THE POSSIBLE MECHANISMS OF CONTRACTING AND PAYING THE OXYGEN DEBT AND THE RÔLE OF LACTIC ACID IN MUSCULAR CONTRACTION

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Although direct evidence of a quantitative relationship between oxygen debt and lactic acid production in man has never been given, there is general agreement with A. V. Hill’s hypothesis that the oxygen debt is due to the delayed oxidation of a fraction of the lactic acid produced during the anaerobic processes of muscular activity. After the “revolution” produced in muscle physiology by the discoveries of the last few years, mainly after Lundsgaard’s work, and the further observations on men, it seemed to us that the lactic acid mechanism alone is inadequate to explain all the processes which occur in the payment of the oxygen debt, particularly for the following reasons:

a. It has been observed in isolated muscle that most of the lactic acid is produced after the contraction is over, during the first minute of recovery; this does not seem to agree with the fact that the payment of the oxygen debt at the beginning shows no lag even if the exercise is of very short duration.

b. In moderate exercise of long duration in man, involving an oxygen debt of 3 to 4 liters, the changes in lactic acid concentration or in pH of blood are negligible in comparison with the values implied by the assumption of an increment of lactic acid in the body corresponding to the amount of oxygen debt. (See, for the lactic acid concentration in blood following muscular exercise, Owles, 1930; Dill, Edwards, Folling, Oberg, Pappenheimer and Talbott, 1931; for data on pH, Margaria and Talenti, 1933.)

c. There exist oxidative recovery processes following muscular contraction other than the glycogen resynthesis from lactic acid; Lundsgaard (1931) has demonstrated in muscles poisoned with iodoacetic acid the partial resynthesis of the phosphocreatine in the presence of oxygen and in the absence of any lactic acid formation or removal; Clark, Eggleton and

1 A preliminary report of this work has been given at the annual meeting of the Federation of American Societies for Experimental Biology in Cincinnati, April, 1933, and the abstract appeared in the Journal of Biological Chemistry, 1933, 100, lxv.

2 Fellow of the Rockefeller Foundation.
Eggleton (1932) found that heart muscle poisoned with iodoacetate and supplied with oxygen can go on almost indefinitely. Moreover, in the normal muscle only a part of the phosphagen can be restored anaerobically at the expense of the formation of the lactic acid, while a considerable fraction is restored only in the presence of oxygen.

It was our purpose to investigate this problem, particularly in regard to any relation between production and removal of lactic acid and amount and payment of oxygen debt in man.

The behavior of lactic acid. There is no means of measuring directly in man the total lactic acid production or the total amount of lactic acid present in the body at a certain time. The only datum available is the concentration of lactic acid in the blood and we must first make certain whether or not this really represents the total amount of lactic acid present in the body.

The promptness of appearance of lactic acid in muscular exercise as well as the rapid decrease in its concentration as blood passes through an inactive region of the body (Barr, Himwich and Green, 1923), proves that lactate ions diffuse freely between tissues and blood. A free diffusion through the isolated frog's muscles has been observed by Hill (1926) and Evans and Eggleton (see Lovatt Evans, 1930) have found in mammals that within half a minute after a short tetanic contraction, the venous blood coming away from the muscle contains lactic acid at a concentration almost equal to that in the muscle. Thus, except when changes in lactic acid production are so rapid that an equilibrium between the concentrations of lactic acid in tissues and in blood has not been reached, we are justified in assuming the concentration of lactic acid in the blood to be proportional to the total amount of lactic acid in the body.

In preliminary experiments a young athlete, Clapham, ran to exhaustion on a treadmill at 18.7 km. per hour on a 5 per cent grade for 4½ to 6 minutes. The excess lactic acid concentration in the blood, disregarding the values of the first 6 to 8 minutes of recovery, was found to decrease logarithmically according to the formula:

\[ L = L_r + 10^a - bt \]  

where \( L \) is the lactic acid concentration at time \( t \), \( L_r \) the concentration of lactic acid in the blood at rest, \( 10^a \) the extrapolated value of excess lactic acid concentration in the blood at the beginning of recovery and \( b \) the velocity constant. The values of the constants \( a \) and \( b \) were calculated from the experimental values obtained after the first 5 minutes of recovery with the method of least squares, assuming the resting value for lactic acid concentration to be 10 mgm. per 100 cc. of blood. As can be seen in table 1, which gives the values of blood lactic acid concentration in 2 experiments in which the subject ran to exhaustion, the calculated values fit very well
with the experimental ones, the differences being of the same order as the methodical error.³

A formula of the type given cannot be applied satisfactorily to the early phase of recovery. This may be due

a. To delayed lactic acid production, though this in isolated frog's muscle has been shown to last less than a minute (see Hartree, 1932).

b. To the slowness of diffusion of lactic acid from the tissues to blood, and
c. To the lower O₂ tension in the tissues in the first part of recovery, due to failure of the O₂ supply to keep pace with the greater oxygen consumption.

This lag in the disappearance of lactic acid is greater the shorter the

³ The method used for determining lactic acid was that of Friedemann, Cotonio and Schaffer (1927); the blood was collected from an antecubital vein unless otherwise noted.

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### TABLE 1

*Observed and calculated values for lactic acid concentration in the blood of Clapham after running to exhaustion at 18.7 km. per hour on a 5 per cent grade*

<table>
<thead>
<tr>
<th>RECOVERY TIME</th>
<th>LACTIC ACID CONCENTRATION IN ARM BLOOD</th>
<th>Δ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed</td>
<td>Calculated by the formula L = 10 + 10^{2.113 - 0.0185t}</td>
</tr>
<tr>
<td>October 14. Duration of performance, 4 minutes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>min.</td>
<td>mgm. per 100 cc.</td>
<td>mgm. per 100 cc.</td>
</tr>
<tr>
<td>¼</td>
<td>120.0</td>
<td>120.0</td>
</tr>
<tr>
<td>3¼</td>
<td>107.0</td>
<td>107.0</td>
</tr>
<tr>
<td>5½</td>
<td>108.0</td>
<td>108.0</td>
</tr>
<tr>
<td>7½</td>
<td>104.2</td>
<td>104.2</td>
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<tr>
<td>15½</td>
<td>77.4</td>
<td>77.4</td>
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<td>27¼</td>
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<tr>
<td>56½</td>
<td>24.7</td>
<td>24.7</td>
</tr>
<tr>
<td>October 28. Duration of performance, 5½ minutes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>min.</td>
<td>mgm. per 100 cc.</td>
<td>mgm. per 100 cc.</td>
</tr>
<tr>
<td>¼</td>
<td>108.0</td>
<td>108.0</td>
</tr>
<tr>
<td>5</td>
<td>111.0</td>
<td>111.0</td>
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<tr>
<td>7</td>
<td>109.0</td>
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</tr>
<tr>
<td>130</td>
<td>10.4</td>
<td>10.3</td>
</tr>
</tbody>
</table>
exercise and the higher the degree of exhaustion. In fact if the exercise is hard and short enough a rise in blood lactic acid concentration may be observed in the first part of recovery (Hill, Long and Lupton, 1924; also see protocol 9). Margaria and Talenti (1933) have found under such conditions an associated increase in hydrogen ion concentration. The lag is nearly eliminated if the period of exercise is made to last longer, say 10 minutes, which shows that factors a or b or both are the most important in determining such a lag.

The fact that the removal of lactic acid from the body is a logarithmic function of time shows that the rate of removal of the excess lactic acid is proportional to the concentration of the excess lactic acid itself. This fits the conception that the removal of lactic acid is due to the combustion of a fraction of it. We must assume, however, that after the first few minutes of recovery the tissue O₂ tension remains practically constant and the physicochemical changes in the body do not interfere with the process of lactic acid oxidation.

The payment of the oxygen debt, on the other hand, has never been shown to be a logarithmic or any other simple function of the time in spite of efforts made in this direction. Hill, Long and Lupton (1924) affirm that “there are clearly two factors at work, one of which accounts for the initial rapid fall in the oxygen intake on the cessation of exercise, the other for the prolonged remainder of recovery occurring after extended or severe exertion. . . . . Each process is exponential in character—one is rapid; one, however, is slow. Moderate exercise is followed to a preponderant degree by recovery of the rapid type.” These authors attribute the first and rapid phase of recovery to the oxidative removal of lactic acid in the muscles where it was formed, while the second and prolonged phase represents the oxidative removal of lactic acid which has had time to escape by diffusion from the muscles.

If this hypothesis were true we ought to find a close proportionality between oxygen debt and lactic acid concentration in the blood, provided that the exercise has been long enough for complete diffusion of lactic acid to have taken place between muscles and blood at the end of the exercise.

Method. We have performed a series of experiments on the same subject in which the exercise lasted 10 minutes. We assume that in this time and for exercise not involving the maximum metabolic rate, equilibrium is reached as regards diffusion of lactic acid from the muscles at work into the blood stream and from this into the tissues which were not producing lactic acid. This assumption has been proved very nearly correct. After such a period of work, provided a steady state has been reached, the concentration of lactic acid in the blood decreases without showing an appreciable lag from the end of the exercise.

Evidence for this statement is given also by protocol 7 in which the
subject ran for 10 minutes at 14 km. per hour on a 2.5 per cent grade. Samples of blood from the femoral vein, and an arm vein and from the femoral artery were taken at various periods after exercise. In spite of the fact that the exercise was very strenuous involving a metabolic rate very near the maximum, there was but little difference in lactic acid concentration or pH of blood samples taken simultaneously from the various sources. Figure 1 shows the phenomenon; the values for lactic acid concentration are the same for arterial and arm vein blood, and only slightly higher in blood from the femoral vein during the first minutes of recovery.

Various amounts of oxygen debt were produced by varying the intensity of the exercise, which consisted of walking or running on a motor-driven treadmill at various speeds and at various grades.

There is some trouble in measuring the extra oxygen consumption as an effect of previous muscular exercise (we shall not use temporarily the term "oxygen debt" which specifies a mechanism as to the use of the oxygen) as the oxygen consumption after a considerable amount of work does not come back, even in two hours, to the pre-work values. For example, the basal O₂ consumption for the subject Clapham was 240 cc. per minute; this value was reached one-half hour after a 10 minute run at 7.4 km. per hour, while after harder exercise his oxygen consumption per minute was still as high as 270 cc. two hours after the end of work. The resting oxygen consumption then is merely a matter of subjective appreciation. So, following A. V. Hill's procedure, in our first calculations we assumed as resting the O₂ consumption one and one-half hour after the end of the work.

Relation between lactic acid production and oxygen debt, as calculated after
A. V. Hill. Plotting in a coordinate system the concentration of lactic acid in the blood at the beginning of recovery against the after-work extra oxygen consumption so calculated, we obtain the curve represented in figure 2.

For the contraction of an excess oxygen consumption during recovery up to 3 or 4 liters we see no appreciable increase of blood lactic acid. For extra oxygen consumption of 6 liters or more, the concentration of lactic acid in the blood is a linear function of the extra oxygen consumption. It seems that the most obvious way of explaining this behavior is to admit that when the excess oxygen is less than 3 liters the lactic acid mechanism is not involved but some other process, at present unknown. The lactic acid mechanism starts coming into play when the extra oxygen consumption is 3 to 4 liters, while for increasing the extra oxygen consumption over 4 liters it seems that only the lactic acid mechanism is involved. That there is no extra accumulation of lactic acid, even localized in the muscles, corresponding to small amounts of extra oxygen consumption after work is also proved by the behavior of the R. Q. which does not increase in the first stages of recovery more than can be accounted for by the retention of CO₂ at the beginning of exercise (see protocols 1 to 4).
Protocol 1. February 1, 1933. Clapham walking at a speed of 7.5 km. per hour for 10 minutes. Corner figure: Oxygen consumption per minute less the minimum basal oxygen consumption. The values for the speed constants of the alactacid process in this and the following protocols are given for the single experimental data in order of time, as well as the value of the alactacid oxygen debt ($\int_0^\infty dO_2$).

Protocol 2. January 25, 1933. Clapham running at a speed of 9.3 km. per hour for 10 minutes. Corner figure: Oxygen consumption per minute less the minimum basal oxygen consumption.
Protocol 3. January 27, 1933. Clapham running at a speed of 11.3 km. per hour for 10 minutes. In the inserted figure in protocols 3 to 8: oxygen consumption per minute less the minimum basal oxygen consumption and less the amount attributable to the combustion of the excess lactic acid on the assumption of a combustion coefficient of $\frac{1}{10}$.

Protocol 4. February 15, 1933. Clapham running at a speed of 11.3 km. per hour on a 1 per cent grade for 10 minutes.
From the slope of the curve in the later and linear part we can see for this subject that 1 liter of extra oxygen consumption corresponds to a concentration change of 12.8 mgm. of lactic acid in 100 cc. of blood. Assuming a uniform distribution of lactic acid in the body, with water contents of 80 per cent in the blood and of 72 per cent in the body as a whole, the body weight of the subject being 61.2 kgm., 12.8 mgm. of lactic acid in 100 cc. of blood would correspond to 7.0 grams in the body. This amount is removed in the body by 1 liter of oxygen. Since in the combustion of lactic acid, 3 mols. of \( O_2 \) are used for 1 mol. of lactic acid, assuming that the increment in extra oxygen consumption after work in the conditions referred to is only used up in the combustion of the lactic acid, 1 liter of oxygen must be used for the combustion of 1.34 grams of lactic acid, the remaining being resynthesized as glycogen. The ratio between lactic acid burned and total lactic acid removed is \( \frac{1.34}{7.0} = \frac{1}{5.2} \). This value corresponds to the lowest given by A. V. Hill and by Meyerhof for the recovery in isolated frog's muscle.

As we shall see later, the assumption that the extra oxygen consumption is only used in the combustion of lactic acid is probably incorrect, as other oxidative processes are going on. The value \( \frac{1}{5.2} \) given above is lower than the average obtained by Hill and Meyerhof. This is due to the fact that in our calculation we avoided the error of using the whole of the extra oxygen consumption for comparison with the whole lactic acid removed, but employed instead the increment of the extra oxygen consumption for comparison with the increment of lactic acid on the straight portion of the curve.

Figure 2 shows also lactic acid concentration in blood as a function of metabolic rate. The assumption that increase in blood lactic acid is proportional to increase in metabolic rate is not supported by the facts. We see that extra lactic acid formation does not occur except in severe work. Also the lactic acid produced does not account for all the extra oxygen consumed after work, particularly for easy work. In easy work there must certainly be an oxygen debt too, which may be accounted for by the fact that the metabolic rate during work does not reach its steady state immediately, but after an initial period during which the oxygen consumption is lower than the corresponding amount of work. We may then distinguish two mechanisms of contracting \( O_2 \) debt, the one due to the lactic acid, which we shall call the "lactacid" mechanism, and an "alactacid" one where there is no apparent lactic acid formation. The lactic acid mechanism in this subject, running on a treadmill, comes into play at an \( O_2 \) consumption of about 2.4 liters per minute which is 60 per cent of his maximum metabolic rate.

The alactacid mechanism occurs then far more frequently in the ordinary
conditions of life than the lactacid mechanism. This fact, together with the fact that, as we shall see later, the alactacid oxygen debt is paid at a much faster rate than the lactacid oxygen debt, raises the importance of the alactacid mechanism of contracting the oxygen debt to a primary degree. The lactacid mechanism has to be considered more like a mechanism of emergency, though its capacity is greater than that of the alactacid O₂ debt mechanism.

Role of lactic acid in muscular contraction. It appears from figure 2 that up to a considerable rate of work, not exceeding two thirds of the maximum aerobic rate of work, no lactic acid excess appears in the blood, and presumably in the muscles, for the case of the athletic subject investigated. Does that mean that no excess lactic acid is formed in the muscles as a consequence of that amount of work?

The concentration of lactic acid in the muscles depends upon an equilibrium between lactic acid formation and lactic acid removal: there is no doubt that, if the rate of lactic acid formation increases without a corresponding increase in the rate of its removal, a new equilibrium will be set up at a higher lactic acid concentration. The removal of lactic acid, being due to the oxidation of a fraction of the lactic acid itself, depends upon the oxygen tension in the muscles: it is highly improbable and contrary to the usual findings that the oxygen tension is higher in the working muscles

Protocol 5. January 25, 1933. Clapham running at a speed of 14 km. per hour for 10 minutes.
than in the ones at rest; therefore, unless the lactic acid removal in these conditions is due to another mechanism which goes at a faster rate than the mechanism of removal of the lactic acid during recovery for a lactacid oxygen debt, for which we have no evidence, it follows that muscular work at such a rate is accomplished without any lactic acid formation.

The slowness of the removal of lactic acid during recovery may be due either \( a \), to the fact that the speed of the oxidation of the lactic acid is low, or \( b \), to the speed of the reaction lactic acid \( \rightarrow \) glycogen being low. In case of \( a \) we have to exclude the possibility of any important part played by the lactic acid in normal aerobic muscular contractions, because, on this assumption, we would reach in moderate exercise excessively high levels of lactic acid in the body.

For example, assuming that the work is all performed at the expense of the combustion of lactic acid and that no lactic acid is resynthesized to glycogen during work, for the subject Clapham working in a steady state at a metabolic rate of 2 liters of oxygen per minute, a calculation, on the basis that the speed constant for the removal of lactic acid is 0.02, leads to a value of increased lactic acid concentration in the blood of 5 grams per liter. Actually, for such a metabolic rate, we do not observe any increase in lactic acid. On the other hand evidence that oxidation of lactic acid is a slow process is found in the facts \( a \), that at the beginning of recovery when
the oxygen consumption is still very high, the decrease in concentration of lactic acid is no greater than in the later period of recovery, and that for all the period of recovery the combustion of lactic acid accounts only for a small fraction of the total oxygen consumption. We would have expected that, given a great excess of lactic acid in the body, there ought to be at least a proportionality between oxygen consumption and lactic acid disappearance. Moreover, as we shall see later, the speed of removal of lactic acid is affected by the oxygen tension in the inspired air and therefore in the tissues, which shows that the slowness of the reaction is due to the

Protocol 7. February 23, 1933. Clapham running at a speed of 14 km. per hour on a 3.8 per cent grade for 10 minutes.

oxidation of the lactic acid and not to the reaction lactic acid → glycogen which must be independent of the oxygen tension.

It is justifiable, therefore, until direct data on the speed of oxidation of lactic acid in the body are available, to assume as more probable the hypothesis that the slowness of removing lactic acid is due to the slowness of the process of its oxidation.

This interpretation does not, of course, exclude the possibility of the interpretation given by A. V. Hill in 1924, i.e., that the lactic acid, though being formed at all rates of muscular work, does not escape out of the muscles below a certain metabolic rate because "it is hemmed in by a zone in which oxygen supply is adequate, and through which it cannot pass: only
when some regions of the muscles become oxygen-free can lactic acid pass through them and escape into the capillaries." We think, however, that this hypothesis can hardly be reconciled with the following facts: a, no sign of the presence or removal of any acid in the body can be detected from the behavior of the R. Q. up to an after-work oxygen consumption of 4 liters. The period required for consuming this amount of oxygen is long enough for such phenomena to be observed, if present; b, the time required for the removal of lactic acid from the blood is certainly much greater than that which could be accounted for by simple diffusion from blood to the muscles. This requires the assumption that lactic acid diffused into the blood cannot be utilized by the muscles again, an assumption for which we have no evidence.

**Oxygen consumption due to the lactic acid removal.** If the lactic acid concentration of the blood decreases logarithmically, its speed of removal decreases also logarithmically. Thus we have, from (1),

\[
- \frac{dL}{dt} = 2.3 \times b \times 10^a - bt
\]  

(2)

Assuming the total amount of lactic acid in the body uniformly distributed per amount of water, then for our subject, 1 mgm. of lactic acid concentration in 100 cc. of blood corresponds to 0.55 gram of lactic acid: and assuming a combustion coefficient of lactic acid of \(\frac{1}{3}\), i.e., \(-\frac{dL}{dO_2} = 6.7\), where \(L\) is expressed in grams in the whole body and \(O_2\) in liters, and substituting in (2) we have

\[
\frac{dO_2}{dt} = \frac{2.3 \times 0.55}{6.7} \times b \times 10^a - bt
\]  

(3)

which expresses the oxygen consumption due to the removal of the lactic acid on the assumption above. The amount of oxygen debt due to this mechanism will be given by

\[
\int_0^\infty dO_2 = \frac{0.55}{6.7} \times 10^a
\]  

(4)

Subtracting from the values of the oxygen consumption after work the amount due to the basal metabolic rate (0.24 liter per min.) and also the amount due to the lactacid oxygen debt (if any) we obtain curves all more similar to each other. The value of the velocity constant \(b\) has been assumed in these calculations to be 0.02.

The fact that the curves of the remaining oxygen consumption become all more similar to each other is particularly interesting as it was known, after A. V. Hill's work, that the payment of small oxygen debts goes on at a
relatively much faster rate than the payment of large oxygen debts. This fits in with the hypothesis that the lactacid payment of the oxygen debt is a slow process and that such a mechanism only enters into play when large amounts of oxygen debt are required. We must remember that the speed of the payment of the lactacid oxygen debt is the same as the speed of disappearance of the lactic acid from the blood; the velocity constant is for both processes about 0.02, which means that 50 per cent of the reaction is not reached until after 15 minutes and that it takes 1 hour to reach 94 per cent of completion.

Protocol 8. January 27, 1933. Clapham running at a speed of 18.6 km. per hour for 7 minutes.

The oxygen consumption curve from which the minimum resting O₂ consumption and the amount attributable to the lactic acid removal have been subtracted. The curve of the oxygen consumption in recovery less the minimum resting oxygen consumption and the oxygen used in paying the lactacid debt seems to be the sum of two curves, corresponding to two processes occurring at very different rates. The composite curve falls rapidly at the beginning of recovery, a process lasting only 3 to 4 minutes, and then falls slowly and rather irregularly, a process lasting perhaps one-half hour in mild work and two hours or more after strenuous exercise.

The possibility arises that the first rapid fall of the oxygen consumption is due to the presence in the body of an oxygen reserve mechanism. Such an oxygen reserve could be the expression of the difference of saturation of
the hemoglobin between rest and work, particularly for the hemoglobin contained in the working muscles. In Henderson's charts (1928) we see that the difference in oxygen saturation of venous blood between rest and work at an oxygen consumption of 1750 cc. per minute in a non-athletic man corresponds to 40 cc. per liter of blood. Assuming the volume of venous blood is 1.5 liter, only 60 cc. of oxygen could be attributed to this mechanism. Taking into account also the difference in saturation of the arterial blood and of the muscle hemoglobin, we believe that we can safely state that the total amount of oxygen debt attributable to this mechanism cannot exceed 100 cc., which is negligible for the present purposes.

The alactacid mechanism of O₂ debt. In mild exercise we may consider the curve of the oxygen consumption in recovery less the minimum resting O₂ consumption without lactic acid formation as resulting from the summation of two processes. Extrapolating to zero recovery time the slow process, the difference between the summated curve and that corresponding to this slow process will permit an analysis of the fast process. The curve that we obtain in this way is within the limits of experimental error, of the same logarithmic type as the curve of the oxygen consumption due to lactic acid removal, only the speed of this process is much greater. As for the lactic acid mechanism, this function is defined by

\[
\log \frac{dO_2}{dt} = a_t - b_t t
\]

\(b_1\), the velocity constant, is easily calculated knowing the value of \(a_t\), which is defined by \(\frac{dO_2}{dt} = 10^{a_t}\) for \(t = 0\).

The fact that this process has the characteristic of logarithmic decrement is good evidence for attributing to it the significance of an oxygen debt payment. This portion of the debt may be called "alactacid" because it takes place without apparent extra lactic acid formation. The more reliable value of \(b_1\) is obtained at \(t = \) about 2 minutes, because for very small values of \(t\) the experimental error may be very considerable, and for higher values of \(t\) errors due to incorrect extrapolation of the slow function may become considerable. The values for \(b_1\), so calculated for the different times, are given in the protocols; the more reliable value is about 0.60.

This alactacid mechanism of paying an oxygen debt is much more convenient than the lactacid mechanism as far as the speed of payment is concerned. This speed is 30 times greater, taking only half a minute to pay 50 per cent of the alactacid debt, while the payment is practically complete (98.5 per cent) in three minutes.

The total amount of oxygen debt contracted by this mechanism is defined by

\[
\int_0^\infty dO_2 = \frac{10^{a_t}}{2.3 \times b_1}
\]
The coefficient of combustion of lactic acid. In experiments where a considerable amount of lactic acid was formed curves may be derived showing the residual oxygen consumption after subtraction of the minimum resting oxygen consumption and of the oxygen consumption due to the payment of the lactacid oxygen debt on the assumption of a combustion coefficient for lactic acid of \( \frac{5}{6} \). These curves are dissimilar in two respects from corresponding curves obtained in mild exercise without lactic acid formation. One dissimilarity is found in the shape of the curve corresponding to the slow process. Values for \( O_2 \) consumption in this process are smaller in mild exercise. The curve may be flat for the first 1 or 2 hours of recovery and in some cases negative values for \( O_1 \) consumption are indicated. Another dissimilarity is observed in the speed constants. Those calculated in experiments where excess lactic acid formation occurs are about one-half the magnitude of corresponding values derived in the absence of apparent lactic acid formation.

If we calculate such curves on the assumption of a combustion coefficient for lactic acid of \( \frac{1}{6} \) the resulting curves appear to be more nearly the same type as the corresponding curves for mild exercise. Values for oxygen consumption are always positive and the oxygen consumption for the slow process tends to decrease with time as in milder exercise. Also uniform values for the speed constants of alactacid recovery are derived by this calculation whether or not excess lactic acid formation occurs. Finally, in a given experiment, the values for speed constants calculated at different times agree better with each other (see protocol 9). Therefore, it seems to us justifiable to assume as more nearly correct a value of \( \frac{1}{6} \) for the combustion coefficient of lactic acid.

The fact that a combustion coefficient of \( \frac{1}{6} \) was found from the data from figure 1 and \( \frac{1}{6} \) from the data of Hill and Meyerhof may be explained by the fact that in these cases the computation of the oxygen involved not only the oxygen removal of lactic acid but also the oxygen used in the slow process, which may amount to nearly the same value.

Also from a theoretical point of view the value of \( \frac{1}{6} \) as the combustion coefficient of lactic acid seems more probable than the value \( \frac{1}{6} \). If the latter value is correct, the heat of combustion of lactic acid as lactate being 3,501 calories per gram of lactic acid and the heat of transformation of 1 g. glycogen to 1 g. lactic acid, as lactate in the muscles, 340 calories, the efficiency of resynthesis of glycogen from lactic acid comes out to be less than 40 per cent. Now the mechanical efficiency of muscular work performed anaerobically at the expense of glycogen breakdown to lactic acid may be not less than 30 per cent. It follows that the efficiency of glycogen breakdown into lactic acid and the transformation of this chemical energy into mechanical has an efficiency of over 75 per cent. It is hardly believable that this process takes place at a higher efficiency than the proce-
OXYGEN DEBT AND LACTIC ACID IN MUSCULAR CONTRACTION 705

cess of resynthesis of glycogen from lactic acid. This, being a pure chemical process not involving transformation into other kinds of energy, occurs presumably at a very high efficiency.

On the assumption of a combustion coefficient of lactic acid of \( \frac{1}{9} \), the efficiency of resynthesis of glycogen from lactic acid would be about 87 per cent.

The increase in basal metabolism after work. The remaining oxygen consumption does not seem to have anything to do with a real oxygen debt as ordinarily defined. In other words, the oxidative processes which account

![Graph](http://ajplegacy.physiology.org/)

Protocol 9. February 15, 1933. Clapham running at a speed of 18.6 km. per hour for 10 minutes. Corner figures: Oxygen consumption per minute less the minimum basal oxygen consumption and less the amount attributable to the combustion of the excess lactic acid on the assumption of a combustion coefficient of \( \frac{1}{9} \), and of \( \frac{1}{2}, \frac{2}{3} \).

for such an amount of oxygen do not appear to provide the energy for the reconstitution of substances which broke down in consequence of the muscular contraction and whose anaerobic breakdown furnished directly or indirectly the energy developed in the muscular contraction. This conception is supported by the fact that this oxygen consumption takes such a long time to reach the zero value; it may still be 10 to 20 per cent of the minimum basal oxygen consumption, 1 or 2 hours after the end of the work, when quantitatively important properties of the blood have returned to normal. The hypothesis of an increase in the basal metabolism after work was advanced by Hill, Long and Lupton (1924) on the basis of
their findings and those of Benedict and Cathcart (1913) of an increased resting oxygen consumption several hours after the end of severe muscular exercise. The former authors assumed a constant value for the increase in metabolism for all the period of recovery, a value that they deduced from measurements of the oxygen consumption 2 or 3 hours after the end of work.

It seems to us that our calculation indicating that the oxygen used in this slow process decreases uniformly explains the phenomenon in a more satisfactory way than does the assumption of a constant increase of oxygen intake for this process. Since the phenomenon is due to muscular work and continues in evidence for several hours of recovery, it appears likely that it will be more pronounced in the early phase of recovery.

Data on the amount of oxygen consumption due to this mechanism are given in the protocols. After exercise of 10 minutes' duration requiring an oxygen consumption of 1550 cc. per minute, in the first 5 minutes of recovery such extra rest oxygen consumption may be 120 cc. per minute (50 per cent of the minimum resting oxygen consumption). It may be 250 cc. per minute (over 100 per cent of the basal oxygen consumption) for harder work. The time required for attaining the minimum resting oxygen consumption is greater the more severe and prolonged the work.

The oxygen debt as computed by our method may differ greatly from the value obtained by A. V. Hill’s method, which does not take into account all the increase in oxygen consumption after work. Thus, in the 10-minute run at 18.7 km. per hour the oxygen debt as calculated after A. V. Hill for 1$\frac{1}{2}$ hours after the end of work was 12.5 liters. According to our calculations the lactacid oxygen debt was 5 liters, the alactacid one 2.3 liters and the oxygen used in that period of time attributable to an increased rest oxygen consumption amounted to 10.6 liters. The amount of oxygen debt as calculated following Hill’s procedure is 70 per cent higher than our value. In the 7.4 km. per hour run our value for oxygen debt is 0.82 liter while following A. V. Hill’s procedure it is 2.55, three times as great.

This increased oxygen consumption may account for the oscillations and irregularities of the values for oxygen consumption after work. They were not seen in this subject in determinations of the basal metabolism carried on for several hours, nor are they detectable in the curves of lactic acid removal from the blood and therefore in the corresponding oxygen consumption.

The delayed lactic acid appearance in arm venous blood. We mentioned before that the curve showing lactic acid concentration in blood during recovery in the first few minutes deviates from the curve calculated on the

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4 In 9 determinations of the basal metabolism performed on the subject Clapham from 8:30 a.m. until 12:30 p.m. the average oxygen consumption came out to be 0.240 liter per minute with a probable deviation from this value of $\pm 0.004$. 
data of a later period. This phenomenon, however, only follows high
degrees of exhaustion, and it is greater the shorter the exercise. The dura-
tion of this delay in various experiments on Clapham was about 6 to 8
minutes, while in another subject, only capable of a poor performance the
curve of the lactic acid removal took 25 to 30 minutes to reach the normal
logarithmic shape (see protocol 10).

Of the possible explanations, pointed out on p. 691, the low oxygen ten-
sion in the tissues at the beginning of recovery does not seem to affect the
speed of removal of lactic acid to such an extent as to explain this phe-
omenon. On the other hand the delayed lactic acid production in isolated
frog muscle at 20° lasts a very short time after contraction, and is complete
in a minute or so. The delayed lactic acid equilibrium in blood then must
be attributed to the slowness of diffusion of the lactic acid from the muscles
to the blood stream and into idle tissues.

Amounts of the lactacid and alactacid oxygen debts and their significance.
If we plot the amount of lactacid and alactacid oxygen debts as calculated
on the assumption of a combustion coefficient for lactic acid of \( \frac{1}{4} \) against
the metabolic rate, for the experiments lasting 10 minutes, we obtain the
curves represented in figure 3.

The alactacid oxygen debt increases linearly with increase in metabolic
rate to reach a maximum of about 2.5 liters at the maximum metabolic rate, 3.6 liters of oxygen per minute in excess of the resting value. So the alactacid oxygen debt amounts in this subject to 700 cc. for an increase in metabolism of 1 liter of oxygen. It does not seem to be related directly to the intensity of work performed since it does not increase as an increasing proportion of the work is carried on by anaerobic processes.

In moderate work the alactacid oxygen debt accounts for nearly all the lag in oxygen consumption at the beginning of work before a steady state is established.

The lactacid oxygen debt in Clapham is not appreciable until the oxygen intake is about 2.5 liters of oxygen per minute. It increases slowly at first, more rapidly later and the curve becomes vertical at the point corresponding to the maximum metabolic rate. In this region it increases with increasing amount of work performed, which shows that at the highest metabolic rates an increase in oxygen debt is made only at the expense of the lactacid mechanism.

The alactacid oxygen debt is very probably the expression of an oxidative
process in which the energy liberated is spent in repaying the amount of energy set free anaerobically during the muscular contraction, i.e., it is a true oxygen debt in the meaning given by A. V. Hill to this term.

We do not know the identity of the substances oxidized nor the nature of the anaerobic process that requires this latter oxidative process. However, the more important anaerobic change in muscle during contraction, excluding the lactic acid formation, is the splitting of phosphagen into creatine and \( \text{H}_3\text{PO}_4 \) and we know that the reverse process requires, at least in part, the presence of an oxidative process. It seems, therefore, justifiable to advance the hypothesis that the resynthesis of the phosphagen is the process which absorbs the energy developed in the oxidative processes attributable to the alactacid oxygen debt payment. This hypothesis could be checked knowing the amount of oxygen which is required in the resynthesis of the phosphagen, and the amount of phosphagen in the muscles at work.

During rest a certain equilibrium must exist in the muscles between phosphagen and its products of scission. Since phosphagen breakdown accompanies muscular contraction, the steady state of exercise is associated with a new equilibrium in which the amount of phosphagen will be less and the amount of the products of its scission will be greater than at rest. At the end of the work there will be a tendency toward reaching the rest equilibrium state again, and this will go at the expense of the oxidative processes responsible for the alactacid oxygen debt.

This all fits with the findings that an oxygen debt is found also at the lowest rates of work and also with the approximate linear relation between the rate of oxygen consumption and alactacid oxygen debt.

Eggleton (1930) has found that the creatine equilibrium concentrations for resting and for fatigued muscle are respectively 0.005 and 0.023 molar. Since 11,000 calories are evolved per gram molecule of phosphagen hydrolyzed (Meyerhof and Lohmann, 1928) the difference in phosphagen content between fatigued and resting muscle would account for 200 calories per kilogram of muscle, which corresponds to about 0.043 liter of oxygen. On the hypothesis that the alactacid oxygen debt accounts for the resynthesis of phosphagen from its components, 2.5 liters correspond to the exhaustion of about 60 kgm. of muscle. Taking into account that the efficiency of this process may lie, presumably, between 40 and 80 per cent, we reach a figure of about the expected order of magnitude.

On the basis that during muscular contraction phosphagen splits down into \( \text{H}_3\text{PO}_4 \) and creatine and that this may account for the alactacid oxygen debt, we have measured inorganic phosphorus and creatine contents of blood after strenuous work. There is quantitatively little change in the content of creatine, and an increase in the concentration of inorganic phosphorus from about 0.0018 mol. in rest to about 0.0025 after work; this
change is much too small to account for the amount of phosphagen split down, as calculated from the oxygen debt. However, this may be due either to the esterification of the H$_2$PO$_4$, originating from the phosphagen, with the glucose, a process which is known to happen, or to the fact that phosphate is practically indiffusible through the muscle membrane (G. Eggleton, 1933); the smallness of the creatine increase in the blood may be explained by its failure also to diffuse out of the muscle cells.

We venture no hypothesis as to the nature of the substances oxidized in payment of the oxygen debt; we have no reason to suppose that they are substances other than those usually burned during other activities of the tissues.

As far as the lactacid oxygen debt is concerned, there is no doubt, after the work of Hill and Meyerhof, that this accounts for the energy of resynthesis of the glycogen from the lactic acid. However, we have no direct evidence for supposing that the destiny of such oxygen is to burn part of the lactic acid itself. The slowness of the removal of the lactic acid may be due to the fact that the resynthesis of the lactic acid into glycogen is a slow process, or to the fact that the oxidative processes furnishing the energy for such a resynthesis are slow. In the latter case we have to assume that the resynthesis of the glycogen cannot take place by oxidation of the usual fuel, because these oxidative processes may go at a much faster rate. This is evident from the behavior of the payment of the alactacid oxygen debt and from the oxidative processes taking place when muscular work is performed aerobically at the highest metabolic rate.

That this really is so is very probable, in view of the influence of the oxygen content in the inspired air on the speed constant of the removal of lactic acid. Then we must conclude that the speed of disappearance of lactic acid is slow because the combustion of the lactic acid is a slow process, and that the resynthesis of glycogen from lactic acid can only occur at the expense of the oxidation of the lactic acid itself.

A fraction of the oxygen debt being due to lactic acid formation, we can increase the capacity of oxygen debt by increasing the capacity of the body for lactic acid. Meyerhof showed that the lactic acid concentration in the exhausted isolated muscle is much greater if the muscle is kept in an alkaline medium.

Also in man the values of blood lactic acid following exhaustion are much higher if the man started the work with higher alkali reserve (see Dill, Edwards and Talbott, 1932). This may mean that we may be able to increase the capacity for work by increasing the alkali reserve.

We performed two experiments on Clapham in which three hours before the performance of work he took 20 grams of sodium bicarbonate: the exercise consisted in running on the treadmill at 18.7 km. per hour on a 5 per cent grade. In table 2 the two experiments are compared with two
other experiments performed in the same conditions but without previous ingestion of alkali.

It seems from these data that really, together with a higher lactic acid concentration in the blood, the performance was better. No appreciable change can be seen in the total O₂ consumption after exercise; however this measurement is subject to large sources of error, certainly greater than the variation expected, which is 1 liter of oxygen for every 24 mg. of increase in lactic acid concentration in the blood.

Calculations of the lactacid oxygen debt, as described in this paper, on the experiments with ingestion of NHCO₃ cannot bring evidence for an increase of the lactacid oxygen debt, as they are made on the assumption that the lactacid oxygen debt is proportional to the lactic acid accumulation.

These two experiments with bicarbonate are perhaps complicated by the fact that the subject was somewhat nauseated when he began running.

| TABLE 2 |
|---------|-----------------|-----------------|-----------------|-----------------|
| DATE    | PREVIOUS        | MAXIMUM         | O₂ DEBT         | SPEED            |
|         | TREATMENT       | L. A. CONCENTRATION | CALCULATED | OF DISAPPEARANCE |
|         |                  | mgm. per 100 cc. | A. V. HILL      | OF L. A.         |
| Oct. 14 | —                | 121             | 12.70           | 4               | 0.0185          |
| Oct. 21 | 20 g. NaHCO₃    | 130             | 11.20           | 5½              | 0.0186          |
| Oct. 28 | —                | 110             | 11.46           | 5½              | 0.020           |
| Nov. 23 | 20 g. NaHCO₃    | 120             | 11.44           | 6½              | 0.023           |

The subject was left to decide when he had reached exhaustion and this decision may have been influenced by extraneous circumstances.

Effect of the oxygen tension on the amount of oxygen debt and on the duration of the performance. Averages of two experiments performed breathing a 40 per cent oxygen mixture and of two experiments breathing in air are compared in table 3 with one experiment performed breathing a 14 per cent O₂ mixture.

An increase in the percentage of oxygen in the inspired air seems to go parallel with a decrease in the capacity to accumulate lactic acid. It may be that a limit to the production of lactic acid is given by the acidity of the tissues. Working at a maximum metabolic rate, the CO₂ tension in the tissues is greater when a high oxygen percentage mixture is breathed, because the CO₂ production is greater, while the pulmonary ventilation, being at its maximum value, cannot vary whatever the oxygen content in the inspired air. Then if the tissue acidity limits lactic acid production, the capacity for accumulating lactic acid decreases with increasing amount
of oxygen in inspired air. This hypothesis is in agreement with the findings obtained in the bicarbonate experiments, which may be explained on the same lines.

On the assumption that the lactacid oxygen debt is proportional to the lactic acid content of the body at the end of work plus that produced during recovery, we conclude that also the lactacid oxygen debt is less when breathing high oxygen mixtures.

The speed constant of the lactacid process increases in the same direction as the amount of oxygen in the inspired air, which is in agreement with the hypothesis that the lactic acid removal is due to an oxidative process. Moreover, if the resynthesis of lactic acid to glycogen were due to the combustion of ordinary fuel, whose speed of oxidation is certainly very high, and if the slowness of removing lactic acid were due to the slowness

Table 3

<table>
<thead>
<tr>
<th>DATE</th>
<th>MIXTURE BREATHE</th>
<th>TIME OF PERFORMANCE (min)</th>
<th>MAXIMUM LACTIC ACID CONCENTRATION (mgm. per 100 cc.)</th>
<th>INITIAL RESIDUAL LACTIC ACID CONCENTRATION (mgm. per 100 cc.)</th>
<th>OXYGEN INTAKE AT END OF EXERCISE (liters per minute)</th>
<th>OXYGEN INTAKE AT LACTIC DEBT (liters)</th>
<th>OXYGEN INTAKE AT LACTIC DEBT (liters)</th>
<th>OXYGEN INTAKE AT LACTIC DEBT (liters)</th>
<th>CALCULATED LACTIC DEBT (liters)</th>
<th>OXYGEN INTAKE AT LACTIC DEBT (liters)</th>
<th>OXYGEN INTAKE AT LACTIC DEBT (liters)</th>
<th>SPEED CONSTANT OF LACTIC DEBT (liters per minute)</th>
<th>SPEED CONSTANT OF LACTIC DEBT (liters per minute)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oct. 14.</td>
<td>Air</td>
<td>4</td>
<td>115</td>
<td>150</td>
<td>3.85</td>
<td>2.5</td>
<td>6.16</td>
<td>0.0195</td>
<td>0.60</td>
<td>0.60</td>
<td>0.60</td>
<td>0.60</td>
<td>0.42</td>
</tr>
<tr>
<td>Oct. 28.</td>
<td>Air</td>
<td>5</td>
<td>115</td>
<td>150</td>
<td>3.85</td>
<td>2.5</td>
<td>6.16</td>
<td>0.0195</td>
<td>0.60</td>
<td>0.60</td>
<td>0.60</td>
<td>0.60</td>
<td>0.42</td>
</tr>
<tr>
<td>Nov. 11.</td>
<td>O₂ 40.5%</td>
<td>4</td>
<td>115</td>
<td>150</td>
<td>3.85</td>
<td>2.5</td>
<td>6.16</td>
<td>0.0195</td>
<td>0.60</td>
<td>0.60</td>
<td>0.60</td>
<td>0.60</td>
<td>0.42</td>
</tr>
<tr>
<td>Dec. 2.</td>
<td>O₂ 43.3%</td>
<td>7½</td>
<td>115</td>
<td>150</td>
<td>3.85</td>
<td>2.5</td>
<td>6.16</td>
<td>0.0195</td>
<td>0.60</td>
<td>0.60</td>
<td>0.60</td>
<td>0.60</td>
<td>0.42</td>
</tr>
<tr>
<td>Jan. 23.</td>
<td>O₂ 13.64%</td>
<td>7½</td>
<td>115</td>
<td>150</td>
<td>3.85</td>
<td>2.5</td>
<td>6.16</td>
<td>0.0195</td>
<td>0.60</td>
<td>0.60</td>
<td>0.60</td>
<td>0.60</td>
<td>0.42</td>
</tr>
</tbody>
</table>

of the reaction lactic acid $\rightarrow$ glycogen, the speed of removing lactic acid would be unrelated to variation in oxygen tension. This finding supports the hypothesis that the slowness of the removal of lactic acid is due to the slowness of the oxidative process of combustion of the lactic acid itself.

We saw that for a constant content of oxygen in the inspired air the amount of alactacid oxygen debt is nearly proportional to the increase in rate of oxygen intake during exercise. It was interesting to see whether the amount of alactacid oxygen debt depended on one or the other of these two processes which run parallel. This problem can be solved by performing work at the same rate but at different rates of oxygen intake. This can be attained by breathing mixtures of various oxygen contents. From formula (6) the amount of alactacid oxygen debt is proportional to the extra oxygen consumption per minute in exercise over the resting and the lactacid oxygen consumption, and inversely proportional to the speed constant of
the alactacid mechanism. If this speed constant increases with an increase in work, the amount of alactacid oxygen debt remains constant. This is what really seems to happen: breathing a 13.6 per cent oxygen mixture the value of the speed constant for this process decreases to about 0.42 with a total alactacid oxygen debt of 2.5 liters. Breathing a 40 per cent oxygen mixture, though there seems to be an increase in the speed constant of the alactacid process, the increase in work metabolism is rather too small to affect this constant significantly.

It seems, therefore, that the amount of alactacid oxygen debt depends on the rate at which the work is carried on; this hypothesis, on the assumption that this oxygen debt is due to the resynthesis of the phosphagen, is in agreement with the current views on the part played by phosphagen in muscular contraction.

The values of the speed constants both for the alactacid and for the lactacid process decrease in the same direction as the oxygen content in the inspired air. Then we must expect that also the speed of payment of the total oxygen debt decreases with decreasing partial pressure of oxygen in the inspired air. This is in agreement with Margaria's (1928) findings on the speed of payment of the oxygen debt at low barometric pressure.

SUMMARY

1. The removal of lactic acid from the blood during recovery is, disregarding the first period, an exponential function of time: i.e., its speed of disappearance is proportional to the concentration of the lactic acid at that moment.

2. Evidence is given for the validity of the assumption that lactic acid is rapidly diffusible and uniformly distributed through the body, so that the concentration of lactic acid in the blood is proportional to the amount of lactic acid in the body at that time.

3. No extra lactic acid appears in the blood up to a rate of work corresponding to about 2/3 of the maximum metabolic rate, after which the lactic acid increases very rapidly, with an increment of 7.0 grams per increment of 1 liter of O₂ debt as calculated after A. V. Hill.

4. The removal of lactic acid in the body is a very slow process, its velocity constant being 0.02; i.e., one half is removed in 15 minutes. Arguments are presented for the validity of the hypothesis that such a speed is limited by the slowness of the process of the oxidation of a fraction of the lactic acid itself.

5. After (3) and (4) it follows that the lactic acid mechanism would not play any important part in muscular contraction except in very strenuous exercise, probably in connection with the anaerobic conditions in which the exercise is performed.
6. The oxygen consumption curve during recovery may be considered in the simplest way as resulting from the sum of four functions:

a. The basal oxygen consumption as measured before the performance of work, a function independent of time.

b. An oxygen consumption attributable to oxidation of the lactic acid: this, as a function of time, is of an exponential character. This process is a very slow one, the value of the velocity constant being 0.02.

c. Another exponential function of time, occurring at a much faster rate, the velocity constant being 0.6 (50 per cent of the reaction takes place in \( \frac{1}{2} \) minute).

d. An oxygen consumption decreasing during recovery very slowly so that this process may be present several hours after the end of the work; this function is not defined mathematically.

Of these four functions only b and c have the meaning of an oxygen debt payment. The function d has been interpreted as an increase of the resting metabolism caused by the exercise.

7. The mechanism of b is the lactic acid mechanism, as described by A. V. Hill. The mechanism c is independent of any lactic acid formation or removal, and therefore it is indicated in this paper as "alactacid."

8. The facts fit better in the four functions in (6) if we assume as coefficient of combustion of lactic acid 1:10 instead of 1:5. The value 1:10 seems therefore more probable, and this is supported also by a more reasonable value obtainable for the efficiency of the resynthesis of glycogen from lactic acid on such an assumption.

9. The alactacid oxygen debt is approximately a linear function of the oxygen intake in exercise. It is supposed to be related to the oxidation of substances (ordinary fuel) furnishing the energy for the resynthesis of phosphagen split down during muscular contraction. A rough calculation made on this assumption shows that that may be a possible interpretation. The maximum amount of oxygen debt by this mechanism was in our subject about 2.5 liters.

10. The lactacid oxygen debt starts coming into play only when there may be reasons to believe that the work is carried on in anaerobic condition. Its amount, relatively to the total amount of oxygen debt, increases particularly rapidly at the maximum rates of work. The maximum absolute amount is about 5 liters. It may be increased by increasing the capacity of the body to accumulate lactic acid, as for example, after ingestion of alkali.

11. The speed of payment of the alactacid oxygen debt and the speed of disappearance of lactic acid from the blood vary with the oxygen tension in the inspired air. Therefore, the payment of the entire oxygen debt is slower at low oxygen tensions.
12. The disappearance of lactic acid from the blood at the beginning of recovery after strenuous exercise shows a lag which does not seem to be fully explained either by a lag in the diffusion of lactic acid from muscles to the blood or by a slower oxidation of lactic acid, or by a delayed lactic acid production.

In a trained subject this lag has a duration of 6 or 8 minutes. In non-athletic and untrained subjects, incapable of good performances, the lag may last two or three times as long.

We are very much indebted to Prof. A. V. Hill of University College, London, for his friendly and helpful criticism of our paper before publication.

REFERENCES


References to papers and work mentioned in this paper and not quoted may be found in the following monographs or reviews:


