THE RÔLE OF LACTIC ACID IN THE LIVING ORGANISM*

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Historical Introduction

Our views concerning the significance of lactic acid both for muscle and for the organism as a whole have undergone progressive development since the fundamental discoveries of Fletcher and Hopkins in 1907[47]. By associating the production of lactic acid with the work of muscle, these observers initiated a new era in physiology. Lactic acid, they found, accumulates in muscle during anaerobic contractions, and the contractions cease, despite continued stimulation, when a maximum concentration of lactic acid is attained. When work has thus stopped, the muscle becomes capable of additional contractions after it is brought into an atmosphere of oxygen in which the lactic acid gradually disappears from the muscle.

Meyerhof[139], working on excised frog muscle, found that glycogen was the source of the lactic acid produced during muscular contraction and that roughly three-fourths of the lactic acid removed in the presence of oxygen was reconverted to glycogen. The inference was that the portion of the lactic acid (one-fourth) which was not reconverted to glycogen was oxidized, since a respiratory quotient of unity was observed (Meyerhof[138]). Moreover, the "extra" oxygen consumption, *i.e.*, the volume beyond the resting intake, was approximately the volume necessary to oxidize the fraction of lactic acid not transformed to glycogen.

These results agreed with those of A. V. Hill[63], who had previously made myothermic measurements, and had concluded that the heat liberated during the contraction of muscle could account for the oxidative removal of but a portion of the lactic acid disappearing during recovery from exercise.

Sources of Energy for Anaerobic Contraction of Muscle

Since glycogen contains more energy than lactic acid, energy is liberated for muscular work (Meyerhof[140]) during the formation of lactic acid. This would appear to account for some of the energy of anaerobic contraction, and it was inferred that this energy was used directly for muscular contraction. Embden and his school, however, did not accept this hypothesis (Embden, Lehnartz and Hentschel[86], Lehnartz[107]). They believed that the production of lactic acid energized relaxation. Evidence in favor of Embden's idea is found in the observation that a portion of the lactic acid may be liberated after and not during muscular contraction (Hartree[56], Meyerhof and

Schulz[151], Cattell and Hartree[21]). Nevertheless, this point of view was not accepted until the striking experiments of Lundsgaard[116, 117, 118, 119, 120] clearly demonstrated that lactic acid was not essential for muscular contraction.

It now appears that the energy for muscular work comes directly from the splitting of phosphocreatin into phosphoric acid and creatin (Lundsgaard[116, 117, 118, 119]). According to the present conception, muscle becomes less acid early in contraction, for phosphoric acid and creatin are more alkaline than is their parent substance, phosphocreatin (Fiske and Subbarow[45], Lipmann and Meyerhof[110]). Only later, when there is an accumulation of lactic acid, is a greater acidity established in muscle. Lundsgaard[116, 117, 118, 119, 120] achieved a great advance when he found that in muscle poisoned with monoiodoacetic acid, contraction takes place which is normal in all respects (Henriques and Lundsgaard[60]), except that it occurs apparently without liberation of lactic acid. However, there is no doubt that lactic acid is involved in the process of anaerobic contraction, for the poisoned muscle can do only a small fraction of the work of a normal one (Lundsgaard[116]). Indeed, the inability to form lactic acid, whether due to the inhibitory effect of fluoride (Lipmann[109]), or to lack of its precursor, glycogen (Meyerhof and Himwich[144], Ochoa[158]), may also serve to diminish the amount of work done by muscle. The next step forward has just been made by Meyerhof and Lohmann[147] who believe that another substance, adenosintriphosphate, discovered in muscle by Embden and Zimmermann[39] intermediates the actions of phosphocreatin and glycogen (Fiske and Subbarow[46], Embden and Schmidt[40], Lohmann[113]). On the hydrolysis of this substance, with the production of phosphoric acid, ammonia, and inosinic acid (Lehnartz[106]), energy is liberated which may be used for the resynthesis of phosphocreatin (Meyerhof and Lohmann[147]). It is thus possible that there are three links in the chain of events occurring during the anaerobic contraction of muscle. The direct energy for the action arises in the splitting of phosphocreatin. Work continues only because phosphocreatin is resynthesized by means of the energy released on the hydrolysis of adenosintriphosphate. Finally, for the reestablishment of adenosintriphosphate, energy is supplied by the breakdown of glycogen to lactic acid.

The function of adenosintriphosphate becomes more clear in the light of Meyerhof's[141] and Meyer's[137] work on the enzyme of glycolysis, *i.e.*, of lactic acid formation. They have been able to show

that this enzyme exists in the form of a complex, consisting of a thermolabile protein-containing portion—the enzyme or group of enzymes which catalyze the splitting of glycogen to lower forms of carbohydrate, glucose and finally lactic acid—, and a dialyzable portion, the co-enzyme. More recently it has been found (Meyerhof, Lohmann and Meyer[148]) that the co-enzyme, in turn, consists of two parts—one autolysable and the other not so. The first proves to be adenosintriphosphate, and the latter magnesium (Lohmann[114]), and both are necessary for the formation of lactic acid. Adenosintriphosphate serves as part of the co-enzyme for on its hydrolysis phosphoric acid is furnished for the formation of hexosephosphate, which is not necessarily the hexosemonophosphate isolated by Embden and Zimmermann[38]. According to the working hypothesis of Meyerhof[141] a labile hexosemonophosphate is an intermediary stage in the breakdown of glycogen to lactic acid. Thus Meyerhof believes that the hydrolysis of adenosintriphosphate subserves two functions. Energy is released for the resynthesis of phosphocreatin, and phosphoric acid for the formation of hexosephosphate. Finally, when the lactic acid maximum has been attained, work ceases until it is paid for by oxidations. The energy thus obtained is used directly for the resynthesis of glycogen and, therefore, indirectly for that of adenosintriphosphate and phosphocreatin. The muscle then is the same as before work, except for the loss of the foodstuffs which were oxidized. The chemical changes occurring during muscular contraction are summarized below:

1. Phosphocreatin → phosphoric acid + creatin + energy for contraction of muscle
2. Adenosintriphosphate → phosphoric acid + inosinic acid + ammonia + energy for resynthesis of phosphocreatin
3. Glycogen → lactic acid + energy for resynthesis of adenosintriphosphate
4. Lactic acid + energy from oxidations → glycogen

Foodstuffs Oxidized by Muscle

A. V. Hill (Furusawa, Hill, Long and Lupton[48]), Macleod[122], and others have contended that only carbohydrate can be oxidized, even by mammalian muscle. On the other hand, there is much evi-

dence that both fat and carbohydrate are utilized (Lusk[121]), for the respiratory quotient of the exercising mammalian organism may vary from 0.7 (that of fat) to 1.0 (that of carbohydrate) (Benedict and Cathcart[9], Anderson and Lusk[1], Krogh and Lindhard[100], Boothby and Barborka[12], Henderson and Haggard[59], Richardson and Levine[164], Wilson, Levine, Rivkin and Berliner[196], and Talbott, Fölling, Henderson, Dill, Edwards, and Berggren[183]), and therefore differs from that of excised frog muscle which is fixed at unity. Another way to decide which foodstuff is oxidized is to determine the respiratory quotient of mammalian muscle rather than that of the entire organism.

Such a direct attack on this problem was made by analyzing the arterial and venous blood of muscles, both during rest and exercise, for carbon dioxide and oxygen to obtain the respiratory quotient (Himwich and Castle[70], Himwich and Rose[86]). In order to avoid an anesthetic, the dogs used as the experimental animals were decerebrated. It was found that during rest and exercise the respiratory quotient of the muscles was not necessarily unity, but varied between 0.7 and 1.0. This gives additional support to the concept that not only carbohydrate but also fats are burned by muscles to supply the energy necessary to reconvert lactic acid to glycogen.

How are the foodstuffs brought to muscle? It has been known for a long time that mammalian muscle removes glucose from the circulating blood. More recently the absorption of fat from the blood passing through the extremities of fasted, phlorhizinized and depancreatized dogs has been observed (Himwich, Chambers, Hunter and Spiers[71]). If some of this lipoid is utilized by muscle the blood stream is the carrier of the fat oxidized in that organ. Thus the quantities of fat and glucose oxidized by muscle depend partly on the respective amounts of these two foodstuffs available; amounts which are determined by diet, storage, and other factors, and also by the condition of the animal, as for example in diabetes.

The respiratory quotient of unity of excised frog muscle (Meyerhof[188]) indicates that either lactic acid or glucose is oxidized, and it has been shown that lactic acid is burned by frog muscle (Lipmann[108], Meyerhof and Boyland[148]). On the other hand, in addition to fat, mammalian muscle burns glucose and not lactic acid. Lactic acid, on the contrary, is reconverted to glycogen. It is possible to gain evidence for such a conclusion only when a distinction can be made between the oxidation of lactic acid and of glucose.

Studies of the respiratory metabolism of the intact mammal (Banting, Best, Collip, Hepburn and Macleod[4], Murlin, Clough, Gibbs and Stokes[153]) reveal that insulin increases the oxidation of carbohydrate. It is likely that insulin is necessary for the combustion of glucose and not of lactic acid, for the brain—the only organ intensively studied which burns lactic acid—does so in the absence of insulin. Since muscles of depancreatized dogs (Doisy, Briggs, Weber and Koechig[34], Himwich, Chambers, Koskoff and Nahum[72]), like those of diabetic patients (Himwich, Loebel and Barr[83], Hetzel and Long[61]), continue to form lactic acid, the respiratory quotient of 0.7 (Richardson, Shorr and Loebel[165]) secured from strips of muscle excised from depancreatized dogs indicates that fat only is oxidized when glucose cannot be utilized in the absence of insulin. The lactic acid which is present is not oxidized.

It is not probable that the inability of mammalian muscle to burn lactic acid is due to the lack of insulin and is, therefore, a phenomenon confined to diabetic muscle. When lactic acid is added to the suspending medium of normal mammalian muscle its oxygen consumption increases, but the respiratory quotient does not rise as it should if the lactic acid were oxidized (Shorr, Loebel and Richardson[176]). It would be a crucial experiment to determine whether carbohydrate could still be oxidized by mammalian muscle in the presence of monoiodoacetic acid.

Insulin is not only necessary for the oxidation of glucose; some observers (Lawrence[104], Rabinowitch and Bazin[162]) believe that it is also needed for the formation of glycogen. Insulin is certainly required for the accumulation of glycogen in skeletal muscle and liver (Banting, Best, Collip, Macleod and Noble[5], Cori[24], Best, Hoet and Marks[10]). In organs which form glycogen, the various intermediary steps in its utilization may be explained by Meyerhof's[142] conception that glycogen supplies the hexose necessary for the formation of hexosemonophosphate. This labile substance may be subjected to anaerobic or aerobic changes. It may form lactic acid and phosphate anaerobically as described above, or in the presence of insulin it may combine with oxygen to produce carbon dioxide, water, and phosphoric acid. Tissues like brain (Ashford and Holmes[3]) which do not form glycogen, oxidize glucose only after its transformation to lactic acid and this is done without any intermediary phosphate compound.

Factors Affecting the Rate of Formation of Lactic Acid

Monoiodoacetic acid and fluoride. The rates both for the formation of lactic acid and its reconversion to glycogen, are changed by various reagents. The fact that monoiodoacetic acid inhibits the formation of lactic acid has already been mentioned. Monobromacetic acid possesses the same action and for the same reason, because the splitting of the intermediary hexosemonophosphate is prevented (Lundsgaard[116]). Since frog muscle oxidizes carbohydrate only after its conversion to lactic acid, under the influence of monoiodoacetic acid the respiratory quotient falls from approximately 1.0 towards 0.7 (Meyerhof and Boyland[143]) as the lactic acid present is consumed. However, if lactic acid is added the respiratory quotient rises towards its usual value. More is known concerning the mechanism of the similar actions of fluoride and oxalate in preventing glycolysis. A hexosediphosphate is formed on the addition of fluoride or oxalate to minced muscle (Embden and Zimmermann[37], Deuticke[31]). Apparently the effect of these substances is to change the labile hexosemonophosphate into a hexosediphosphate which breaks down to lactic acid only with difficulty. Fluoride, like monoiodoacetic acid, has a lesser effect on oxidations, for in its presence amphibian muscle will oxidize lactic acid added to the suspending medium (Lipmann[108]).

Amylase. Amylase, whether secured from the pancreas or from the submaxillary gland, also prevents the formation of lactic acid from glycogen. Ronzoni, Glaser and Barr[167], and others, have demonstrated that no esterification of phosphate takes place in the presence of pancreatic amylase. Since muscle amylase and that of the digestive glands split glycogen to different end-products, Case[20a] believes that pancreatic amylase displaces muscle amylase in the Meyerhof enzyme complex, thus changing the intermediary steps in the cleavage of glycogen and preventing the production of the hexose necessary for the formation of the labile hexosemonophosphate.

It is interesting to note that glycolysis of excised malignant tissue may be inhibited by pancreatic amylase or monoiodoacetic acid (Harrison and Mellanby[53, 54]). However, the mechanisms of inhibition are not the same as in muscle, since cancer tissue forms no intermediary hexosemonophosphate in the process of glycolysis. It has been mentioned before that the existence of this labile hexosemonophosphate is regarded by Meyerhof[141] as a working hypothe-

sis. It must be remembered that changes in the concentration of this labile substance were not determined by direct analyses, but were only inferred from those of inorganic phosphate.

Tumors acquire energy not only anaerobically, but also from oxidations, and malignant tumors in the rat have been arrested (Warburg, Wind and Negelein[193], Campbell and Cramer[17]) or even cured by placing the animal in an atmosphere of reduced oxygen tension (Sundstroem and Giragossintz[181]).

Acid-base equilibrium. The effect of changes of the acid-base equilibrium is definite. The accumulation of lactic acid, whether occurring in exercise or as a result of injections of adrenaline (Tolstoi, Loebel, Levine and Richardson[184]), causes a diminution of the alkali reserve of the blood and an acidosis (Peters and Geyelin[161], Barr and Himwich[8]). Injections of alkali also cause the accumulation of lactic acid (Macleod and Knapp[123]). This liberation of lactic acid acts as a protective device, as does a simultaneous increase in ketone substances (Davies, Haldane and Kennaway[29]). In the pernicious vomiting of pregnancy (Underhill[185]) and in the cyclic vomiting of childhood (Underhill and Steele[187]) the alkalosis associated with the vomiting (Hastings, Murray and Murray[57]) is accompanied by the excretion of lactic acid and ketone substances in the urine. The studies of the heart-lung preparation (Anrep and Cannan[2], Eggleton and Evans[35]) reveal that with increased alkalinity of the perfusing fluid, its lactic acid content is increased, and with greater acidity the lactic acid disappears. Thus in times of emergency lactic acid may act as one of the many factors which aid in the maintenance of the acid-base equilibrium.

Irradiation. The action of irradiation in causing more rapid glycolysis is unexplained (Stivin[180]). This effect is exerted in a solution free of tissue, but containing Meyerhof's enzyme of glycolysis.

Deficiency of the antineuritic vitamin. According to Kinnersley and Peters[96] the antineuritic portion of the vitamin B complex is associated with the intermediary metabolism of carbohydrate. These authors believe that the opisthotonus occurring in pigeons on a diet devoid of this fraction of vitamin B is caused by the stimulating effect of the increased lactic acid concentration localized in the lower parts of the brain.

Narcosis. There are at least two possible explanations for the accumulation of lactic acid during narcosis. It may be either a

specific effect of the narcotic or a result of oxygen lack. The rate of production of lactic acid is increased by gaseous narcotics, both in an intact animal (Ronzoni, Koechig and Eaton[168]) and in excised muscle (Graham[52]). In addition, the reconversion to glycogen is delayed (Long[115]) in dogs under amytal narcosis. This may be imputed, in part, to diminished oxidations (Warburg[190]), since oxygen consumption is decreased during amytal anesthesia (Deuel, Chambers and Milhorat[30]).

Changes in lactic acid caused by ingestion of carbohydrate foodstuffs. Glucose is not the only carbohydrate foodstuff which may yield lactic acid in the body; for other forms of carbohydrate do so even more readily. Analyses of blood collected after oral or parenteral administration of various foodstuffs reveal that dioxyacetone causes the largest accumulation of lactic acid, next comes fructose which in turn is followed by sucrose, probably because the latter yields fructose on digestion. Galactose and glucose form smaller amounts of lactic acid. Since the same effects may be obtained whether dioxyacetone and fructose are given by mouth (Campbell and Maltby[18]), subcutaneously (Himwich, Rose and Malev[87], La Victoire[103]), or intravenously (Wierzuchowski and Laniewski[195], Wierzuchowski[194]) the ability to change these foodstuffs to lactic acid is wide-spread throughout the body (Rose, Giragossintz and Kirstein[169]). Fructose is readily transformed to glycogen in the liver (Cori[24]) and to lactic acid in muscle (Laquer and Meyer[102], Bornstein and Völker[13]), but not by brain (Loebel[111]) nor malignant tissue (Minami[152]).

The rapid rise of the respiratory quotient following the ingestion of dioxyacetone or fructose is probably due to the liberation of carbon dioxide from bicarbonate by lactic acid, though Carpenter and Fox[20] suggest that the change in respiratory quotient produced by fructose signifies its conversion to fat (McClellan, Biasotti and Hannon[130]).

Efficiency of the Reaction: Lactic Acid ⟶ Glycogen

The efficiency of the resynthesis of glycogen from lactic acid by muscle is not the same as the efficiency of muscular contraction. Rather it is one of the many factors upon which muscular efficiency depends. The efficiency of the synthesis of glycogen from lactic acid may be defined as the caloric equivalent of the lactic acid removed, divided by the caloric equivalent of the oxygen consumed in the process. This fraction is known as the Meyerhof quotient.

In the introduction to this discussion it was pointed out that in amphibian muscle four parts of lactic acid disappear for one which is oxidized (Meyerhof[139]). Later work with more refined methods has only substantiated the original observations. Meyerhof and Schulz[150] found a Meyerhof quotient of 4.7 for frog muscle. Hartree and Hill's[55] myothermic measurements permitted a quotient varying from 4.7 to 6.0. Of even greater interest is the Meyerhof quotient of mammalian muscle, for here both carbohydrate and fat are oxidized in the resynthesis of glycogen. Though the Meyerhof quotients for rat (Meyerhof and Himwich[144]) and rabbit muscle (Boyland[15]) are low, those for dog (Shorr, Loebel and Richardson[176]) and bovine muscle (Boyland[15]) vary between 3 and 6.

Hill, Long and Lupton[64] applied these conceptions to human beings, and on the basis of certain assumptions found a Meyerhof quotient of 5.2. Despite the speeding-up of the respiratory, cardiac, and vascular mechanisms which occurs during exercise, the supply of oxygen is often insufficient to meet the emergency, and there is an accumulation of lactic acid in muscle and blood. In the blood and tissues, lactic acid reacts with sodium and potassium bicarbonate, with the consequent liberation of carbon dioxide. This carbon dioxide raises the apparent respiratory quotient above the true one, since the latter depends on the carbon dioxide produced by oxidations. However, during recovery, as lactic acid is removed carbon dioxide is retained in its place, and the apparent respiratory quotient is lower than the true one. The "extra" oxygen, that is, the volume used over the basal amount, is necessary for the oxidative removal of lactic acid. Thus the fraction of carbon dioxide retained, divided by the "extra" oxygen absorbed, affords information regarding the efficiency of the resynthesis of glycogen.

Oxygen Debt

Hill and Lupton[65] compared the reactions of the entire organism with those of muscle and found many similarities. For example, the accumulation of lactic acid during exercise requires the consumption of "extra" oxygen after work is completed, both in muscle and the body as a whole. This is of great importance, since it indicates the ability of the organism to work at a greater rate than is permitted by the immediate supply of oxygen. Thus the consumption of "extra" oxygen has been likened to an oxygen debt, because

it signifies that the body has been working at the cost of future oxidations, *i.e.*, that lactic acid has accumulated. The accumulated lactic acid is the security that the debt will be paid, and the puffing after exercise is the payment. Just as in the isolated muscle, so in the intact animal, lactic acid is a stimulant of respiration, and the greater oxygen requirement of muscle is satisfied by the acceleration of the cardiorespiratory mechanisms. This is possible because the integrated response of the organism is conditioned by the effects of lactic acid, among other factors, on centers (respiratory and others) situated in the medulla and brain (Gesell[51]).

Studies of the respiratory quotient indicate that the "extra" oxygen required for the payment of the debt combines with fat and carbohydrate as the lactic acid is reconverted to glycogen (Marsh[127], Rapport and Ralli[168]).

The most frequent cause for the accumulation of lactic acid is the relative asphyxia of muscle occurring during physical exertion. However, the oxygen supply of tissues may also be insufficient in pathological conditions, especially in those involving the cardiorespiratory system and the blood. Schjerning [172] and Le Blanc[105] have demonstrated a diminished oxygen saturation of the arterial blood whenever a portion of the blood flows through unaerated parts of the lung. This explains the increased concentration of lactic acid which may be observed in tuberculosis and pneumonia (Jervell[94]). In shock, as well as in patients with cardiac disease, a decreased oxygen supply to the tissues may result from the slowed circulatory rate. Meakins and Long[134] have shown that severe circulatory failure is accompanied by an increase in blood lactic acid, even during rest, and that the concentration of the lactic acid varies with the severity of the condition. As might be expected, the rise in the lactic acid level of the blood produced by a given amount of exercise is greater in cardiac patients than in normal subjects. Eppinger, Kisch and Schwarz[41] believe that in cardiac failure the efficiency of the reconversion of lactic acid to glycogen is diminished, so that a greater amount of foodstuffs must be used to accomplish this recovery. Such a change may be one of the causes for cardiac dyspnea. It may also be a factor in sick or debilitated people without lesions of the cardiorespiratory system, for Himwich, Loebel and Barr[88] observed concentrations of lactic acid in the blood of exercising diabetic patients greater than those of people in good physical condition. Another possible explanation for the greater concentration of blood lactic acid

may be a diminished oxygen saturation of the hemoglobin in the arterial blood. This is found during moderate exercise of patients even if they have no lesions of the cardiorespiratory system (Himwich and Loebel[82]). Thus, the oxygen supply of tissues is decreased. In contrast is the effect of exercise in normal subjects in whom the oxygen saturation of hemoglobin increased even with greater exertion (Himwich and Barr[69]). In severe anemia or after hemorrhage, with the diminished ability of the blood to carry oxygen, lactic acid may accumulate (Jervell[94]).

Pituitrin

Subcutaneous injections of comparatively large doses of pituitrin and of pitressin (Himwich and Haynes[77, 78]) diminished the oxygen consumption of rats. The same reaction was observed (Cushing[28]) in patients after injections of pituitrin into the ventricles of the brain. The effect may be due to a direct action on the hypothalamus in which the chief centers of the autonomic nervous system lie. However, pituitrin and pitressin also decrease the oxygen intake of excised diaphragm, liver, and testicle,—tissues which are therefore removed from nervous control (Himwich, Finkelstein and Humphreys[74]). In any case, as a result of the oxygen lack, there is an accumulation of lactic acid in the blood (Himwich and Fazikas[73], Bischoff and Long[11]).

Removal of Lactic Acid by Organs Other Than Skeletal Muscle

Although A. V. Hill was able to obtain valuable information concerning the removal of lactic acid by means of simplifying assumptions, the actual process is not a simple one. Whenever the rate of formation of lactic acid is greater than its removal the concentration in the muscle increases (Martin, Field and Hall[128, 129]) and lactic acid appears in the blood (Barr, Himwich and Green[6], Hill and Lupton[65]), where it may rise to as much as five times the normal value of 10 to 25 milligrams per cent. Lactic acid may then leave the body in the urine and in the perspiration. Whenever its concentration in the blood exceeds the renal threshold of 30 to 40 milligrams per cent (Hewlett, Barnett and Lewis[62]), lactic acid appears in the urine, and during exercise large amounts may be lost in the perspiration (Snapper and Grünbaum[177]). However, the lactic acid

which has accumulated in the blood is removed to the largest extent by organs other than the skin and kidney. It must not be forgotten that the exercising muscles are reconverting as much lactic acid to glycogen as their increased oxygen supply will permit. Resting muscles absorb some of the lactic acid liberated by working muscles (Barr and Himwich[7], Martin, Field and Hall[128, 129]). The lactic acid thus absorbed may be changed to glycogen or returned, after temporary storage, as the lactic acid concentration of the blood diminishes[80, 93a]. Heart, brain, and liver also actively take lactic acid out of the blood.

Heart. The heart is composed of a type of tissue different from that of skeletal muscle, and it may function in a different manner. When lactic acid attains a concentration of about 0.3 per cent the work of skeletal muscle must stop (Meyerhof and Himwich[144]). The heart, on the other hand, can no longer contract after it achieves the comparatively low concentration of 0.07 per cent (Katz and Long[95]). Cardiac muscle is therefore capable of developing only a comparatively small oxygen debt and must rely to a greater extent on immediate oxidations. The fatigue of the heart, resulting from the accumulation of lactic acid, would not only mean the cessation of its work, but because of the rôle which that organ plays in the animal economy, the actual death of the organism. Such a disaster is prevented by the great oxygen supply of the heart. The heart receives a large volume of blood (Markwalder and Starling[126])—much greater than that furnished to an equal weight of voluntary muscle (Himwich and Castle[70]). Thus an abundance of oxygen is brought to the heart and the change of lactic acid to glycogen is accelerated. Indeed, studies of the heart *in situ* revealed that that organ not only did not pour out lactic acid to the blood, but actually removed it from the blood. Despite the distressing conditions of an open thorax and the use of artificial respiration which were necessary in order to examine the heart of dogs, that organ constantly removed lactic acid from the blood passing through the coronary system (Himwich, Koskoff and Nahum[80], McGinty[132]). The normal heart therefore has the ability to remove all of the lactic acid formed within it and, in addition, is provided with an excess of oxygen which is a factor of safety, as is evidenced by the removal of lactic acid from the blood. In diseased conditions when the coronary blood supply is diminished, an accumulation of lactic acid and "cramp" might not be unexpected.

The respiratory quotients of 0.71 of perfused hearts of depancreatized dogs (Starling and Evans[179]) and 0.72 of depancreatized cats (Peserico[160]) indicate that fat only is oxidized. If insulin is not necessary for the combustion of lactic acid, the heart does not oxidize that substance, and the higher respiratory quotients of the heart of normal animals (Visscher and Mulder[189]) point to the simultaneous oxidation of fat and glucose, but not of lactic acid.

Smooth muscle. Although the reversible reaction between glycogen and lactic acid obtains in smooth muscle, just as it does in skeletal muscle, the precise function of glycolysis in the contraction of smooth muscle has not been elucidated. During stimulation of smooth muscle lactic acid is formed from glycogen and, in an atmosphere containing oxygen, lactic acid is reconverted to glycogen (Evans[42]). However, heat, which increases the rate of formation of lactic acid, produces rigor in skeletal muscle, but brings on paralysis of smooth muscle.

Invertebrate muscle. There are interesting differences between the muscles of vertebrate and those of invertebrate animals. In crustacean muscle, for example, arginin takes the place of creatin so that "phosphoarginin" (Meyerhof and Lohmann[146]) is the substance that causes contraction. However, the relationships between glycogen and lactic acid in crustacea are the same as in vertebrata (Boyland[15]). On the other hand, molluscan muscle cannot change its ample glycogen stores to lactic acid. The small amounts of lactic acid formed in molluscan muscle do not originate from glycogen, for the chemical characteristics of molluscan lactic acid are different from those of the lactic acid arising from glycogen (Mendel and Bradley[136]).

Brain. Another organ involved in the removal of the lactic acid liberated chiefly by muscle is the brain. Although brain tissue has the faculty of splitting carbohydrate to lactic acid (Warburg, Posener and Negelein[192], Loebel[111], McGinty and Gesell[133], Holmes and Holmes[92], Himwich and Jacobson[79]) either from glycogen through a hexosephosphate intermediary or from glucose without such an intermediary (Ashford and Holmes[3]), it does not convert lactic acid to glycogen[90], nor does the glycogen of the brain in the living animal appear to enter into the metabolic processes of that organ (Takahashi and Asher[182]). Nevertheless, lactic acid and glucose are absorbed from the blood by the brain of normal (McGinty[131]), phlorhizinized and depancreatized (Himwich and Nahum[84], Nahum, Himwich and

Koskoff[154]) dogs. It is probable that these substances are subjected to an oxidative fate, for the respiratory quotient of the brain is unity (Himwich and Nahum[85]). The brain loses its insulin after pancreatectomy (Nothmann[157]), nevertheless, a study of depancreatized dogs discloses that the cerebral respiratory quotient remains 1.0 (Himwich and Nahum[85]), even in the absence of insulin which is necessary for the combustion of glucose. This indicates that lactic acid, rather than glucose, is oxidized. There are other reasons for the belief that glucose is not oxidized as such, but rather after its conversion to lactic acid. The oxygen intake of brain tissue increases on the addition of glucose. However, if glycolysis is prevented by fluoride, no increase in oxygen intake is observed, yet the presence of fluoride does not inhibit the greater oxidation due to the addition of lactic acid to brain tissue (Holmes[89]). The respiratory quotient of unity observed after pancreatectomy (Himwich and Nahum[85]) may also be explained by the oxidation of lactic acid, since brain tissue of depancreatized cats (Holmes and Holmes[93]), like that of normal animals, is able to oxidize lactic acid. It is possible that carbohydrate, either from cerebroside or nucleoprotein, may be utilized by brain tissue though not necessarily so by brain in the living animal.

It should be pointed out that this process of katabolism of glucose allows the brain two sources of energy instead of one and, therefore, constitutes a factor of safety. Nahum and Himwich[155] have found that large doses of adrenaline may cause the brain to depend on glycolysis more than on oxidations, so that the brain, instead of removing lactic acid from the blood-stream, pours increased amounts of lactic acid into the blood.

Peripheral nerve. The part played by lactic acid in nerve conduction is not clear. Glycolysis may be involved in this process, since in an atmosphere of nitrogen, monoiodoacetic acid, which prevents the formation of lactic acid, also brings about a more rapid loss of excitability (Ronzoni[166]). Gerard and Meyerhof[49] have shown that oxygen prevents the accumulation of lactic acid, for the concentration of that substance is increased by anaerobiosis, even though oxidations do not cause any lactic acid already present to disappear. In contrast to the brain and especially to the gray matter, isolated peripheral nerve does not oxidize lactic acid (Holmes, Gerard and Solomon[91]). Nevertheless, nerve conduction depends on oxidations (Schmitt[173]). The foodstuff used by nerve, at least for its resting metabolism, is probably fat (Fenn[44]), since the

respiratory quotient is low (Gerard and Meyerhof[49], Meyerhof and Schmitt[149]). An increase in inorganic phosphate is ascribed by Gerard and Wallen[50] to the oxidation of organic phospholipids. During activity the respiratory quotient is higher, indicating the oxidation of carbohydrate. The actual observation of foodstuffs consumed by excised nerve discloses a gradual decrease of carbohydrates (Holmes, Gerard and Solomon[91]), and the respiration declines if glucose or galactose are not added to the suspending medium (Sherif and Holmes[175]).

Liver. Perhaps the most important organ in the removal of lactic acid from the blood is the liver. Under the most varying circumstances that organ continues to absorb lactic acid (Himwich, Koskoff and Nahum[80, 81]). On comparing the concentration of the lactic acid in the blood of the hepatic vein with that of the portal and arterial vessels, it was found that the liver of dogs takes significant amounts of lactic acid from the blood passing through it. As might be expected, conditions in which the liver parenchyma has been subjected to severe injury interfere with the removal of lactic acid. Fatty degeneration of the liver, cirrhosis, metastatic carcinoma, acute yellow atrophy, and phosphorus poisoning are often accompanied by an increased concentration of blood lactic acid (Büttner[16], Valentin[188], Noah[156], Schumacher[174], Jervell[94]).

In the liver lactic acid is converted to carbohydrate (Mandel and Lusk[124]), probably glycogen (Cori and Cori[27]), and the glycogen so formed may not only be retained in the liver, but may also reappear in the blood as glucose (Mann and Magath[125], Soskin[178]). The liver makes lactic acid more useful to the organism by reconverting it to glycogen. There thus appears to be a carbohydrate cycle between muscle and liver, muscle sending lactic acid through the blood to the liver, and the liver returning glucose via the blood to muscles so that recovery from the work done by muscle may take place in the liver (Himwich, Koskoff and Nahum[80, 81]). Cori and Cori[26] came to the same conclusion, chiefly as a result of determining the changes, caused by injections of adrenaline and insulin, in the glycogen content of the liver and muscle of rats. The knowledge of this functional relationship is important for an understanding of one of the mechanisms involved in the maintenance of diabetic hyperglycemia.

Hyperglycemia may be regarded as a shift in the equilibrium between glycogen and glucose, away from glycogen and toward glucose. In diabetes there is difficulty in retaining stored glycogen,

which fact may be recognized in the characteristic hyperglycemia of the disease. By analyses of the afferent and efferent blood of liver and muscle for glucose and lactic acid, it was found that the muscles of depancreatized dogs continue to produce lactic acid just as do those of normal animals (Doisy, Briggs, Weber and Koechig[84]). The liver continues to remove lactic acid; but now, unlike the normal animal, carbohydrate is probably not oxidized in the liver nor retained to any extent as glycogen. Instead, the lactic acid reappears in the blood as glucose, accounting for two-fifths of the glucose liberated by the liver (Himwich, Chambers, Koskoff and Nahum[72]). It is probable that the lactic acid is reconverted to carbohydrate at the expense of energy obtained by the oxidation of fat.

Adrenaline. The oxidation of fat in the reconversion of lactic acid to glycogen is increased by injections of adrenaline which simultaneously accelerate the glucose-lactic acid cycle existing between muscle and liver. Adrenaline causes the breakdown of glycogen in the liver (Sahyun and Luck[171]) which releases glucose and thus produces hyperglycemia (Underhill and Closson[186]). At the same time, muscle liberates lactic acid which appears in the blood. Much of the excess lactic acid in the blood is removed by the liver, so that finally there is a greater hepatic supply of glycogen than existed before the injection of adrenaline (Kuriyama[101], Cori and Cori[26]). For a time it was thought that the foodstuff used to supply energy for these processes was predominantly carbohydrate (Cannon[19]), but more recently it has become increasingly evident that there is a shift in the proportions of the foodstuffs oxidized, so that relatively more fat and less carbohydrate is utilized for the resynthesis of glycogen. After injections of adrenaline, the body acts as if it were suddenly put on a higher fat diet, as is indicated by a diminished respiratory quotient (Cori and Cori[26], Colwell and Bright[28]). There is a concomitant lipemia, due to mobilization of the fat depots, thus affording the tissues increased amounts of that foodstuff for oxidation (Himwich and Spiers[88]).

Emotion. In view of these effects of injections of adrenaline it becomes of interest to study conditions in which increased amounts of adrenaline are poured into the blood-stream by the adrenal gland. In emotional crises (fear and rage) (Himwich and Fulton[75]), pain (Fazikas, Spiers and Himwich[48]), stimulation of sensory nerve (Koskoff and Dusser de Barenne[97]), and while shivering (Haynes, Mandelbaum and Himwich[58]), an increased concentration of fat has

been observed in the blood of cats and dogs. Such conditions may increase the amount of fat oxidized. It may be possible that fat, rather than carbohydrate, is the chief fuel during emergencies.

Glands and malignant growths. The formation of lactic acid in organs other than muscle has been extensively studied in excised organs. In column (3) of the following table, taken from Warburg[191], the organs are listed in accordance with their ability to form lactic acid. The integers of column (3) represent the number of milligrams of lactic acid formed per hour per milligram of tissue in an atmosphere of nitrogen. It may be seen that the organs, with the exception of the brain and possibly spleen, testis, and thymus, do not form lactic acid readily. It is doubtful whether lactic acid plays as important a part in the energetics of these glands as it does in muscle.

GLYCOLYSIS AND THE ANTIGLYCOLYTIC EFFECT OF RESPIRATION

Organ	*Animal*	*Ability to glycolyse*	*Effect of respiration*
(1)	(2)	(3)	(4)
Kidney	Rat	+ 3	— 39
Thyroid	Rat	+ 2	— 24
Liver	Rat	+ 3	— 21
Intestinal mucosa	Rat	+ 4	— 20
Spleen	Rat	+ 8	— 16
Testicle	Rat	+ 8	— 16
Pancreas	Rabbit	+ 3	— 7
Pancreas	Dog	+ 4	— 2
Submaxillary	Rabbit	+ 3	— 5
Thymus	Rat	+ 8	— 4
Cortex	Rat	+ 19	— 3
Embryo	Rat (3 mg.)	+ 13	— 11
Embryo	Rat (9 mg.)	+ 23	— 3
Embryo	Chicken	+ 20	0
Hyperplastic tonsils	Man	+ 18	0
Placenta	Rat	+ 14.9	+ 00.3
Papilloma of bladder	Man	+ 26	0
Nasal papilloma	Man	+ 14	+ 4
Carcinoma of bladder	Man	+ 36	+ 16
Chicken sarcoma	Chicken	+ 30	+ 20
Round cell sarcoma	Man	+ 28	+ 18
Retina	Rat	+ 88	+ 26

On the other hand, cerebral cortex, retina, and rapidly growing tissues, whether embryonal or malignant (column 3), have the well-

developed powers of glycolysis which may furnish significant amounts of energy as already considered in the discussion of the brain. Minami[152], in Warburg's laboratory, has calculated that the energy liberated by glycolysis in tumor tissue is 40 per cent of that released by respiration.

The effect of respiration on glycolysis is presented in column (4) of the table. The integers represent the differences of lactic acid in milligrams per milligram of tissue per hour between the amount of lactic acid formed in nitrogen and that removed by oxidations. Thus the negative numbers indicate that oxidations could remove more lactic acid than is produced in nitrogen, while the positive numbers disclose that oxidations are insufficient to prevent the accumulation of lactic acid. In most organs of the body oxidations are of such magnitude that they can account for the disappearance, not only of all the lactic acid formed in the various glands, but even of a greater amount. Thus respiration of these glands is greater than is necessary merely for the removal of lactic acid.

Additional evidence that the formation of lactic acid is not all-important for glandular work is afforded by observations of the submaxillary gland. It was demonstrated that glycogen is the precursor of the lactic acid formed by excised submaxillary gland (Himwich and Adams[67]). However, when the submaxillary gland was examined *in situ*, both during rest and while secreting saliva, there was neither a disappearance of glycogen nor an increase in lactic acid. Moreover, although it was possible to measure a decrease in the blood sugar in its passage through the gland, there was no accumulation of lactic acid in venous blood or saliva to indicate that energy for secretion was obtained predominantly by glycolysis (Himwich and Adams[68]).

The respiration of chicken embryo is just able to check glycolysis (column 4). In contradistinction to rapidly growing embryonal tissue, the respiration of malignant growths is not sufficient to prevent the accumulation of lactic acid. Cori and Cori[25] and Warburg, Wind and Negelein[193] have found that the venous blood returning from tumors contains increased amounts of lactic acid. However, in carcinomatous patients lactic acid content of the venous blood of the arm is not raised (Mendel and Bauch[135]), for lactic acid is removed by normal tissues which therefore supply energy for its reconversion to glycogen.

It should be pointed out that the metabolism of resting excised muscle of dogs (Shorr, Loebel and Richardson[176]) resembles that of other excised organs to the extent that the ability to oxidize is more than sufficient to prevent an accumulation of lactic acid. However, this is not the case for rat, rabbit or bovine muscle (Boyland[15]). Moreover, the amount of oxygen actually afforded to resting muscle *in situ* (Krogh[99]) is not enough to prevent completely the accumulation of lactic acid (Himwich, Koskoff and Nahum[81]), and certainly the metabolism of exercising muscle is more like that of malignant tissue, since muscle may function beyond its oxidative capacities as lactic acid accumulates and finally pours out into the blood.

Krebs[98] noted that testicle and sarcoma, like brain, oxidize lactic acid and not glucose. However, the fact that a gland may oxidize lactic acid does not indicate that lactic acid is the only substance burned, as in the brain; on the contrary, the respiratory quotient of testicle *in situ* was found to vary between 0.7 and 1.0 (Himwich and Nahum[84]). Nevertheless, organs which oxidize lactic acid may do so in proportion to their ability to glycolyse. As a result of a study of surviving tissues, Dickens and Simer[32, 33] conclude that organs which do not glycolyse readily possess low respiratory quotients, *i.e.*, burn chiefly fat. The one exception is tumor tissue which has a low respiratory quotient despite its ability to glycolyse.

Classification of Organs According to Ability to Oxidize either Glucose or Lactic Acid

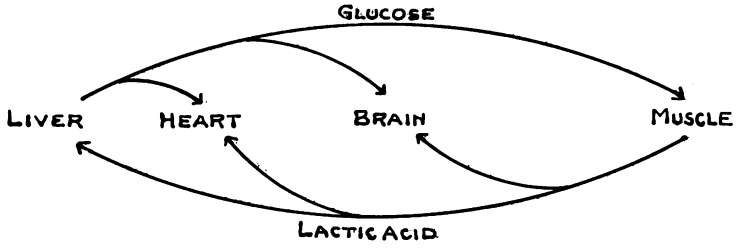
The body may remove lactic acid in two ways: it may be converted to glycogen or oxidized. In frog muscle both processes take place (Meyerhof[139], Lipmann[108], Meyerhof and Boyland[143]). In the mammal, on the contrary, it is not likely that oxidation and reconversion occur in the same organ. Although a Meyerhof quotient, *i.e.*, the disappearance of more lactic acid than can be accounted for by oxidations, has been observed (Meyerhof and Lohmann[145], Warburg, Posener and Negelein[192]) in all organs examined, the actual synthesis of glycogen from lactic acid has been demonstrated only in muscle of frog (Meyerhof[139]), and liver of turtle (Parnas and Baer[159]), and rat (Cori and Cori[27]). Thus mammalian muscle which may convert lactic acid to glycogen does not burn lactic acid, and requires insulin for the oxidation of glucose. On the other hand, brain which oxidizes lactic acid without insulin does not change it to glycogen.

Probably cardiac muscle, smooth muscle, and liver act like skeletal muscle, while testicle behaves like the brain in its nutritional requirements. Mammalian organs may then be divided into two groups; one which oxidizes glucose directly and another which can oxidize carbohydrate only after its conversion to lactic acid. This is of great importance in determining the organs which are the site of production of toxic ketone substances. It is known that the oxidation of a sufficient amount of carbohydrate is necessary to prevent the accumulation of these ketone substances. Organs oxidizing carbohydrate after its conversion to lactic acid are not ketogenic, for lactic acid is antiketogenic (Satta[170]) and may be burned in the absence of insulin. Only those organs which oxidize glucose and fat normally will produce ketone substances when the oxidation of carbohydrate is diminished as it is in starvation, high fat feeding, or diabetes. On the other hand, the testicle which oxidizes lactic acid and fat, may even cause the disappearance of ketones. The brain, however, does not utilize fat and probably has no effect on the concentration of ketone substances. Analyses of blood entering and leaving the various organs have revealed that the liver, muscle and portal organs liberate ketones in the blood-stream of animals rendered diabetic by phlorhizin or pancreatectomy (Himwich, Goldfarb and Weller[76]). Previous work also indicates that the liver may produce ketone substances (Chaikoff and Soskin[22]). This classification of organs as ketogenic, neutral, and antiketogenic is provisional (Himwich[66]) and must await further confirmation.

Summary

The reactions attendant on the formation and removal of lactic acid are of utmost significance in the economy of the body. During rest and exercise they are involved in processes which deliver energy for the work of life. Though the splitting of phosphocreatin furnishes the energy for the contraction of muscle, exercise cannot continue long without the formation of lactic acid, for the energy thus made available is the direct cause of the resynthesis of adenosintriphosphate and therefore indirectly that of phosphocreatin. Liver as well as muscle is involved in the processes of recovery as lactic acid is reconverted to glycogen. The reversible reactions between glycogen, glucose and lactic acid are important not only for skeletal muscle, but they are also concerned in the work of cardiac and smooth muscle, the brain, and perhaps in that of peripheral nerve

conduction. At present there is no proved connection between lactic acid formation and glandular secretion. The exchanges of glucose and lactic acid in the blood of liver, heart, brain, and skeletal muscle are indicated in the diagram. It may be seen that muscle is the chief source of the blood lactic acid while the liver is that of glucose. Heart and brain remove both glucose and lactic acid from the blood.



The action of the liver in removing lactic acid from the blood and supplying it with glucose is an etiological factor in the maintenance of the hyperglycemia of diabetes. When this mechanism is interfered with, as a result of severe injury to the liver, lactic acid may accumulate. Since oxidations are necessary for the resynthesis of glycogen, oxygen lack is always followed by an increased concentration of lactic acid in the body. Such a condition occurs most frequently in exercise. It is also found in patients, especially those with cardiorespiratory disease or anemia.

It is possible that the mammalian organs may be classified in two groups, depending on whether lactic acid is oxidized as in the brain and testicle, or converted to glycogen as in liver and muscle. In mammalian muscle, whether skeletal, cardiac, or smooth, glycogen breaks down to lactic acid which, in turn, may be entirely reconverted to glycogen during recovery, either in muscle or in liver. Lactic acid is not fuel, but part of the machinery, since the energy for the resynthesis of glycogen does not come from the oxidation of lactic acid, but from that of fat and glucose. Thus, during diabetes, when, because of lack of insulin, no glucose can be oxidized by skeletal muscle or heart, the respiratory quotient indicates that fat is the only foodstuff burned in these organs. If lactic acid were oxidized the respiratory quotient could not be that of fat.

On the other hand, the kind of foodstuff oxidized by the brain is not changed in diabetes, since insulin is not required for the oxidation

of lactic acid, which is the only substance burned in that organ. Though the brain utilizes carbohydrate exclusively, it cannot oxidize glucose but must first change it to lactic acid. It is probable that other organs also (*e.g.*, testicle) oxidize lactic acid. However, unlike brain, testicle may also oxidize fat.

The ability to burn glucose or lactic acid determines, during diabetic conditions, whether an organ will be forced to oxidize fat only, and therefore give rise to ketone substances, or will keep the character of its oxidations essentially unchanged.

Bibliography

1 Anderson, R. J., and G. Lusk: Animal calorimetry. 13. The interrelation between diet and body condition and the energy production during mechanical work. J. Biol. Chem., 1917, *32*, 421.

2 Anrep, A. V., and R. K. Cannan: The concentration of lactic acid in the blood in experimental alkalaemia and acidaemia. J. Physiol., 1923, *58*, 244.

3 Ashford, C. A., and E. G. Holmes: Contributions to the study of brain metabolism. V. Rôle of phosphate in lactic acid production. Biochem. J., 1929, *23*, 748.

4 Banting, F. G., C. H. Best, J. B. Collip, J. Hepburn, and J. J. R. Macleod: The effect produced on the respiratory quotient by injections of insulin. Trans. Roy. Soc. Can., 1922, *16*, Series 3, Section 5, 35.

5 Banting, F. G., C. H. Best, J. B. Collip, J. J. R. Macleod, and C. E. Noble: The effect of insulin in the percentage amounts of fat and glycogen in the liver and other organs of diabetic animals. Trans. Roy. Soc. Can., 1922, *16*, Series 3, Section 5, 39.

6 Barr, D. P., H. E. Himwich, and R. P. Green: Studies in the physiology of muscular exercise. I. Changes in acid-base equilibrium following short periods of vigorous muscular exercise. J. Biol. Chem., 1923, *55*, 495.

7 Barr, D. P., and H. E. Himwich: Physiology of muscular exercise. II. Comparison of arterial and venous blood following vigorous exercise. J. Biol. Chem., 1923, *55*, 525.

8 Barr, D. P., and H. E. Himwich: Studies in the physiology of muscular exercise. III. Development and duration of change in acid-base equilibrium. J. Biol. Chem., 1923, *55*, 539.

9 Benedict, F. G., and E. P. Cathcart: Muscular work. Carnegie Inst. Pub., 1913, 187.

10 Best, C. H., J. P. Hoet, and H. P. Marks: The fate of the sugar disappearing under the action of insulin. Proc. Roy. Soc. Lond., 1926, *100B*, 32.

11 Bischoff, F., and M. L. Long: The posterior pituitary hormone in metabolism. I. The effect of pitressin upon the carbohydrate reserves of the normal rabbit. Am. J. Physiol., 1931, *97*, 215.

12 Boothby, W. M., and J. Barborka: Energy transformation at rest and at work with high and low respiratory quotients. J. Am. Med. Asso., 1924, *82*, 1990.

13 Bornstein, A., and H. Völker: Uber das Verhalten der Kohlehydrate bei Muskeldurblutungen am Extremitätenpräparat. Biochem. Ztschr., 1929, *209*, 103.

14 Boyland, E.: Chemical changes in muscle. II. Invertebrate muscle. Biochem. J., 1928, *22*, 362.

15 Boyland, E.: Uber den Oxydation Quotient der Milchsäure im Muskelgewebe des Warmblüters. Biochem. Ztschr., 1931, *237*, 418.

16 Büttner, H. E.: Blutmilchsäure und Carcinom. Klin. Wchnschr., 1926, *5*, 1507.

17 Campbell, J. A., and W. Cramer: Some effects of alteration of oxygen pressure in the inspired air upon cancer growth and body weight of rats and mice. Lancet, 1928, *i*, 828.

18 Campbell, W. J., and E. J. Maltby: On the significance of respiratory quotients after administration of certain carbohydrates. J. Clin. Invest., 1928/9, *6*, 303.

19 Cannon, W. R.: Bodily changes in pain, hunger, fear and rage. New York and London, 1929. D. Appleton and Company, xvi + 404 pp.

20 Carpenter, T. M., and E. L. Fox: The effect of muscular work upon the respiratory exchange of man after the ingestion of glucose and fructose. Arbeitsphysiol., 1931, *4*, 570.

20a Case, E. M.: The relation between amylase and lactic acid formation in muscle. Biochem. J., 1931, *25*, 561.

21 Cattell, McK., and W. Hartree: Delayed anaerobic heat of stimulated muscle. [In press.]

22 Chaikoff, I. L., and S. Soskin: The utilization of acetoacetic acid by normal and diabetic dogs before and after evisceration. Am. J. Physiol., 1928/9, *87*, 58.

23 Colwell, A. B., and E. M. Bright: The use of constant glucose injections for the study of induced variations in carbohydrate metabolism. Am. J. Physiol., 1930, *92*, 543.

24 Cori, C. F.: The fate of sugar in the animal body. III. The rate of glycogen formation in the liver of normal and insulinized rats during absorption of glucose, fructose and galactose. J. Biol. Chem., 1926, *70*, 577.

25 Cori, C. F., and G. T. Cori: The carbohydrate metabolism of tumors. II. Changes in the sugar, lactic acid and CO_2—combining power of blood passing through a tumor. J. Biol. Chem., 1925, *65*, 397.

26 Cori, C. F., and G. T. Cori: Mechanism of epinephrine action. II. The influence of epinephrine and insulin in the carbohydrate metabolism of rats in the postabsorptive state. J. Biol. Chem., 1928, *79*, 321.

27 Cori, C. F., and G. T. Cori: Glycogen formation in the liver from d- and l- lactic acid. J. Biol. Chem., 1929, *81*, 389.

28 Cushing, H.: Neurohypophyseal mechanisms from a clinical standpoint. Lancet, 1930, *ii*, 119, 175.

29 Davies, H. W., J. B. S. Haldane, and E. L. Kennaway: Experiments on the regulation of the blood's alkalinity. J. Physiol., 1920/1, *54*, 32.

30 Deuel, H. J., W. H. Chambers, and A. T. Milhorat: Animal calorimetry. 33. The influence of amytal upon the metabolism of the dog. J. Biol. Chem., 1926, *59*, 249.

31 Deuticke, H. J.: Uber die Bedeutung von Ionen für die Muskelfunktion. Ztschr. Physiol. Chem., 1924, *141*, 196.

32 Dickens, F., and F. Simer: Metabolism of normal and tumor tissue. II. The respiratory quotient and the relationship of respiration to glycolysis. Biochem. J., 1930, *24*, 1301.

33 Dickens, F., and F. Simer: Metabolism of normal and turmor tissue. IV. The respiratory quotient in bicarbonate-media. Biochem. J., 1931, *25*, 985.

34 Doisy, E. A., A. P. Briggs, C. J. Weber, and I. Koechig: The formation of lactic acid by depancreatized dogs. Proc. Soc. Exper. Biol. & Med., 1924/5, *22*, 57.

35 Eggleton, M. G., and C. L. Evans: Lactic acid formation and removal with change of blood reaction. J. Physiol., 1930, *70*, 261.

36 Embden, G., E. Lehnartz, and H. Hentschel: Der Zeitliche Verlauf der Milchsäurebildung bei der Muskelkontraktion. Ztschr. Physiol. Chem., 1927, *165*, 255.

37 Embden, G., and M. Zimmermann: Uber die Chemie des Lactacidogens. Ztschr. Physiol. Chem., 1924, *141*, 225.

38 Embden, G., and M. Zimmermann: Uber die Chemie des Lactacidogens. Ztschr. Physiol. Chem., 1927, *167*, 114.

39 Embden, G., and M. Zimmermann: Uber die Bedeutung der Adenylsäure für die Muskelfunction. Ztschr. Physiol. Chem., 1927, *167*, 137.

40 Embden, G., and G. Schmidt: Uber Muskeladenylsäure und Hefeadenylsäure. Ztschr. Physiol. Chem., 1929, *181*, 130.

41 Eppinger, H., F. Kisch, and H. Schwarz: Das Versagen des Kreislaufes. Berlin. 1927. Julius Springer, 238 pp.

42 Evans, C. L.: Physiology of plain muscle. Physiol. Rev., 1926, *6*, 358.

43 Fazikas, J., M. A. Spiers, and H. E. Himwich: The effect of shivering on blood fat. Proc. Soc. Exper. Biol. & Med., 1931, *29*, 236.

44 Fenn, W. O.: Gas exchange of nerve during stimulation. Am. J. Physiol., 1927, *80*, 327.

45 Fiske, C. H., and Y. Subbarow: Phosphocreatin. J. Biol. Chem., 1929, *81*, 631.

46 Fiske, C. H., and Y. Subbarow: Phosphorous compounds of muscle and liver. I. Muscle. Science, 1929, *70*, 381.

47 Fletcher, W. M., and F. G. Hopkins: Lactic acid in amphibian muscle. J. Physiol., 1907, *35*, 247.

48 Furusawa, K., A. V. Hill, C. N. H. Long, and H. Lupton: Muscular exercise, lactic acid, and the supply and utilization of oxygen. VIII. Muscular exercise and oxygen requirement. Proc. Roy. Soc. Lond., 1924, *97B*, 167.

49 Gerard, R. W., and O. Meyerhof: Untersuchungen über den Stoffwechsel des Nerven. III. Chemismus and Intermediärprozesse. Biochem. Ztschr., 1927, *191*, 125.

50 Gerard, R. W., and J. Wallen: Studies in nerve metabolism. V. Phosphates. Am. J. Physiol., 1929, *89*, 110.

51 Gesell, R.: The chemical regulation of respiration. Physiol. Rev., 1925, *5*, 551.

52 Graham, H. T.: Lactic acid increase in muscle under the influence of anesthetics. Proc. Soc. Exper. Biol. & Med., 1928/9, *26*, 641.
53 Harrison, S. T., and E. Mellanby: The inhibition of lactic acid formation in cancer and muscle. Biochem. J., 1930, *24*, 141.
54 Harrison, S. T., and E. Mellanby: A note on the inhibitory effect of monoiodoacetic acid in lactic acid production in cancer tissue. Biochem. J., 1931, *25*, 770.
55 Hartree, W., and A. V. Hill: The anaerobic processes involved in muscular activity. J. Physiol., 1923, *58*, 127.
56 Hartree, W.: The analysis of the initial heat production of muscle. J. Physiol., 1931, *72*, 1.
57 Hastings, A. B., C. D. Murray, and H. A. Murray: Certain chemical changes in the blood after pyloric obstruction in dogs. J. Biol. Chem., 1921, *46*, 223.
58 Haynes, F. W., T. Mandelbaum, and H. E. Himwich: [In preparation.]
59 Henderson, Y., and H. W. Haggard: The maximum of human power and its fuel. Am. J. Physiol., 1925, *72*, 264.
60 Henriques, V., and E. Lundsgaard: Die Milchsäurefreie Muskelkontraktion. Biochem. Ztschr., 1931, *236*, 19.
61 Hetzel, K. S., and C. N. H. Long: Metabolism of the diabetic individual during and after muscular exercise. Proc. Roy. Soc. Lond., 1925/6, *99B*, 279.
62 Hewlett, A. V., G. D. Barnett, and J. K. Lewis: The effect of breathing oxygen-enriched air during exercise upon pulmonary ventilation and upon the lactic acid content of blood and urine. J. Clin. Invest., 1926/7, *3*, 317.
63 Hill, A. V.: The oxidative removal of lactic acid. J. Physiol., 1914, *48*, x.
64 Hill, A. V., C. N. H. Long, and H. Lupton: Muscular exercise, lactic acid and the supply and utilization of oxygen. Proc. Roy. Soc. Lond., 1924, *97B*, 127. (Part VI.)
65 Hill, A. V., and H. Lupton: Muscular exercise, lactic acid and the supply and utilization of oxygen. Quart. J. Med., 1923, *16*, 135.
66 Himwich, H. E.: Organs capable of producing acetone substances. Science, 1931, *74*, 606.
67 Himwich, H. E., and M. A. Adams: Studies in glandular metabolism. I. The source of the lactic acid produced on incubation of the testicle and the submaxillary gland. Am. J. Physiol., 1929, *91*, 172.
68 Himwich, H. E., and M. A. Adams: Studies in glandular metabolism. II. The carbohydrates of resting and secreting submaxillary gland. Am. J. Physiol., 1930, *93*, 568.
69 Himwich, H. E., and D. P. Barr: Studies in the physiology of muscular exercise. V. Oxygen relationships in the arterial blood. J. Biol. Chem., 1923, *55*, 539.
70 Himwich, H. E., and W. B. Castle: Studies in the metabolism of muscle. I. The respiratory quotient of resting muscle. Am. J. Physiol., 1927, *83*, 92.
71 Himwich, H. E., W. H. Chambers, L. Hunter, and M. A. Spiers: Changes in blood fat produced by fasting, phlorhizin and pancreatectomy. [In press.]

72 Himwich, H. E., W. H. Chambers, Y. D. Koskoff, and L. H. Nahum: Studies in carbohydrate metabolism. II. Glucose-lactic acid cycle in diabetes. J. Biol. Chem., 1931, *90*, 417.

73 Himwich, H. E., and J. Fazikas: Effects of posterior pituitary extracts on the lactic acid of the blood. Proc. Soc. Exper. Biol. & Med., 1930, *28*, 331.

74 Himwich, H. E., R. Finkelstein, and K. E. Humphreys: Effects of posterior pituitary extracts on oxygen consumption of excised tissue. Proc. Soc. Exper. Biol. & Med., 1931, *29*, 233.

75 Himwich, H. E., and J. F. Fulton: The effect of emotional stress on blood fat. Am. J. Physiol., 1931, *97*, 533.

76 Himwich, H. E., W. Goldfarb, and A. Weller: Effects of organs on the acetone content of the blood. J. Biol. Chem., 1931, *93*, 337.

77 Himwich, H. E., and F. W. Haynes: Effects of posterior pituitary extracts on basal metabolic rate. Proc. Soc. Exper. Biol. & Med., 1930, *27*, 815.

78 Himwich, H. E., and F. W. Haynes: Effects of posterior pituitary extracts on basal metabolism. Am. J. Physiol., 1931, *96*, 640.

79 Himwich, H. E., and S. A. Jacobson: Formation of lactic acid in excised organs. Proc. Soc. Exper. Biol. & Med., 1927, *25*, 53.

80 Himwich, H. E., Y. D. Koskoff, and L. H. Nahum: Changes in lactic acid and glucose in the blood on passage through organs. Proc. Soc. Exper. Biol. & Med., 1928, *25*, 347.

81 Himwich, H. E., Y. D. Koskoff, and L. H. Nahum: Studies in carbohydrate metabolism. I. A glucose-lactic acid cycle involving muscle and liver. J. Biol. Chem., 1930, *85*, 571.

82 Himwich, H. E., and R. O. Loebel: The oxygen saturation of hemoglobin in the arterial blood of exercising patients. J. Clin. Invest., 1927, *5*, 113.

83 Himwich, H. E., R. O. Loebel, and D. P. Barr: Studies of the effect of exercise in diabetes. I. Changes in acid-base equilibrium and their relation to the accumulation of lactic acid and acetone. J. Biol. Chem., 1924, *59*, 265.

84 Himwich, H. E., and L. H. Nahum: The respiratory quotient of testicle. Am. J. Physiol., 1929, *88*, 680.

85 Himwich, H. E., and L. H. Nahum: Respiratory quotient of brain. Am. J. Physiol., 1930, *90*, 389.

86 Himwich, H. E., and M. I. Rose: Studies in the metabolism of muscle. II. The respiratory quotient of exercising muscle. Am. J. Physiol., 1929, *88*, 663.

87 Himwich, H. E., M. I. Rose, and M. R. Malev: Changes in the respiratory quotient produced by subcutaneous injections of dioxyacetone and glucose. Proc. Soc. Exper. Biol. & Med., 1926, *24*, 238.

88 Himwich, H. E., and M. A. Spiers: The effects of adrenalin, ephedrine, and insulin on blood fat. Am. J. Physiol., 1931, *97*, 648.

89 Holmes, E. G.: Oxidations in central and peripheral nervous tissue. Biochem. J., 1930, *24*, 914.

90 Holmes, E. G., and C. A. Ashford: Lactic acid oxidation in brain with reference to the Meyerhoff cycle. Biochem. J., 1930, *24*, 1119.

91 Holmes, E. G., R. W. Gerard, and E. I. Solomon: Studies in nerve metabolism. VI. Carbohydrate metabolism of active nerve. Am. J. Physiol., 1930, *93*, 342.

92 Holmes, E. G., and B. E. Holmes: Contributions to the study of brain metabolism. I. Carbohydrate metabolism. Biochem. J., 1925, *19*, 492.

93 Holmes, B. E., and E. G. Holmes: Contributions to the study of brain metabolism. IV. Carbohydrate metabolism of the brain tissue of depancreatized cats. Biochem. J., 1927, *21*, 412.

93a Janssen, S., and H. Jost: Uber den Wiederaufbau des Kohlenhydrats im Warmblütermuskel. Ztschr. Physiol. Chem., 1925, *148*, 41.

94 Jervell, O.: Investigation of the concentration of lactic acid in blood and urine under physiological and pathological conditions. Act. Med. Scand. Supplem., 1928, *24*, 1.

95 Katz, L. N., and C. N. H. Long: Lactic acid in mammalian cardiac muscle. I. The stimulation maximum. Proc. Roy. Soc. Lond., 1925, *99B*, 8.

96 Kinnersley, H. W., and R. A. Peters: Carbohydrate metabolism in birds. II. Brain localization of lactic acidosis in avitaminosis B and its relation to the origin of symptoms. Biochem. J., 1930, *24*, 711.

97 Koskoff, Y. D., and J. G. Dusser de Barenne: On reflex-hyperlipaemia. Science, 1931, *74*, 550.

98 Krebs, H. A.: Uber die Wirkung der Monoiodoessigsäure auf den Zellstoffwechsel. Biochem. Ztschr., 1931, *234*, 278.

99 Krogh, A. The anatomy and physiology of capillaries. New Haven: Yale University Press. 1929. xiii + 422 pp.

100 Krogh, A., and J. Lindhard: The relative value of fat and carbohydrate as sources of muscular energy. Biochem. J., 1920, *14*, 290.

101 Kuriyama, S.: The adrenals in relation to carbohydrate metabolism. I. The influence of repetition of epinephrine injections upon the intensity of glycosuria hyperglycemia and the glycogen content of the liver. J. Biol. Chem., 1918, *34*, 269.

102 Laquer, L., and P. Meyer: Uber den Abbau der Kohlehydrate im Quergestreiften Muskel. Ztschr. Physiol. Chem., 1923, *124*, 211.

103 La Victoire, I. N.: The relative rates of oxidation of fructose and galactose. Thesis: Yale University School of Medicine. 1928.

104 Lawrence, R. D.: The action of insulin in glycogen formation and its therapeutic application. Quart. J. Med., 1926, *20*, 69.

105 Le Blanc, E.: Respiratorescher Gasaustausch und Lungendurchblutung unter normalen und krankhaften Zuständen der Atmungsorgane. Beitr. z. Klin. Tuberk., 1922, *50*, 21.

106 Lehnartz, E.: Uber Verknupfung des Aufbaus und Abbaus von Tätigkeitssubstanzen des Muskels. Ztschr. Physiol. Chem., 1929, *184*, 1.

107 Lehnartz, E.: Uber die nachträgliche Milchsäurebildung beim Tetanus und bei der Zuckung isolierter Froschmuskeln. Ztschr. Physiol. Chem., 1931, *197*, 55.

108 Lipmann, F.: Versuche zum Mechanismus der Fluoridwirkung. Biochem. Ztschr., 1928, *196*, 3.

109 Lipmann, F.: Uber den Tätigkeitsstoffwechsel des fluoridvergifteten Muskels. Biochem. Ztschr., 1930, *227*, 110.

110 Lipmann, F., and O. Meyerhof: Uber die Reaktionsänderung des tätigen Muskels. Biochem. Ztschr., 1930, *227*, 84.
111 Loebel, R. O.: Beiträge zur Atmung und Glycolyse tierischer Gewebe. Biochem. Ztschr., 1925, *161*, 219.
112 Loebel, R. O., D. P. Barr, E. Tolstoi, and H. E. Himwich: Studies of the effect of exercise in diabetes. II. Lactic acid formation in phlorhizin diabetes. J. Biol. Chem., 1924, *61*, 9.
113 Lohmann, K.: Uber das Vorkommen und dem Umsatz von Pyrophosphat in Zellen. Biochem. Ztschr., 1928, *202*, 466.
114 Lohmann, K.: Untersuchungen über die chemische Natur des Koferments der Milchsäurebildung. Biochem. Ztschr., 1931, *237*, 445.
115 Long, C. N. H.: The effect of anesthesia on the recovery process in mammalian skeletal muscle. J. Biol. Chem., 1928, *77*, 563.
116 Lundsgaard, E.: Untersuchungen über Muskelkontraktionen ohne Milchsäurebildung. Biochem. Ztschr., 1930, *217*, 162.
117 Lundsgaard, E.: Die Monoiodoessegsäurewirkung auf die enzymatische Kohlenhydratspaltung. Biochem. Ztschr., 1930, *220*, 1.
118 Lundsgaard, E.: Uber die Einwirkung der Monoiodoessigsäure auf den Spaltungs und Oxydationsstoffwechsel. Biochem. Ztschr., 1930, *220*, 8.
119 Lundsgaard, E.: Weitere Untersuchungen über Muskelkontraktionen ohne Milchsäurebildung. Biochem. Ztschr., 1930, *227*, 51.
120 Lundsgaard, E.: Uber die Energetik der anaeroben Muskelkontraktion. Biochem. Ztschr., 1931, *233*, 322.
121 Lusk, G.: Die Energiequelle bei der Muskelarbeit. Biochem. Ztschr., 1925, *156*, 334.
122 Macleod, J. J. R.: The fuel of life. Princeton: Princeton University Press. 1928. ix + 147 pp.
123 Macleod, J. J. R., and H. J. Knapp: The influence of alkali administration on the urinary excretion of lactic acid and the possible significance of the latter in maintaining neutrality in the body. Am. J. Physiol., 1918, *47*, 189.
124 Mandel, A. R., and G. Lusk: Lactic acid in intermediary metabolism. Am. J. Physiol., 1906, *16*, 129.
125 Mann, F. C., and T. B. Magath: Studies in the physiology of the liver. II. The effect of the removal of the liver on the blood sugar level. Arch. Int. Med., 1922, *30*, 73.
126 Markwalder, J., and E. H. Starling: A note on some factors which determine the blood-flow through the coronary circulation. J. Physiol., 1913/14, *47*, 275.
127 Marsh, M. E.: The character of energy metabolism during work. J. Nut., 1928, *1*, 57.
128 Martin, E. J., J. Field II, and V. E. Hall: Tissue lactates and blood lactates as affected by muscular exercise. Proc. Soc. Exper. Biol. & Med., 1929, *26*, 292.
129 Martin, E. J., J. Field II, and V. E. Hall: Factors affecting the distribution of lactates between blood and muscles. Am. J. Physiol., 1930, *93*, 672.
130 McClellan, W. S., A. Biasotti, and R. R. Hannon: Clinicalcalorimetry. 42. A comparison of the effect of glucose and dihydroxyacetone on metabolism. J. Biol. Chem., 1928, *78*, 719.

131 McGinty, D. A.: The regulation of respiration. 25. Variations in the lactic acid metabolism in the intact brain. Am. J. Physiol., 1929, *88*, 312.
132 McGinty, D. A.: Studies in the coronary circulation. I. Absorption of lactic acid by the heart muscle. Am. J. Physiol., 1931, *98*, 244.
133 McGinty, D. A., and R. Gesell: On the chemical regulations of respiration. II. A quantitative study of the accumulation of lactic acid in the isolated brain during anaerobic conditions and the rôle of lactic acid as a continuous regulator of respiration. Am. J. Physiol., 1925, *75*, 70.
134 Meakins, J., and C. N. H. Long: Oxygen consumption, oxygen debt and lactic acid in circulatory failure. J. Clin. Invest., 1924, *4*, 273.
135 Mendel, B., and M. Bauch: Uber den Milchsäuregehalt des Blutes unter Physiologischen und Pathelogischen Bedingungen. Klin Wchnschr., 1926, *5*, 1272.
136 Mendel, L. B., and H. C. Bradley: Experimental studies on the physiology of molluscum. Am. J. Physiol., 1906/7, *17*, 167.
137 Meyer, K.: Uber einege Eigenshaften des Milchsäure bildenden Ferment im Muskel. Biochem. Ztschr., 1927, *183*, 216.
138 Meyerhof, O.: Zur Verbrennung der Milchsäure in der Erholungsperiode des Muskels. Pfluger's Arch. ges. Physiol., 1919, *175*, 88.
139 Meyerhof, O.: Die Energieumwandlungen im Muskel. III. Kohlehydrat und Milchsäure umsatz im Froschmuskel. Pfluger's Arch. ges. Physiol., 1920, *185*, 11.
140 Meyerhof, O.: Die Energieumwandlungen im Muskel. VII. Weitere Untersuchungen über den Ursprung der Kontraktionswärme. Pfluger's Arch. ges. Physiol., 1924, *204*, 295.
141 Meyerhof, O.: Uber die enzymatische Milchsäurebildung im Muskelextrakt. II. Die Spaltung der Polysaccharide und der Hexosediphosphorsäure. Biochem. Ztschr., 1926, *178*, 462.
142 Meyerhof, O.: Recent investigations of the aerobic and anaerobic metabolism of carbohydrates. J. Gen. Physiol., 1927, *8*, 531.
143 Meyerhof, O., and E. Boyland: Uber den Atmungsvorgang jodessigsäurevergifteter Muskeln. Biochem. Ztschr., 1931, *237*, 406.
144 Meyerhof, O., and H. E. Himwich: Beiträge zum Kohlehydratestofwechsel des Warmblütermuskels, insbesondere nach einseitiger Fetternährung. Pfluger's Arch. ges. Physiol., 1924, *205*, 415.
145 Meyerhof, O., and K. Lohmann: Uber Atmung und Kohlehydratumsatz tierischer Gewebe. Biochem. Ztschr., 1926, *171*, 381.
146 Meyerhof, O., and K. Lohmann: Uber die naturlichen Guanidenophosphosäure in der quergestreifter Muskelature. Biochem. Ztschr., 1928, *196*, 22.
147 Meyerhof, O., and K. Lohmann: Uber die Energetik der anaeroben Phosphagensynthese im Muskelextrakt. Naturwiss., 1931, *19*, 575.
148 Meyerhof, O., K. Lohmann, and K. Meyer: Uber das Koferment der Milchsäurebildung im Muskel. Biochem. Ztschr., 1931, *237*, 437.
149 Meyerhof, O., and F. O. Schmitt: Uber den respiratorischen Quotienten des Nerven bei Ruhe und Tätigkeit. Biochem. Ztschr., 1929, *208*, 445.
150 Meyerhof, O., and W. Schulz: Uber des Verhaltniss von Milchsäurebildung und Saurestoff verbrauch bei der Muskelkontraktion. Pfluger's Arch. ges. Physiol., 1927, *217*, 547.

151 Meyerhof, O., and W. Schulz: Uber das Verhaltniss von Milchsäurebildung und Kreatinphosphorsäurespaltung bei der aneroben Tätigkeit des Muskels. Biochem. Ztschr., 1931, *236*, 54.

152 Minami, S.: Versuche an überlebenden Carcinomgewebe. Biochem. Ztschr., 1923, *142*, 334.

153 Murlin, J. R., H. D. Clough, C. B. F. Gibbs, and A. M. Stokes: Aqueous extracts of pancreas. I. Influence on the carbohydrate metabolism of depancreatized animals. J. Biol. Chem., 1923, *56*, 253.

154 Nahum, L. H., H. E. Himwich, and Y. D. Koskoff: The effect of the brain on the glucose and lactic acid content of the blood. [In preparation.]

155 Nahum, L. H., and H. E. Himwich: Effect of adrenalin on the glucose and lactic acid exchange of the brain. Proc. Soc. Exper. Biol. & Med., 1931, *29*, 72.

156 Noah, G.: Milchsäureuntersuchungen im Blut insbesondere bei Leberkrankungen. Klin. Wchnschr., 1927, *6*, 1465.

157 Nothmann, N.: Uber die Verteilung des Insulin im Organismus des Normalen und pankreasdiabetischen Hundes. Arch. exper. Path. u. Pharm., 1925, *108*, 1.

158 Ochoa, S.: Uber den Tätigkeitsstoffwechsel Kohlenhydratarmer Kaltblüter Muskeln. Biochem. Ztschr., 1930, *227*, 116.

159 Parnas, J., and J. Baer: Uber Zuckerabbau und Zuckeraufbau im tierischem Organismus. Biochem. Ztschr., 1912, *41*, 386.

160 Peserico, E.: L'azione della insulina sul ricambio respiratorio del cuore isolato di mammifero. Arch. di Fisiol., 1925, *23*, 488.

161 Peters, J. P., and H. R. Geyelin: The relation of adrenalin hyperglycemia to decreased alkali reserve of the blood. J. Biol. Chem., 1917, *31*, 471.

162 Rabinowitch, I. M., E. V. Bazin: Simultaneously determined arterial venous blood-sugars and respiratory quotient—Time curves of diabetics following insulin administration. Brit. J. Exper. Path., 1927, *8*, 302.

163 Rapport, D., and E. Ralli: The nature of the foodstuffs oxidized to provide energy in muscular exercise. Am. J. Physiol., 1928, *83*, 450.

164 Richardson, H. B., and S. Z. Levine: Clinical calorimetry. 39. Exercise and the respiratory quotient in diabetes. J. Biol. Chem., 1925, *66*, 161.

165 Richardson, H. B., E. Shorr, and R. O. Loebel: Tissue metabolism. II. The respiratory quotient of normal and diabetic tissue. J. Biol. Chem., 1930, *86*, 551.

166 Ronzoni, E.: The source of energy of nerve activity. J. Biol. Chem., 1931, *92*, iii.

167 Ronzoni, E., J. Glaser, and D. P. Barr: Studies of the inhibitory action of an extract of pancreas upon glycolysis. J. Biol. Chem., 1928, *80*, 309.

168 Ronzoni, E., I. Koechig, and E. P. Eaton: Ether anesthesia. III. Rôle of lactic acid in the acidosis of ether anesthesia. J. Biol. Chem., 1924, *61*, 465.

169 Rose, M. L., G. Giragossintz, and E. L. Kirstein: Formation of lactic acid following administration of glucose and fructose. Proc. Soc. Exper. Biol. & Med., 1929, *27*, 523.

170 Satta, G.: Studien über die Bedingungen der Acetonbildung im Tierkörper. IV. Uber die Hemmungsstoffe und ihre Wirkung. Beitr. Chem. Physiol. u. Pathol., 1905, *6*, 376.

171 Sahyun, M., and J. M. Luck: The influence of epinephrine and insulin on the distribution of glycogen in rabbits. J. Biol. Chem., 1929/30, *85*, 1.

172 Schjerning, J.: Uber das Problem der Zyanose und der Begriff der Pneumonose. Beitr. z. Klin. Tuberk., 1922, *50*, 96.

173 Schmitt, F. O.: On the nature of the nerve impulse. I. The effect of carbonmonoxide in medullated nerve. Am. J. Physiol., 1930, *95*, 650.

174 Schumacher, H.: Untersuchungen über den Milchsäuregehalt des Blutes bei Karzinomkranken. Klin. Wchnschr., 1926, *5*, 497.

175 Sherif, M., and E. G. Holmes: A note on the oxygen consumption of nerve in the presence of glucose and galactose. Biochem. J., 1930, *24*, 400.

176 Shorr, E., R. O. Loebel, and H. B. Richardson: The lactic acid cycle in excised mammalian muscle. Am. J. Physiol., 1931, *97*, 559.

177 Snapper, I., and A. Grünbaum: Uber die Milchsäureausscheidung im Harn und Schweiss während Fussballwettkämpfen. Biochem. Ztschr., 1929, *206*, 319.

178 Soskin, A.: Muscle glycogen as a source of blood sugar. Am. J. Physiol., 1927, *81*, 382.

179 Starling, E. H., and C. L. Evans: The respiratory exchanges of the heart in the diabetic animal. J. Physiol., 1914, *49*, 67.

180 Stivin, D.: Lactic acid formation in muscle extracts. VI. The influence of irradiation on lactic acid formation and phosphoric ester accumulation from glycogen. Biochem. J., 1930, *24*, 172.

181 Sundstroem, E. S., and G. Giragossintz: A demonstration of the curability of malignancy in rats by a low pressure environment. Proc. Soc. Exper. Biol. & Med., 1930, *27*, 511.

182 Takahashi, K., and L. Asher: Uber experimentelle Kohlehydratverarmung und den Kohlehydratstoffwechsel des Gehirns. Biochem. Ztschr., 1925, *154*, 444.

183 Talbott, J. H., A. Fölling, L. J. Henderson, D. B. Dill, H. T. Edwards, and R. E. L. Berggren: Studies in muscular activity. V. Changes and adaptations in running. J. Biol. Chem., 1928, *78*, 445.

184 Tolstoi, E., R. O. Loebel, S. Z. Levine, and H. B. Richardson: The production of lactic acid in diabetes following the administration of insulin. Proc. Soc. Exper. Biol. & Med., 1924, *21*, 449.

185 Underhill, F. P.: A note on the presence of lactic acid in the urine of pernicious vomiting of pregnancy. J. Biol. Chem., 1906/7, *2*, 485.

186 Underhill, F. P., and O. E. Closson: Adrenalin glycosuria and the influence of adrenalin upon nitrogenous metabolism. Am. J. Physiol., 1906, *17*, 42.

187 Underhill, F. P., and H. M. Steele: The presence of lactic acid in the urine of cyclic vomiting of childhood. Am. J. Dis. Child., 1914, *8*, 127.

188 Valentin, F.: Uber den Milchsäuregehalt des Blutes. Munch. Med. Wchnschr., 1925, *72*, 86.

189 Visscher, M. B., and A. G. Mulder: The carbohydrate metabolism of the heart. Am. J. Physiol., 1930, *94*, 630.

190 Warburg, O.: Physikalische Chemie der Zellatmung. Biochem. Ztschr., 1921, *119*, 134.
191 Warburg, O.: Uber die Klassifizierung tierischer gewebe nach ihrem Stoffwechsel. Biochem. Ztschr., 1927, *184*, 484.
192 Warburg, O., K. Posener, and E. Negelein: Uber den Stoffwechsel der Carcinomzelle. Biochem. Ztschr., 1924, *152*, 309.
193 Warburg, O., F. Wind, and E. Negelein: Uber den Stoffwechsel von Tumoren im Körper. Klin Wchnschr., 1926, *5*, 829.
194 Wierzuchowski, M.: Intermediärer Kohlenhydratstoffwechsel. VIII. Respiratorische Gaswechsel der Glykose Fructose und Galaktose bei ihrer intravenösen Injektion. Biochem. Ztschr., 1931, *230*, 187.
195 Wierzuchowski, M., and M. Laniewski: Intermediärer Kohlenhydratstoffwechsel. VII. Milchsäure Production bei intravenöser Dauerinjektion der Glykose Fructose und Galaktose. Biochem. Ztschr., 1931, *230*, 173.
196 Wilson, J. R., S. Z. Levine, H. Rivkin, and F. Berliner: Respiratory metabolism in infancy and childhood. Am. J. Dis. Child., 1927, *33*, 618.