatus being similar in principle to that used by Campbell, Douglas, and Hobson (5). The subject, on cessation of exercise, adopted the standard resting position, adjusted the valves and nose-clip, and commenced to expire into the first bag. At the end of about $\frac{1}{2}$ min. (end of nearest expiration) the first bag was turned off, and the second one turned on for a like interval. This process was continued, the intervals of collection being gradually increased. After the eighth bag the valves were attached successively to separate bags, if the recovery was being followed for longer periods.

Table II gives the results obtained in three typical experiments.

TABLE II.

Exp. 1. Subject, L. *Exercise,* flat running at 211 metres per min. for 4 mins. Resting (sitting): O_2 intake, 251 c.c. per min.; CO_2 output, 227 c.c. per min.; R. Q., 0·91. Total oxygen used in recovery in 24 min. = 2,837 c.c. Oxygen requirement at this speed 2,790 c.c. per min.

Interval of Collection.	Mid-point of Interval from End of Exercise.	Recovery, excess Oxygen: Total in Interval.	Recovery, excess Oxygen: per min.
33·3 secs.	16·7 secs.	1096	1975
35·2 ,,	51 ,,	416	709
35·6 ,,	1 min. 26·3 ,,	229	386
1 min. 3·2 ,,	2 ,, 15·7 ,,	238	226
2 ,, 3·3 ,,	3 ,, 49 ,,	333	162
2 ,, 6·1 ,,	5 ,, 53·6 ,,	86	41
3 ,, 7·4 ,,	8 ,, 30·4 ,,	259	83
3 ,, 4·1 ,,	11 ,, 36·1 ,,	64	21
5 ,, 6·1 ,,	15 ,, 41·2 ,,	82	16
5 ,, 35·8 ,,	21 ,, 2·2 ,,	34	6

Results shown in Fig. 1.

Exp. 2. Subject, L. *Exercise,* violent jumping for 36 secs. Resting (sitting): O_2, 243 c.c. per min.; CO_2, 197 c.c. per min.; R. Q., 0·81.

Interval of Collection.	Mid-point of Interval from End of Exercise.	Recovery, excess Oxygen: Total in Interval.	Recovery, excess Oxygen: per min.
33·7 secs.	17 secs.	1105	1969
33·1 ,,	50 ,,	761	1382
32·3 ,,	1 min. 23 ,,	463	860
1 min. 5·2 ,,	2 ,, 11·7 ,,	554	514
1 ,, 3·6 ,,	3 ,, 16·1 ,,	368	347
2 ,, 3·3 ,,	4 ,, 49·6 ,,	536	261
4 ,, 2 ,,	7 ,, 52·2 ,,	633	157
6 ,, 31·2 ,,	13 ,, 8·8 ,,	743	114
6 ,, 33 ,,	19 ,, 41 ,,	537	82

Exp. 3. Subject, L. *Exercise,* flat running for 6 min. at 250 metres per min. Resting (sitting): O_2, 262 c.c. per min.; CO_2, 211 c.c. per min.; R. Q., 0·81. Oxygen requirement for this speed, 5,360 c.c. per min. Actual max. excess

intake, 3,483 c.c. per min. Hence a rapidly increasing oxygen debt, amounting to 7,160 c.c. at the end of 6 min. running.

Interval of Collection.	Mid-point of Interval from End of Exercise.	Recovery, excess Oxygen: Total in Interval.	per min.
33·5 secs.	17 secs.	1542	2763
36 ,,	52 ,,	927	1548
35·1 ,,	1 min. 28 ,,	502	858
1 min. 1 ,,	2 ,, 15 ,,	568	559
2 ,, 3·5 ,,	3 ,, 48 ,,	642	312
2 ,, 4·2 ,,	5 ,, 51 ,,	418	202
3 ,, 6·3 ,,	8 ,, 27 ,,	533	172
4 ,, 12 ,,	12 ,, 26 ,,	436	104
4 ,, 2·7 ,,	16 ,, 13 ,,	344	85
5 ,, 2·3 ,,	20 ,, 46 ,,	479	95
5 ,, 4·8 ,,	25 ,, 49 ,,	254	50
5 ,, 4 ,,	30 ,, 53 ,,	182	36
5 ,, 2·7 ,,	35 ,, 56 ,,	283	56
5 ,, 4·7 ,,	40 ,, 59 ,,	51	10

Results in Fig. 1.

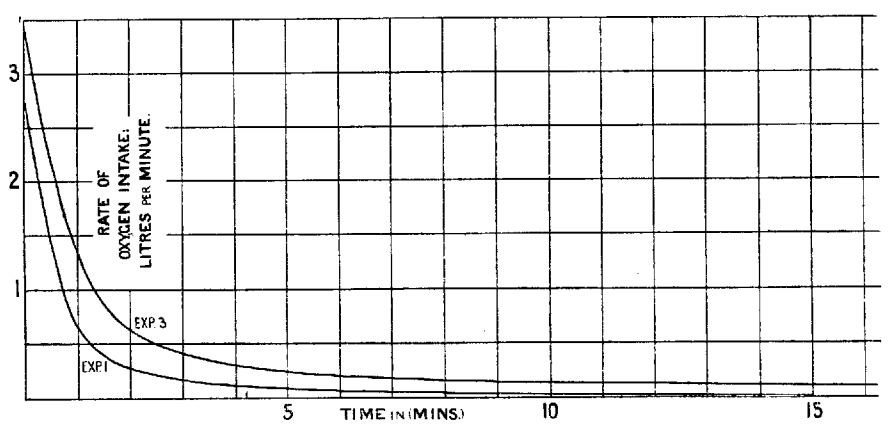

FIG. 1. Oxygen intake during recovery. Horizontally, time from cessation of exercise; vertically, rate of oxygen intake in excess of standing. The lower curve, falling rapidly to the base line, represents recovery from a short bout of moderate exercise. The upper curve, falling less rapidly, represents recovery from a rather longer bout of much more strenuous exertion.

The results indicate that on cessation of the exercise there is an immediate rapid fall in the oxygen intake, which occurs both after severe and after moderate exercise. This rapid fall is complete within 6 to 8 min. If, however, the exercise was severe, the oxygen intake falls to a level somewhat above the original resting level, the excess being maintained for prolonged periods, depending on the severity and extent of the exercise. There is thus a difference between the curves obtained—(*a*) after moderate exercise carried out for a short time, and (*b*) after severe or extended exercise. Even in moderate exercise, where the oxygen supply is adequate, if the exercise be maintained for a long period there is a prolonged recovery, and the total oxygen in the recovery period is larger in amount than in the case where the same exercise is maintained only for a short period. Now since, in such exercise, the heart, lungs, and circulation are all able to cope with the demands of the

muscles for oxygen, the only debt for oxygen should be that produced at the beginning of the exercise, i.e. before the respiratory, circulatory, and oxidative mechanisms have attained the rate of working equivalent to the exercise. The only explanation of the increased debt, after a prolonged period of such moderate exercise, appears to be that when the exercise is prolonged the steady maintained concentration of lactic acid, corresponding to the rate of oxidation as in Section I below, causes gradual diffusion of the acid to points distant from the oxidative recovery mechanism of the muscle (e.g. into lymph and other tissues), from which it returns by diffusion only very slowly to be oxidized in recovery. The exhaustion resulting from long-continued, comparatively moderate exercise is to be attributed therefore to the presence, outside the muscles, of noticeable quantities of lactic acid, the oxidative removal of which occurs only very slowly, as the acid diffuses gradually back—under a low concentration gradient—to the oxidative mechanism inside the fibre.

I. *The 'Steady State' in Exercise.*

In this section we shall deal with recovery occurring during the exercise itself. In prolonged steady exercise a balance must be struck between break-down and restoration, the rate of break-down being determined by the vigour of the exercise, that of restoration (*a*) by the concentration of lactic acid in the active muscles, and (*b*) by their oxygen supply. We shall consider here the characteristics of the dynamic equilibrium attained during steady exercise.

It was shown recently by Hartree and Hill (17) that the total magnitude of the recovery process is proportional, as was to be expected, to the extent of the 'initial' break-down preceding and initiating it. They showed also, in a muscle in oxygen, that the velocity of this recovery process is increased—not only absolutely but relatively—by an increase in the effort from which recovery is necessary. Thus, given a constant oxygen pressure in the muscle, the rate at which recovery occurs increases very rapidly as the break-down from which recovery is necessary is increased. In other words, oxidation is more rapid the greater be the concentration in the muscle of the bodies—e.g. lactic acid—whose removal constitutes recovery. This is the chemical law of 'Mass Action'. In human muscular exercise the process is more complex: here we have an oxygen pressure in the muscle which decreases to some degree as the amount of exercise increases, so tending to diminish the rate of oxidation: for severe continued exercise this limit to the oxygen supply is the predominant factor and will be further considered below; for moderate exercise, however, where the oxygen supply is adequate, we may expect the rate of oxidation in the muscle to increase continuously as the concentration of lactic acid in it is increased. When muscular exercise is taken in man at a constant speed the lactic acid content of his active muscles increases gradually from its resting minimum at the start. This rise in lactic acid content increases the rate of oxidation, so that finally, if the oxygen supply be adequate, a 'steady state' is reached in which the rate of

lactic acid production is balanced by the rate of its oxidative removal, and its concentration remains constant in the muscle as long as exercise at that speed is maintained. Hence, the rate of oxygen consumption should rise continuously during the exercise, from its resting minimum at the start to a steady value depending on the severity of the effort; here it should be maintained throughout the exercise. Conversely, when the effort terminates, the lactic acid should continue to be oxidized, but at a decreasing rate as its concentration falls, so that the rate of oxygen consumption should fall continuously from its steady exercise value to its original resting minimum. The latter phenomenon we have discussed in Section H above. These expectations are well verified in certain experiments we have made on the rise in the rate of oxygen intake after

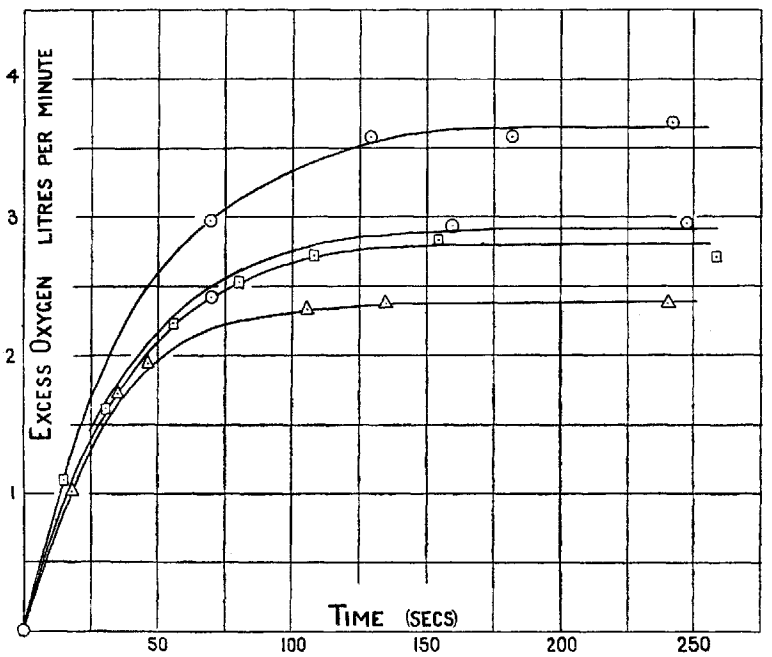

FIG. 2. The attainment of a 'steady state', in running at various constant speeds. Horizontally, time from commencing to run; vertically, rate of oxygen intake in excess of standing. Speeds of 181, 203, 203, and 267 metres per min. The lower three curves represent a genuine steady state, the uppermost curve only an apparent steady state in which the oxygen intake is at its maximum and the oxygen debt is rapidly increasing.

the beginning of exercise. In these experiments the subject started to run, at a given constant speed, around a circular grass track 92½ yds. (84½ metres) in circumference. The subject (H.) is a practised runner and was able to maintain constancy of speed for long periods, especially with the aid of a timekeeper calling out (and recording) the times of successive laps. He carried a small Douglas bag with a side pipe (much more convenient for running than a top pipe), a three-way tap, and a mouthpiece fitted with rubber valves. During each run the expired air was collected in the bag for a period of about 30 secs., the tap being turned on and off at the end of suitable expirations, the exact interval being recorded by the timekeeper on signals from the runner. During running, respiration is so rapid and free that a 30-sec. sample is quite adequate,

as is seen from the consistency of the points in Fig. 2. After a sufficient interval of rest (about 10 or 12 min.) for the oxygen consumption to return to its resting level, the run was repeated, and the expired air collected in a different 30-sec. interval. In this way a series of observations can be made on the rate of oxygen intake at various moments during the process of 'warming up' to the steady state represented by the final constant level of exercise. In Fig. 2 each result, expressed as the rate of oxygen consumption per minute due to the exercise (i. e., after subtraction of the resting rate), is plotted as the ordinate against an abscissa representing the time, measured from the commencement of running, of the *middle* moment of the interval during which the expired gases were collected. The curves show that the rate of oxygen intake due to the exercise in this subject rises rapidly from the start, reaching its final exercise value in 100 to 150 secs., and half its final value in about 25 secs. Further details of the experiments are given in the following table. The ventilation of the lungs at the highest speed is notable, especially when account is taken of the hindrance offered by valves and mouthpiece.

TABLE III.

Subject H. O_2 and CO_2 in c.c. dry and at N.T.P. Ventilation in litres per min. moist and at 37° C., and at the actual atmospheric pressure. S = standing.

Speed: Metres per min.	Mid-point of Sample: secs.	O_2 per min.	Excess Oxygen due to Exercise, per min.	CO_2 per min.	$\frac{CO_2}{O_2}$.	Total Ventilation.
181	S	269	—	248	0·92	9·16
	47	2220	1943	1780	0·80	48·7
	106	2618	2341	2242	0·86	56·1
	135	2652	2375	2405	0·91	59·3
	240	2655	2378	2622	0·99	67·8
	S	285	—	261	0·92	9·3
203	S	372	—	304	0·82	11·26
	70	2792	2420	2250	0·81	62·1
	159	3300	2928	3010	0·91	76·75
	247	3320	2948	2990	0·90	82·1
	362	3205	2833	2905	0·91	84·7
203	S	306	—	259	0·88	10·18
	15	1406	1096	1300	0·92	37·46
	31	1933	1623	1616	0·84	45·3
	56	2548	2238	2095	0·82	52·7
	80	2846	2536	2370	0·83	57·2
	108	3030	2720	2618	0·86	62·7
	154	3140	2830	2890	0·92	67·7
	258	3012	2702	2870	0·95	69·4
	S	315	—	275	0·87	10·3
267	S	373	—	328	0·88	11·84
	69	3340	2967	3310	0·99	87·6
	129	3950	3577	4040	1·02	114·0
	182	3950	3577	4360	1·10	132·6
	242	4055	3782	4335	1·07	138·4

So far we have discussed a genuine steady state of exercise in which the lactic acid concentration of the muscle attains a constant value, and the subject would be able (apart from extraneous disturbances, such as blisters on the feet) to continue the exercise almost indefinitely. This was almost certainly the case in the experiments recorded in the three lower curves of Fig. 2. In the highest

curve, at a speed of about 10 miles per hour, it was quite certainly not the case for the subject of our experiments, carrying the bag, pipes, and tap, and breathing through valves: he would manifestly have been unable to continue at this speed for more than 10 min., if so long. In such severe exercise the lactic acid is continuously accumulating in the muscles, the maximum oxygen intake (depending upon the capacity of heart and lungs) being inadequate to maintain the recovery at a level high enough to cope with the production of lactic acid. Hence, in such cases, the fact that the intake of oxygen has reached a constant value within 2½ min. represents nothing more than the fact that its *maximum* level has been attained: *it does not imply that the body has reached a state of dynamic equilibrium in which break-down is balanced by recovery.* Considering the case of running, there is clearly some critical speed for each individual, below which there is a genuine dynamic equilibrium, break-down being balanced by restoration, above which, however, the maximum oxygen intake is inadequate, lactic acid accumulating, a continuously increasing oxygen debt being incurred, fatigue and exhaustion setting in. The absolute magnitude of the maximum oxygen intake will be considered below.

The failure to realize the true nature of the steady state of exercise and its dependence on the maximum oxygen intake has led to some curious and paradoxical results. It is obvious that if the oxygen and energy consumption associated with a given type of exercise be required, it is necessary to continue it until a genuine steady state is attained. In running, the true oxygen consumption corresponding to a given speed can be measured only after the subject has been running at that speed for about 2½ min. If, moreover, the exercise be so vigorous that a steady state is impossible, the rate of oxygen consumption corresponding to the exercise can be measured only by adopting a technique which we will describe later (Section K). The value actually attained is only the *maximum oxygen intake* for that type of exercise, and may not correspond in the least to the oxygen *requirement* of the body: in such a case what we require is (oxygen income) + (rate of increase of oxygen debt), and in severe exercise this cannot be measured directly by such means as we have described hitherto. An amusing paradox in this connexion has been recorded by Liljestrand and Stenström (28). These observers recorded the oxygen intake during horizontal running, and found that the oxygen consumption (per metre travelled) *decreased* as the speed increased over the range 140 to 300 metres per min. It was apparently more economical to run fast than slow! Now the opposite is notoriously the case, and these observations of Liljestrand and Stenström (of which, on technical grounds, we have no criticism) obviously need an explanation. The explanation is simple: the subjects of their experiments were not in a genuine steady state at the higher speeds. In the case, e.g., of their subject N. S. ((28), p. 183) it is clear that the maximum oxygen intake of about 3·3 litres per min. was attained at a speed of about 186 metres per min. Hence, however fast N. S. ran above this speed he did not use more oxygen, not because he did not require it, but because he could not get it. Consequently, since he

ran more metres per min. at the higher speed, the apparent oxygen consumption, i.e. the oxygen intake *per metre*, diminished as the speed increased. The real fact is that the true oxygen requirement per metre (as distinguished from the oxygen intake) increases continuously as the speed of running increases.

The finite time occupied in the attainment of the maximum oxygen intake allows an interesting comment on a well-known practice in athletics, viz. that of running the first part of a middle or long distance race very rapidly. For example, the times of the winner for successive laps ($\frac{1}{3}$ mile) in the mile race of the 1890 Oxford and Cambridge Sports were 80 secs., 93 secs., 88 secs., and this represents only partially the speed at which the first few hundred yards are run in a half-mile or mile race. The advantage of a high initial speed is that it rapidly raises the oxygen intake and the recovery oxidation to their maximum values. The speed at which a race is run depends upon—(*a*) the maximum oxygen debt, and (*b*) the amount of oxidation possible during the race. Clearly the more rapidly the oxygen intake can be pushed up to its limiting value, the greater will be the maximum effort that can be made.

J. *The Maximum Oxygen Intake.*

In this section we will consider shortly—(*a*) the factors in exercise which cause a high oxygen requirement, and (*b*) those which facilitate a high oxygen intake. We shall then give experimental values of the oxygen intake, considerably higher than have been recorded before, and shall discuss shortly the bearing of these values on the problem of the vigour and efficiency of the circulation in man.

Running on the flat is a form of exercise peculiarly well adapted to a high oxygen intake, and specially subject to a high oxygen requirement. As regards the *oxygen intake*, the body is free, respiration is unimpeded, movements are considerable and very rapid, and the muscles are rigid during only a small fraction of the cycle of each step; consequently there is very little hindrance to a free and rapid circulation of the blood, while the extensive and frequent movements of the limbs, together with an unimpeded and rapid respiratory cycle, assist largely in the venous flow of blood back to the heart. These factors are not so potent in the case of exercise of the types of swimming, rowing, and gymnastics. For example, Lindhard (31) has shown that in the severe effort of holding the weight of the body with arms bent, there is little excess oxygen intake during the exercise, fatigue comes on rapidly, and the excess oxygen consumption occurs mainly after the exercise is over. The circulation through the active muscles is impeded by their continued rigidity.

In oxygen *requirement*, as distinguished from *intake*, running also takes first place among types of muscular exercise. Running consists of rapid, vigorous alternating movements, each maintained only for the minimum of time. Experiments on the heat-production of isolated muscles have shown that, to set up a contraction in a muscle and to maintain it, both require a certain liberation of energy (16), while other experiments (22) have shown that in man the maintenance of the contraction is far less expensive than its setting up,

that indeed to maintain a contraction for 5 secs. requires only as much energy as to set it up initially. Hence it may be calculated that to make four steps in a second, as in running 100 yds. at top speed, should require more than three times as much energy as to set up a maximal contraction in the same muscles and to maintain it for a second. This calculation of course is very rough, but it illustrates the reason why rapid vigorous alternating efforts require far more energy than equally vigorous maintained ones. The setting up of a contractile effort in a muscle is much more expensive than its maintenance. In running, the efforts are almost entirely dynamic, and therefore expensive; in rowing, the cycles are much less rapid, and the effort of maintaining the contraction provides a much larger part of the whole expense, which is correspondingly smaller. The fatigue associated with maintained contraction is due, not to its expensiveness, but to the difficulty placed in the way of an adequate oxygen supply by the rigidity of the muscle.

Very many observations have been made by physiologists of the maximum oxygen intake in man, and in the following table we give a selection of the highest values:

TABLE IV.

Oxygen Intake during Exercise (Maximum Values).

Subject.	Reference.	Exercise.	Oxygen, c.c. per min.
L. Zuntz	(1)	Bicycling	2310
Kolmer	(1)	Swimming	2320
Durig	(1)	Climbing	2245
Kolmer	(1)	,,	2660
Ranier	(1)	—	2580
Reichel	(1)	—	2670
M. A. M.	(1)	Bicycling (15 min.)	3000
M. A. M.	(1)	,, (70 min.)	2850
Douglas	(2)	,,	2795
Hobson	(2)	,,	2680
Douglas	(2)	Pushing motor bicycle up hill	2940
Haldane	(2)	,, ,, ,,	2790
Boothby	(2)	,, ,, ,,	2750
J. J.	(3)	Bicycling (4 min.)	3200
J. L.	(3)	,, (3 min.)	2550
V. M.	(3)	,, (4 min.)	2520
N. S.	(4)	Running	3500
G. L.	(4)	,,	2570
E. S.	(4)	,,	2904
N. S.	(4)	Skiing	3750
G. L.	(4)	,,	2800
E. S.	(4)	,,	3480
N. S.	(4)	Skating	3060
E. S.	(4)	,,	2530
N. S.	(5)	Swimming	2800
G. L.	(5)	,,	2080

(1) Benedict and Cathcart, *Publication No. 187, Carnegie Institution of Washington*, 1913.
(2) Campbell, Douglas, and Hobson, *Phil. Trans., B.*, 210 1920, p. 1.
(3) Lindhard, *Pflügers Arch.*, 1915, clxi. 318.
(4) Liljestrand und Stenström, *Skand. Arch. f. Physiol.*, 1920, xxxix. 167.
(5) *Ibid.*, p. 1.

Thus running, skiing, and skating take the highest places in the series, all of these, in the accomplished performer, being types of exercise in which rapid

and violent alternating movements occur. Even the notoriously exhausting effort of pushing a motor bicycle up a hill does not approach them in its actual oxygen consumption! We have made a number of observations on various individuals running, some of which considerably exceed the values given in the above table; the following are well-substantiated maximum values:

Subject.	Age: Yrs.	Weight: Kilos.	Oxygen: c.c. per min.
S.	—	—	3985
W.	19	72	3995
J.	21	77	4040
L.	21	65	3535
H.	35	73	4175

All the subjects of the above experiments are of athletic disposition; none, however, are first-class athletes. S. is a University Rugby footballer, W. is a good short-distance runner, J. could probably be a first-class mile runner if he tried, H. is a practised runner (see section L), and L. is a well-built athletic person. In comparing these results with those in the previous table we must remember, also, that N. S. weighed 81 kilos, so that, reckoned per kilo, our numbers are still higher than those previously recorded. It is obvious, therefore, that up to about 4,175 c.c. of oxygen per min. can be taken in during running by a man of 73-kilo body-weight.

Let us consider what this means in circulation of the blood. Assuming a normal oxygen capacity of his blood, viz. 0·185 c.c. of O_2 per c.c. of arterial blood, and a utilization coefficient of 60 per cent., an oxygen intake of 4,175 c.c. per min. implies a blood-flow of $4{\cdot}175/0{\cdot}185 \times 0{\cdot}6 = 37{\cdot}6$ litres per min. Lindhard (30) in severe exercise found a utilization coefficient of 57½ per cent. when his subject J. J. was taking in 2,410 c.c. of O_2 per min., and of 79 per cent. when he himself was using 2,550 c.c. per min., while he states that the mean of all his higher experiments was 67 per cent. His subject V. M. gave a value of 58 per cent., and a mean for higher experiments of 51 per cent. Even if a utilization coefficient of 80 per cent. be assumed in our experiments, the blood-flow corresponding to an oxygen intake of 4,175 c.c. must have been 28 litres a minute. During such exercise the brain and other relatively inactive parts of the body are being liberally supplied with blood, and the mixed venous blood can scarcely have been 80 per cent. unsaturated: neither is it likely that the arterial blood was competely saturated. It would seem fairly certain, therefore, that in running the blood-flow may attain a value between 30 and 40 litres per min., an enormous amount which it is difficult to realize more effectively than by turning it into gallons (8 to 10) and inquiring how long an ordinary water-tap would require to pass the same amount. It is obviously impossible to be a runner without possessing a powerful heart.

Other investigators have measured the circulation-rate by more exact methods. Meakins (32) found values at rest round about 8 litres per min., and during bicycle ergometer exercise about 17. Similar values were found by Douglas and Haldane (8). Liljestrand and Lindhard (29) found considerably

smaller values at rest. Lindhard (30) found up to 20 litres per min. during work. It would be difficult or impossible to measure the circulation-rate during vigorous running by such methods as these authors employed, and one is constrained to fall back on the rougher method of calculation given here, a method previously suggested by Y. Henderson and Prince (18); this method, however, shows values, during running, which are unquestionably higher than have ever been recorded in another type of exercise. We have made no exact observations of the pulse-rate during such running: it is not, however, extremely rapid, so that the output per beat in running must be exceptionally great. This is probably due to a good venous return.

That these large outputs can be maintained for a considerable time was shown by the experiment of Benedict and Cathcart (3 *b*) on their subject M. A. M., who for 15 min. maintained, while bicycling, an oxygen intake of 3,000 c.c. per min., and for 70 min. one of 2,850 c.c. Their subject was very exhausted by the longer effort. To maintain such an oxygen consumption for a long time while running is, however, quite easy, and the following experiment shows a much higher one. The subject (H.) ran at a steady speed of 240 metres per min. (9 miles per hour), carrying a large Douglas bag and breathing through valves and mouthpiece. At intervals the equipment was discarded and the expired gas sampled and measured, while the subject continued running at the same speed. The gradual rise in oxygen consumption is probably to be attributed to a painful blister on the foot causing inefficient movement.

Experiment.

Interval of collection.	Mid-point of interval from start.	Oxygen intake, c.c. per min.	CO_2 output, cc. per min.	$\frac{CO_2}{O_2}$	Total ventilation, litres, moist and at 37° C.
75 secs.	3 min. 3 secs.	3590	3420	0·95	90
63 secs.	10 min. 48 secs.	3785	3800	1·0	100
77·5 secs.	17 min. 54 secs.	3910	3910	1·0	108
63 secs.	26 min. 32 secs.	3910	3930	1·0	118

This oxygen intake must have required a total blood-flow of not much (if any) less than about 30 litres per min., and it was maintained for half an hour. In a highly trained athlete it is obvious that still higher values must be possible.

It is open to question whether the oxygen intake is limited by the heart or by the lungs. It is possible that, at the higher speeds of blood-flow, the blood is only imperfectly oxygenated in its rapid passage through the lung; on the other hand, the limit may be placed simply by the sheer capacity of the heart. It would seem probable that, in the healthy normal man, both factors work together. A diminished oxygen tension in the coronary blood-supply, owing to the shortness of its stay in the capillaries of the lung, would lower the output of the heart itself, so tending to diminish the flow and to drive the oxygen tension up again. In abnormal persons one factor or the other may preponderate.

K. *The Relation between Speed and Oxygen Consumption in Running.*

The effect of speed on the oxygen intake during horizontal walking has been investigated by a variety of authors, and their results have been fully

summarized by Benedict and Murchhauser (3 *a*). Similar determinations during 'level and grade walking' have been recorded recently by Monmouth Smith (43). The effects of speed upon the oxygen intake during walking, running, swimming, skating, and skiing have been investigated by Liljestrand and Stenström (27, 28). We have made a number of observations on the actual oxygen *intake* during running, over as wide a range of speeds as possible; since, however, at the higher speeds, a genuine steady state is never attained (as pointed out in Section I above), we have amplified these observations by others in which the oxygen *requirement* of the exercise is determined by a different method.

In determining the rate of oxygen intake during running at various speeds, the subject ran (as in Section I) with a constant measured velocity around a grass track, carrying a Douglas bag, and breathing through mouthpiece and valves, the tap being turned to allow the expired air to escape into the atmosphere. After continuing this for a time known, from the experiments of Section I, to be sufficient for the oxygen intake to attain a steady value, the tap was turned for a measured interval (usually about 1 min.) to allow a sample of expired air to be collected in the bag, the running being continued at the same speed. After the end of the interval the running ceased, and the measurement and analysis of the expired air were carried out in the usual manner. Experiments were made at a variety of speeds, and on several subjects (which amply confirm one another), and in Fig. 3 the curve A summarizes the observations of the excess oxygen intake made on our most usual subject (H., aged 35, weight 73 kilos, vital capacity 5 litres, normal resting pulse-rate about 60, in fair general training owing to a daily slow run of about one mile before breakfast). It must not be supposed that this line represents accurately the same subject's excess oxygen intake when running without the respiration apparatus, which provided a small but appreciable hindrance, especially at the higher speeds: probably when unhampered he is noticeably more efficient, and might, with freer respiration, attain a rather higher oxygen intake. It is seen that the rate of oxygen intake per minute due to the exercise, i.e. in excess of standing, increases as the speed increases, reaching a maximum, however, for speeds beyond about 260 metres per min. (9·7 miles per hour). However much the speed be increased beyond this limit, no further increase in oxygen intake can occur: the heart, lungs, circulation, and the diffusion of oxygen to the active muscle-fibres have attained their maximum activity. At the higher speeds the requirement of the body for oxygen is far higher, but cannot be satisfied, and the oxygen debt continuously increases.

Curve A of Fig. 3 expresses the relation between speed and oxygen *requirement* (as distinguished from *intake*) only at speeds of less than about 210 metres per min. (7·8 miles per hour), where the body can attain a genuine steady state. At higher speeds the same relation can be investigated by another method, not involving the attainment of such a steady state. The procedure measures the total *excess oxygen intake during, and in recovery from,* a given muscular effort of short duration. The subject stands for some minutes, ready

to run and breathing through the apparatus, his expired air escaping to the atmosphere, until his standing resting minimum oxygen intake is likely to be reached. He turns the tap, causing the expired air to flow into the bag, and immediately proceeds to run a given distance (say 100 yds.) at a measured speed. At the end of the run, and for the succeeding 10 or more minutes (the interval required depending on the magnitude of the recovery), he stands breathing into the bag until recovery is expected to be complete, the total

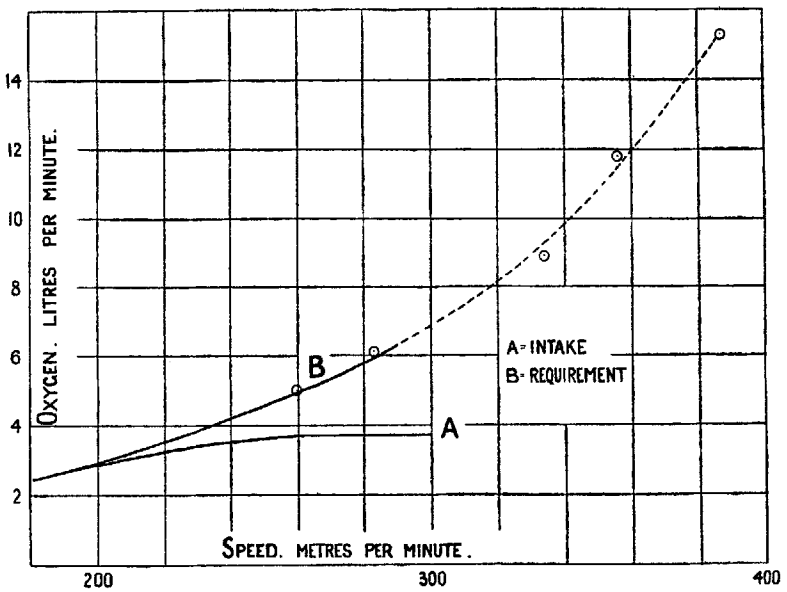

FIG. 3. Relation between oxygen intake (curve A), or oxygen requirement (curve B), and speed, in running at various speeds. The circles on curve B, and the dotted curve through them, were obtained indirectly by a calculation described in Section L.

interval of collection being measured. The total oxygen intake during this interval is then determined in the usual manner, and from this is subtracted the amount of oxygen which would have been used in the same time, *had no exercise been taken.* The difference gives the total oxygen consumption caused by the exercise, during the run and in recovery therefrom. Suitable observations of the standing resting oxygen intake are made before, and sometimes after the run. The following example illustrates the procedure:

Subject, H. Resting (standing): O_2, 346 c.c. per min.; CO_2, 277 c.c. per min.; R.Q., 0·80. *Exercise:* ran $1\frac{3}{4}$ laps (148 metres) in 30·5 secs., breathing into bag from start. Speed, 291 metres per min. Interval of collection, 8 min. 5 secs. Total oxygen used, 5,950 c.c.; resting (standing) value, same interval, 2,795 c.c.; difference due to exercise, 3,155 c.c. Hence oxygen requirement at this speed = 6,200 c.c. per min.

Here no assumption is made that a steady state of any kind has been attained: the only assumption indeed is that the excess oxygen intake is to be credited to the exercise. This method has been used to measure the real oxygen requirement of running at various speeds, and the result of our experiments are shown in curve B (unbroken portion), Fig. 3. It is seen that the

oxygen requirement rises continuously, at an increasing rate, as the velocity increases, attaining enormous values—far beyond the possibility of satisfying them contemporaneously—at the higher speeds. The curve B diverges from the curve A beyond about 220 metres per min.: at lower speeds they are the same. In H., carrying the respiration apparatus, all speeds greater than 220 metres per min. imply an increasing oxygen debt, with gradually oncoming exhaustion caused by the accumulation of lactic acid. At high speeds the accumulation of acid is rapid, the oxygen requirement exceeding considerably the maximum oxygen intake.

These methods and results might bear some application to the case of persons whom metabolic, cardiac, or other disturbances have rendered incapable of prolonged exercise, of any but the mildest type. By walking or running a short given distance, or indeed by any standard given effort, the oxygen requirement of that effort could be determined, without any assumption of the attainment of a steady state, and compared either with the value found in normal man or with the maximum oxygen intake attainable or allowable for the abnormal individual in question.

The curve of Fig. 3 really represents what we may call the 'efficiency' factor in running. A man may fail to be a good runner by reason of a low oxygen intake, a low maximum oxygen debt, *or a high oxygen requirement*; clumsy and uneconomical movements may lead to exhaustion, just as well as may an imperfect supply of oxygen.

L. *Distance and Speed in Athletics.*

The results of the preceding section have an interesting application to athletics. The subject H. was able ten years ago, with a maximum effort, to run the following distances in the following times, i.e. at the following speeds:

Distance.	¼ mile.	⅓ mile.	½ mile.	1 mile.	2 miles.
Time	53 secs.	1 min. 17 secs.	2 min. 3 secs.	4 min. 45 secs.	10 min. 30 secs.
Average speed, metres per min.	455	419	392	333	306

This considerable variation of speed with the duration of the effort can be explained quantitatively by considerations of oxygen supply alone. Let us assume that his maximum oxygen intake per minute, in excess of standing, was 4·0 litres (i.e. 0·2 litres greater than it is now), and that his maximum oxygen debt was 10 litres (i.e. about the maximum recorded in this paper). Let us further assume that at the end of the race his oxygen supply, actual and potential, was completely exhausted. Then in a race lasting for 1 min. the total oxygen available would be $(10+4) = 14$ litres, i.e. for 1 min. he could run at a speed requiring 14 litres of oxygen per min. In a race lasting 5 min., however, the total oxygen would be $(10+5\times4) = 30$ litres, i.e. for 5 min. he could run at a speed requiring $30/5 = 6$ litres per min. Thus in the longer

race the speed must be considerably reduced. On these lines the following table may be calculated:

Distance.	¼ mile.	⅓ mile.	½ mile.	1 mile.	2 miles.
Average speed, metres per min.	455	419	392	339	306
Total oxygen potentially available	13·5	15·1	18·2	29·0	52
Oxygen requirement per min.	15·3	11·8	8·9	6·1	4·95

This table gives us immediately a relation between speed and oxygen requirement, which we may compare with that given, for the same subject, in Fig. 3 above. Before doing so, however, we must note that the respiration apparatus used in the experiments recorded in Fig. 3 offered a definite, if small, hindrance to movement, and we may allow for this provisionally by assuming that, for a given oxygen requirement, the speed is reduced 15 per cent. by the apparatus carried. Hence, if we reduce all the speeds in the above table by 15 per cent. we obtain the following set of numbers, which are shown as circles in Fig. 3 above:

Distance.	¼ mile.	⅓ mile.	½ mile.	1 mile.	2 miles.
Speed (reduced for respiration apparatus)	387	356	334	283	260
Oxygen requirement per min.	15·3	11·8	8·9	6·1	4·95

We see that the last two of these calculated quantities lie close to the curve actually observed for H., while the first three appear to make a good continuation of it. We have been unable hitherto to continue the observations on H. at the higher speeds, owing to the smallness of our track making faster running on it impossible. There can be little doubt, however, that if the observations were made they would lie close to the values calculated as above: a few isolated observations on other subjects at higher speeds confirm the general rise of the curve. Hence, we may conclude that *the maximum duration of an effort of given intensity is related to the intensity in a manner depending simply upon the supply of oxygen, actual or potential*, i.e. upon the maximum rate of oxygen intake and the maximum oxygen debt of the subject in question. This is a striking confirmation, from another aspect, of the truth of the principles discussed in this paper. It would appear to be of importance in the scientific study of athletics and physical training, both in health and in disease.

M. *The Importance of Tissue Buffers in Muscular Effort.*

In recent years the fundamental part played by the buffers of the blood, in respiration and muscular exercise, has been very fully discussed. The importance, however, of the buffers present in the muscles themselves has been largely neglected, partly owing to their relative inaccessibility to investigation, partly because of a failure to realize the magnitude of the neutralization process occurring in the muscles during exercise. Moreover, the study of buffers, and of the principles governing their behaviour, has been somewhat obscured by a logarithmic notation of hydrogen-ion concentration, which has made even the comparatively expert feel that there is something unduly subtle in their

action. As a matter of fact, given an elementary knowledge of the principles governing the behaviour of electrolytes in solution, the action of buffers is extremely simple and intelligible, and since it is of the utmost importance to an understanding of muscular activity, of respiration, of dyspnoea, and the like, we have given below a rather full discussion of the subject. We have avoided throughout the use of the logarithmic notation (pH), as leading only to obscurity, and have dealt with the simple and intelligible conception of the hydrogen-ion concentration itself, for which we have adopted the usual symbol cH. As a prelude, we may state that the action of a buffer in solution consists merely in the substitution of a weak acid for a strong one, the strong acid in the case of muscle being lactic acid, the weak ones being carbonic acid, phosphoric acid, and protein.

If a very small quantity of strong acid be added to pure water, or to a neutral salt solution, e.g. of NaCl, a very large change in the hydrogen-ion concentration (cH) results. For example, at 22° C. the cH of pure water is 10^{-7} grm.-ions per litre (i.e. one ten-millionth part of a milligramme of ionic hydrogen per c.c.): if now 1 c.c. of normal hydrochloric acid, containing 36·5 mg. of HCl, be added to a litre of such water, the cH rises ten thousand times, to a value of 10^{-3}. According to our observations, some 90 grm. of lactic acid may be liberated in the body as the result of severe exercise. Dissolved in 60 litres of water this amount of lactic acid would produce a cH of about $1{\cdot}5 \times 10^{-3}$; the cH of blood is about 4×10^{-8}; thus the result of exercise, in the absence of some mechanism able to eliminate this effect of added acid, would be to raise the cH of the body fluids some 40,000 times. Actually the change of cH is very small: the maintenance of bodily processes, in particular of respiration, and of the physical state of the colloidal proteins of the tissues, demands an extremely high constancy of cH: this constancy is maintained by the 'buffers', both of blood and tissues. As Ritchie (41) has shown, the change of cH of an isolated muscle on moderate stimulation is almost inappreciable.

Weak acids, e.g. carbonic acid H_2CO_3, boric acid H_3BO_3, phosphoric acid H_3PO_4 (in its second and third dissociations), amino-acids, and in particular proteins such as haemoglobin or those of muscle (which act as acids at the cH of the body), are only very slightly dissociated into hydrogen ions and anions. Calling such a weak acid HA, the reaction $H^+ + A^- \rightarrow HA$ goes almost entirely to the right. Now, in the body many such weak acids exist, but normally they are largely in the form of their sodium or potassium salts, NaA or KA, which are fairly highly ionized into Na^+ (or K^+) and A^- ions. Now imagine that we add a strong acid, e.g. HX, ionized largely as H^+ and X^-, to a solution of such a salt of a weak acid, the following mixture is obtained: $Na^+ + A^- + H^+ + X^-$. But the acid HA is an extremely weak one, i.e. the ions H^+ and A^- cannot exist side by side in appreciable concentrations, they must form the undissociated acid HA. Hence, provided the buffer salt NaA be present in sufficient excess, practically all the H^+ is removed by the reaction

$H^+ + A^- \rightarrow HA$, leaving only the neutral or approximately neutral salt Na^+X^- and the excess of buffer salt Na^+A^-. Thus the buffer salt has, so to speak (and this is the origin of the term 'tampon', mistakenly translated 'buffer'), 'absorbed', or 'mopped up', the hydrogen ions of the added acid, and turned them into undissociated weak acid and approximately neutral salt. Such buffers are extremely effective, reducing the change of cH caused by added acid many thousands or even tens of thousands of times. In the body the most effective buffer salts are bicarbonates, phosphates, proteins, and particularly haemoglobin.

The matter can be expressed in another way. Buffer salts may be regarded as stores of sodium (or potassium). An added acid requires sodium to neutralize it: the stronger acid seizes sodium from the weaker; if the anion of the buffer salt were that of a strong acid the effect would be *nil*, one strong acid would be exchanged for another; actually, however, the buffer is a salt of a very weak acid, and the strong added acid is replaced, therefore, by a neutral salt and a very weak acid, which raises only slightly the cH of the solution.

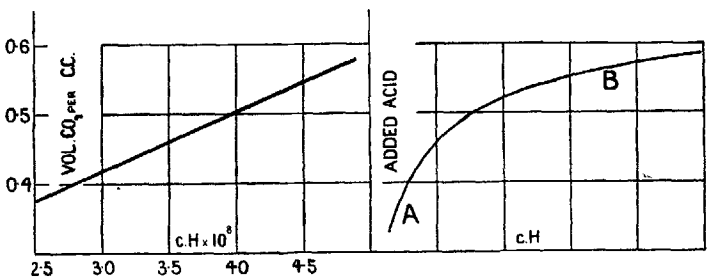

FIG. 4. Curves showing the 'efficiency of buffering'. Horizontally, hydrogen-ion concentration (cH); vertically, acid (or CO_2) added to attain that cH. Left, actual curve for blood. Right, hypothetical curve for muscle.

The quantity of acid which must be added to a solution to change the cH by a given amount may be used to measure the efficiency of buffering of that solution, *to that acid, at that cH.* For example, the efficiency of buffering of blood, to carbonic acid, can be deduced from the left-hand diagram of Fig. 4. The relation between vCO_2 (the total volume of CO_2 held by 1 c.c. of blood in solution and combination) and cH is there given as a straight line, and the slope of this line represents the efficiency of buffering: the greater the slope the more efficiently the blood is buffered; if it were not a straight line the efficiency of buffering at any cH would be given by the slope of the tangent to the curve at the corresponding point. The study is still in its infancy, but there can be no doubt of the existence of similar buffer curves for lymph, tissue fluids, and living muscle substance; the efficiency of buffering of these determines the amount of lactic acid which can be taken up without fatigue or exhaustion, without escape of unneutralized acid into the blood, and corresponding excessive respiration. This buffer curve is probably represented by a line such as that in the right-hand diagram of Fig. 4. To produce a given change in cH the quantity of added acid is largest at the start, and becomes less and less as the cH of the solution increases, so that the efficiency of buffering (as measured by

the slope of the curve) is greatest at first, and becomes less and less as more and more acid is added. If now the resting condition of a muscle be represented on the curve by a point such as A, then considerable violent exercise can be taken and noticeable quantities of acid produced, without much disturbance of the cH, and therefore without much fatigue in muscles or distress in respiration. If, however, the resting condition of the muscle be represented on the curve by a point such as B, the efficiency of buffering will be less, the effects of exercise and acid production will be relatively greater, and distress will rapidly ensue. Moreover, if the muscle were to start at a resting state such as A, it might, as the result of exercise and lactic acid production, pass along the curve to B; here the effects of further exercise and of further acid production would be relatively more severe, owing to the less efficient buffering at B than at A. This additional effort might lead to far more than the corresponding additional distress.

Lactic acid compared with an acid such as HCl is fairly weak: its dissociation constant is given as $1{\cdot}38 \times 10^{-4}$ at 25° C. It is, however, a very much stronger acid than carbonic acid, for which the dissociation constant (at 37° C.) is about 6×10^{-7}: than leucin ($3{\cdot}1 \times 10^{-10}$) and other amino-acids: than haemoglobin (oxy-, 6×10^{-7}, and reduced, $7{\cdot}5 \times 10^{-9}$; see (4)) and other proteins: than phosphoric acid in its second and third dissociations ($2{\cdot}1 \times 10^{-7}$ and $5{\cdot}6 \times 10^{-13}$). Indeed a 0·1 per cent. solution of lactic acid in water is about 10 per cent. ionized. In the body, therefore, *lactic acid will never occur as such: it will always obtain base from some weaker acid to form sodium, potassium, or ammonium lactate, in which forms alone it will exist in muscle, lymph, and blood.* This is borne out by the fact that the reaction of isolated muscle never becomes appreciably acid, even in severe fatigue. The consequence, however, is that exercise, liberating lactic acid, increases the concentration of these other weaker acids in the muscles and body fluids; hence, owing to the presence of these other weaker acids, the cH does actually rise, though much less than it would in the absence of buffer salts. One only of these other weaker acids, viz. carbonic, is volatile; hence an immediate after-effect of a short burst of severe exercise is to drive off excessive quantities of CO_2. This fact has appeared in the work of other authors, e.g. Krogh and Lindhard (26), and Campbell, Douglas, and Hobson (5). It is shown more vividly by the first experiment given in Table V below, where the apparent respiratory quotient of the excess metabolism produced by exercise is as high as 2·6 two minutes after a very violent effort: in other words, for every CO_2 molecule produced by oxidation, another 1·6 molecules were being displaced by lactic acid. It is obvious that CO_2 driven out by lactic acid will have to be restored later if the lactate formed at its expense be oxidized or removed. (If, however, the lactate were excreted by the kidneys, it might appear in the urine as sodium lactate, so depriving the body of sodium and preventing a corresponding amount of CO_2 from being restored later.). Hence, at some later stage in recovery, we find that the apparent respiratory quotient of the excess metabolism falls far below unity—indeed it may become negative—as also has been found by previous

authors (3 *b*, 26, 5), but is shown more clearly in the second experiment quoted. It is obvious that, in the later stages of recovery, such a very low value of the apparent R. Q. cannot represent a genuine metabolic change: it is due simply to the restoration of CO_2 driven away earlier by lactic acid.

TABLE V.

Exp. 1. Subject, L., 3 hours after meal. *Exercise*, jumping with rapid skipping movement for 36 secs. Room temp., 14° C. Resting resp. exchange (sitting, before exercise, for 10 min.): oxygen, 243 c.c. per min.; CO_2, 197 c.c. per min.; R. Q., 0·81. The expired gases were collected during successive intervals, one bag being turned on at the instant the previous bag was turned off. All gases in cubic centimetres at N. T. P.

Interval of collection.		Mid-point of interval from end of exercise.		Recovery excess oxygen:		Recovery excess CO_2:		Apparent R. Q. of excess metabolism.
				per min.	Total in interval.	per min.	Total in interval.	
min.	secs.	min.	secs.					
	33·7		17·0	1969	1105	2763	1551	1·40
	33·1		50·2	1382	761	2448	1350	1·77
	32·3	1	23	860	463	1863	1001	2·17
1	5·2	2	12	514	554	1343	1460	2·62
1	3·6	3	16	347	368	828	879	2·39
2	3·3	4	50	261	536	598	1229	2·29
4	2·0	7	52	157	633	292	1178	1·86
6	31·2	13	9	114	743	135	880	1·19
6	33·0	19	41	92	537	79	567	0·86

By 'excess oxygen' and 'excess CO_2' are meant the amounts taken in or given out over and above the resting sitting values.

Exp. 2. Subject, L., 3 hours after meal. *Exercise*, horizontal running round grass track at 9¾ miles per hour, maintained for 4¼ min. Temp. 16° C. Resting resp. exch. sitting: oxygen, 262 c.c. per min.; CO_2, 211 c.c. per min.; R. Q., 0·81. Rate of oxygen *intake during* exercise, measured after 2 min. 48 secs. of exercise, 3,745 c.c. per min.: rate of CO_2 output, ditto, 3,755 c.c. per min. Oxygen *requirement* of exercise, measured as on p. 157 above, 5,360 c.c. per min. The vigour of the exercise, therefore, was considerably in excess of that corresponding to the maximum oxygen intake, and a heavy oxygen debt was incurred.

Interval of collection.		Mid-point of interval from end of exercise.		Recovery excess O_2:		Recovery excess CO_2:		Apparent R. Q. of excess metabolism.
				per min.	Total in interval.	per min.	Total in interval.	
min.	secs.	min.	secs.					
	33·5		17	2763	1542	2984	1666	1·08
	36		52	1548	928	2189	1313	1·42
	35·1	1	28	858	502	1507	881	1·76
1	1	2	15	559	568	1079	1097	1·93
2	3·5	3	48	312	642	568	1170	1·82
2	4·2	5	51	202	418	292	604	1·45
3	6·3	8	27	172	534	230	714	1·34
4	12	12	26	104	437	79	332	0·76
4	2·7	16	13	85	344	44	178	0·52
5	2·3	20	46	95	479	33	166	0·35
5	4·8	25	49	50	254	−1	−5	−0·02?
5	4·0	30	53	36	182	−11	−56	−0·31?
5	2·7	35	56	56	282	25	126	+0·45?
5	4·7	40	59	10	51	−12	−61	−1·20?

The values denoted with queries (?) are doubtful because of the smallness of the quantities involved.

TABLE V (*continued*).

Exp. 3. *Subject*, H., 10 hours after meal. *Exercise*, easy horizontal running round grass track at 7·6 miles per hour. Temp., 13° C. During recovery (standing) for 7 min. 2 secs. following 4 min. 10 secs. exercise, the total excess oxygen used (over and above standing) was 2,485 c.c. and of CO_2 excreted was 2,508 c.c.: R. Q. of recovery metabolism = 1·01. The oxygen debt, therefore, was relatively small, and the recovery R. Q. can be sufficiently explained by the oxidation of carbohydrate.

Conditions.	Oxygen intake:		CO_2 output:		R. Q.		Ventilation: litres* per min.
	c.c. per min.	Excess over standing.	c.c. per min.	Excess over standing.	of total.	of excess.	
Basal (bed)	217	—	195	—	0·90	—	6·1
Standing before exercise	306	—	269	—	0·88	—	10·2
Standing after exercise	315	—	275	—	0·88	—	10·3
During exercise (after 4 min.)	3012	2702	2870	2598	0·95	0·96	69·0

* Moist, at 37° C., and at 754 mm. Hg pressure.

Moderate continued exercise in man does not lead to this driving off of CO_2, as is shown by Exp. 3 above. Apparently when lactic acid is formed in moderate amount during exercise its neutralization is effected by the protein buffers of the muscle, and possibly in part by phosphates, but not by the bicarbonates present in blood and tissue fluids; hence there is no dyspnoea, and the R. Q. of the excess metabolism remains at or near that of carbohydrate. This is confirmed by recent work on isolated muscle, in which (17) the total heat-production in the initial anaerobic phase of contraction can be attributed to simple causes, (*a*) the break-down of glycogen into lactic acid, and (*b*) the neutralization of that acid, provided only that we may assume *the neutralization to take place by protein buffers and not by phosphates or bicarbonates.* The heat of neutralization of acid, as shown by Meyerhof (38), is large if it be effected by protein buffers, but small if it be effected by others. Hence in an unfatigued muscle we must assume a protein salt to be the neutralizing agent; only when the supply of suitable protein buffer has run out, and when the cH inside the muscle has risen far enough, may we suppose the lactic acid to attack the bicarbonate, and so to drive off CO_2: it is probably at this stage that laboured respiration begins.

Little is known about the buffers of the muscle, more is known about the buffers of the blood. In blood the buffers are bicarbonates and phosphates, serum proteins and haemoglobin. All the serum proteins are capable, to a small degree, of acting as buffers; there is strong evidence, however, that one protein only, haemoglobin, is a really effective agent in neutralizing added CO_2, and its effectiveness appears to be enhanced by its confinement within the semi-permeable walls of the blood corpuscle (7). The efficiency of haemoglobin

as a buffer is really due to the fact that as an acid it is extremely weak. Moreover reduced haemoglobin is a weaker acid than oxyhaemoglobin (4) and should correspondingly be a better buffer: Christiansen, Douglas, and Haldane (6) found that reduced blood takes up appreciably more CO_2 than oxygenated blood at the same CO_2 pressure. Now it is obvious that human individuals may differ enormously from one another in the degree to which their muscles can tolerate sudden and violent exercise, and the same individual will vary enormously from time to time. A sudden effort which will make one man exhausted and stiff and lead to extreme dyspnoea will not affect another, or the same man when he is in better training. This is doubtless partly a matter of the buffers in the blood: lack of haemoglobin, as in anaemia, may cause a much greater rise in cH for a given addition of acid or CO_2 (7); this, however, is not the sole cause, and the blood is only a small part of the total tissue fluids. Muscular stiffness may result, in a powerful individual 'out of training', from a few seconds only of severe exercise, at a time when his blood is quite reasonably normal in its buffering power. Indeed, it is continually observed that, even when in good training for running, moderate unaccustomed exercise, of the type (say) of climbing a rope in a gymnasium, may lead to severe stiffness in the muscles concerned in that process. It would appear that training is able somehow to increase the *local* buffering power of the muscle proteins, possibly by a relative increase in the amount of the salt of the *weaker* protein acids. The salt of the weaker acid is the more effective buffer; it will surrender more rapidly and readily its available alkali, and it will cause a smaller rise of cH when it has done so. If it be present only in small amount it will be used up first of all in neutralizing added acid: its rôle must then be taken on by some less effective agent, the efficiency of buffering will fall, and the cH will rise more rapidly as acid continues to be liberated. The excessive rise of cH so produced may cause a semi-permanent physico-chemical effect in the colloidal structure of the tissue, something analogous to precipitation or coagulation of some constituent, so leading to stiffness, pain, and loss of power in the muscle, and, by diffusion into the blood and lymph, to excessive respiratory movements and dyspnoea.

We shall consider later the question of oxidation in its bearing on this subject. By very violent exercise for a short time, even—or possibly particularly—in the best trained man, it is possible to exceed many times over any possible oxidative recovery during the exercise, and to produce enormous quantities of lactic acid in the muscles, so that fitness for short-lived effort denotes almost entirely the ease with which the acid products of activity can be dealt with *without oxidation*, i.e. through neutralization by the tissue buffers. It may denote, also, doubtless the relative immunity of the body at large to the harmful or painful effects of a sudden change of cH; in the main, however, fitness for violent short-lived effort would seem to depend upon the quality of the tissue buffers. If this be the case, we may perhaps inquire why the body does not maintain the presence of the more effective buffers, i.e. of the

salts of the weaker protein acids, *all the time and independently of 'training'*. This inquiry lies within the province rather of the biologist than of the physical chemist, but there is no reason why the biologist should not inquire in physico-chemical terms. An answer may be suggested as follows: The more effective buffer is the less stable one, in so far as it is the salt of the weaker acid. The salt of a very weak acid readily surrenders its sodium, even to a weak acid, and as soon as it has done so it ceases to be a buffer. Hence in the less vigorous metabolic processes of the untrained or abnormal man, in the distorted processes of disease, or after excesses of meat or drink, the highly unstable and most efficient buffers may be partly saturated with other rather stronger acids, may surrender their sodium, and so become inoperative. A relatively unstable system has been displaced by a stabler, if less effective one, and can only be restored as a gradual adaptation to an external need. In the muscle there are buffers of all kinds, salts of stronger and of weaker protein acids, phosphates, and bicarbonates. The salts of the weaker acids may be transformed into their undissociated acids by chance acidic metabolic products, and even by an undue excretion of sodium or potassium by the kidney. Exercise, especially regular exercise, stimulating and regulating the oxidative and excretory functions of the cells, may protect the more unstable protein buffers from such acid contamination, and so lead to those three essentials of bodily fitness, (*a*) quickness of muscular response and relaxation, (*b*) immunity from fatigue, dyspnoea, and their unpleasant consequences, and (*c*) a high upper limit of the effort which can be made, beyond the range of a contemporary oxygen supply.

The subject of tissue buffers is at present of necessity speculative. A further study of the physico-chemical properties of muscle proteins, unchanged as far as possible by chemical or manipulative treatment, may throw much further light upon the problem of muscular effort, muscular stiffness, and dyspnoea. In applying such results to muscular exercise in man it is well to make a clear mental separation of the two great types of effort—(*a*) the sudden, violent, and anaerobic type, and (*b*) the long-continued type, involving contemporary oxidation. Short-lived, vigorous efforts are made almost entirely by the expenditure of 'capital', in the form of lactic acid production: long-continued, milder efforts by the expenditure of 'income', in the form of rapidly ensuing, almost contemporary oxidation. Thus short and violent exercise depends largely, if not mainly, on the ease with which lactic acid is dealt with by the tissue buffers; long-maintained exercise on the efficiency of oxidation, and the ease and liberality of oxygen supply.

N. *The Oxidative Factor in Muscular Fitness.*

An efficient oxidative metabolism will tend to maintain a low resting lactic acid minimum in the muscle, and probably to restrain the appearance of acid metabolites likely to neutralize the more efficient but less stable buffers of the

muscle substance. When the organism is subjected to a low oxygen pressure, the initial discomfort and muscular disability are doubtless to be associated partly with the lower oxygen pressure in the brain and heart, partly with the fact that the rate of oxidative recovery from exercise is diminished. In addition, however, it would seem probable that a reduced oxygen pressure, by slowing the last stages of recovery and by diminishing the resting oxidative break-down of waste products of metabolism, would decrease the efficiency of the most potent protein buffers of the muscle, and so lead to greater discomfort following a sudden effort. It would be of great interest, therefore, to ascertain the extent of the maximum oxygen debt—(*a*) at sea-level, and (*b*) at high altitudes, before and after acclimatization.

The chief oxidative factor in muscular effort is concerned, however, with its prolongation by means of a rapid and efficient recovery. The 'efficiency' of recovery we have discussed already above: it appears to change with the condition of the muscle, and may well vary from one individual to another. The rapidity of recovery depends upon a variety of factors, upon the oxygen supply and pressure, upon the temperature, *and upon the intrinsic oxidative power of the living cells.* It is usual to treat capacity for exercise, and freedom from the unpleasant symptoms of dyspnoea, as though they resided merely, or at any rate mainly, in the supply of oxygen through the lungs and circulation, and in the degree of buffering of the blood. Indeed, books and articles are written on respiration which take little or no account of the oxidative function of the cell, the mechanism thereof, and the factors which influence it. This is natural, in a sense, since so little is known about the oxidative mechanism. Something, however, is known, and a short discussion of the oxidative mechanism may be of interest here. It will emphasize how many possibilities there are in explaining the various abnormalities of response to exercise.

The oxygen supply to the active muscles in man, depending as it does on the efficiency of heart, lungs, and circulation, on the corpuscles, haemoglobin, and alkalies in the blood, on diffusion of oxygen in the tissues, and on the pressure of oxygen in the air, has been already the subject of innumerable investigations. We have been able to add little to these, beyond the experimental proof that the rate of oxygen supply can attain considerably higher values than had previously been supposed. Experiments with isolated muscles have made it clear, even apart from experiments on man, that the oxidative process of recovery is intimately dependent on the pressure of oxygen, increasing rapidly in speed as the latter is raised. Hence, even in moderate prolonged exercise, a vigorous circulation is advantageous in maintaining a higher average oxygen pressure in the active muscles, and so ensuring a lower level of the lactic acid in the final 'steady state' attained, with less resultant fatigue and smaller after-effects. A higher oxygen pressure would appear to be always an advantage. *It must be regarded, however, as merely antecedent, and contributory to the speed of the oxidative cell process itself.* Of this latter little can be said, because so little yet is known; with further research, however, it will almost

certainly prove to be the most important factor of all in facilitating and completing the cycle of muscular activity.

It might have been supposed that in man the speed of the recovery process depends simply upon the supply and the pressure of oxygen, that the muscle restores itself, with the oxidative removal of lactic acid, exactly as fast as the supply of oxygen enables it; if this were so the curves of Fig. 1 would represent merely the oxygen supply to the active muscles, falling gradually to its resting value on the cessation of exercise. The form of the curves makes this, *a priori*, very improbable; there is conclusive evidence, however, from another direction that it is definitely not the case; the oxidative recovery process has an intrinsic speed of its own, like other katalysed chemical reactions, even in the presence of a completely adequate supply of dissolved oxygen. Hartree and Hill (17), in recent experiments, have analysed the course of the recovery heat-production of

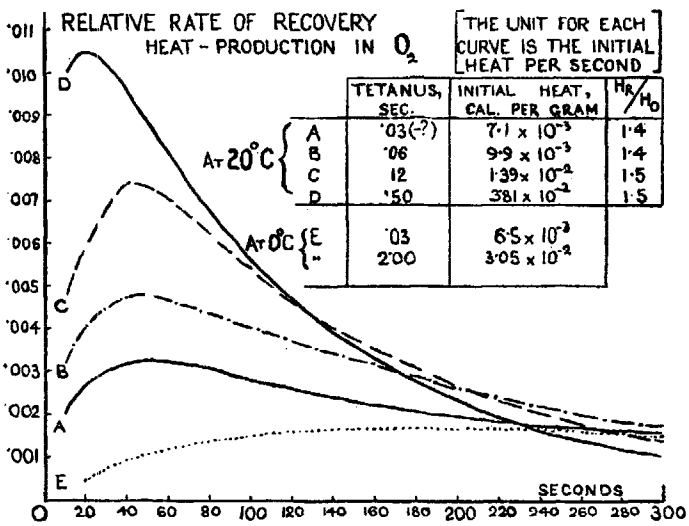

FIG. 5. Recovery heat-production of frog's sartorius muscles in oxygen.

a frog's sartorius muscle suspended in pure oxygen; here the amount of oxygen dissolved in the muscle itself must be far more than adequate to complete the oxidations of recovery from a short tetanic stimulus, so that no delay is interposed by the diffusion of oxygen to the places where it is required. In spite of this the recovery process is very protracted, as is shown in Fig. 5. In 5 min. at 20° C. recovery is by no means complete: at 0° C. it has barely attained its maximum speed. The rate of recovery increases rapidly as the temperature rises, but decreases rapidly as the pressure of oxygen falls. Hence, at 37° C. in man, with a comparatively low oxygen pressure in the active muscle, the rate of recovery is not far different from that in the frog's sartorius at 20° C. and in pure oxygen. The rate at which the chemical processes of recovery occur starts at a low level, rises to a maximum, and then slowly falls again to zero. Moreover, the greater the initial effort from which recovery is necessary, the greater is the relative (not merely the absolute) rate of that recovery. Here, in Fig. 5,

we are dealing with the intrinsic oxidative capacity of the cell itself, uninfluenced by any considerations of oxygen supply. The characteristics of these curves may guide us in the further analysis of the chemistry of the recovery metabolism of muscle.

Many factors are known to influence the speed of oxidative recovery; of these we have mentioned temperature and oxygen pressure, but there are other important chemical agencies which do the same. Cyanides prohibit oxidation (and therefore recovery) completely, even in minute doses. According to Warburg (44) this is due to the removal of traces of katalytic iron, by chemical combination with the cyanide, from its place of action in some formed constituent of the cell. Many narcotic substances hinder or prevent oxidation, probably (according to Warburg (44)) owing to their preferential adsorption to the same formed constituents of the cells. There is strong evidence, derived from a study of the red corpuscles of birds, that the solid parts of the cells are the seat of oxidation. Laking the red corpuscles barely diminishes their oxygen consumption: removal of the 'ghosts' of the laked corpuscles abolishes it entirely. Apparently oxidation takes place at the surfaces of such formed constituents of living cells, by adsorption of the oxidizable body, and through a reaction katalysed by traces of adsorbed iron. Narcotics displace the oxidizable body, cyanides remove the iron; both, therefore, hinder or prevent oxidation.

In another direction, recent work by Hopkins (25) has shown the existence in active cells of a chemical body ('glutathione') capable of katalysing oxidations by acting as a 'hydrogen acceptor', so enabling oxidation to occur without the direct and immediate utilization of molecular oxygen. The total quantity of this 'hydrogen acceptor' in muscle is probably very small, so that no appreciable amount of oxidation can occur without the aid of molecular oxygen: there is no possibility, for example, of the 'oxygen debt' in man being noticeably increased by such means. On the other hand, however, the speed and vigour of muscular oxidation may depend largely on the presence of an adequate quantity of such bodies, though the relative importance of this and other factors cannot, as yet, be assessed.

It is obvious, therefore, that—apart from temperature, and pressure of oxygen—there are many possible ways in which the rate of oxidation in a living muscle-cell could be altered. The surfaces, which are the seat of oxidation, might vary in their chemical or colloidal nature: preferential adsorption of bodies analogous to Warburg's narcotics might displace the proper food-stuffs, for example, in disturbances of metabolism; physical or chemical interference with the katalytic iron might diminish the rate of oxidation of the appropriate bodies, even when properly adsorbed; a decrease in the amount or activity of suitable hydrogen acceptors might weaken an essential link in the oxidative chain. These matters still are of necessity largely speculative, and we must wait for further improvements in knowledge of the physical chemistry of living cells. Little, however, is gained by regarding the phenomena of exercise,

respiration, and dyspnoea as simpler than they really are: further knowledge will certainly introduce these other factors.

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