A REVIEW

Lactic Acidosis

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LACTIC ACID, long recognized as an important product of normal metabolism,[42] was first associated with a metabolic acidosis by Barr, Himwich and Green in 1924.[9,10] These investigators recognized metabolic acidosis following strenuous physical exercise and linked it with the observed accumulation of blood lactic acid. They called the condition "lactic acid acidosis."

Following that report, sporadic references have been made to lactic acid as a demonstrated or suspected cause of metabolic acidosis in a variety of conditions. These have included the demonstrations of increased lactate accompanying the acidosis of diarrheal dehydration in infants,[23] anoxia,* muscular exercise,† hemorrhagic and endotoxin shock,‡ glycogen storage disease,[70,103] inadequate blood flow during cardio-pulmonary bypass procedure,[7,100] hyperthermia,[43] hyperventilation,[33,76,80] guanidine intoxication,[99] methyl alcohol poisoning,[13] salicylate intoxication,[36] nonketotic diabetic acidosis,[4,24,90,113] paraldehyde intoxication,[62] and feeding of lactic acid milk to infants.[52]

It was not until the introduction of the clinical concept of lactic acidosis by Huckabee, in 1961,[77,78] that it was recognized that severe metabolic acidosis related to the accumulation of large amounts of lactic acid in body water was of real clinical significance. Since Huckabee's initial report of nine patients with lactic acidosis, at least 62 additional cases have been reported.§ This presentation will concern itself with the entity of lactic acidosis, and will deal with current concepts of the mechanisms and control of lactate production and disposition, the clinical syndrome of lactic acidosis and the current concepts of pathogenesis, symptoms and therapy. No attempt has been made to include all possible references on these subjects and, where possible, previous reviews are cited.

For purposes of clarity in discussion, a definition of lactic acidosis is required. Lactic acidosis, chemically, is defined as a metabolic acidosis characterized by a significant reduction in arterial pH and the presence of a significant accumulation of lactate in extracellular fluids. As a practical consideration, lactic acid has rarely been shown to be responsible for a significant metabolic acidosis at blood levels of less than seven or eight millimols per liter. It is apparent that buffering mechanisms are capable of preventing clinically significant acidosis at blood lactate levels of less than this level. Exceptions to this are seen in the presence of pronounced respiratory or metabolic alkalosis in which very large amounts of lactate may accumulate without the development of a significant decrease of the pH.[72,77]

We have carefully refrained from inserting clinical considerations in the above definition of lactic acidosis. Such considerations serve as a means of differentiating the two major classes of lactic acidosis that have been recognized. Lactic acidosis which accompanies or results from well recognized clinical situations such as anoxia, severe anemia, shock, cardiac failure, severe exercise, severe pulmonary disease, or other clinical states known to result in significant decreases in tissue oxygenation or lactate utilization, may be conveniently labeled "secondary lactic acidosis." Huckabee was the first to identify a group of patients with lactic acidosis in whom the underlying disease process could not clearly be shown to have resulted in tissue anoxia.[78] Such cases have since been reported by

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*References Nos. 31, 46, 54, 74, 112.
†References Nos. 10, 45, 63, 80, 86, 106.
‡References Nos. 11, 20, 56, 87, 88, 96, 114, 115.
§References Nos. 14, 26, 39, 40, 53, 116, 128, 129, 130, 135.

a number of observers¶ and may be given the label "spontaneous lactic acidosis[135]" or "idiopathic lactic acidosis." Since the word *spontaneous* implies something of the mechanism of lactic acidosis which remains unknown, and the term *idiopathic* maintains a neutrality in our ignorance of the origins of this type of lactic acidosis, we prefer the latter term. Etiologic definition will lead to the extrication of lactic acidosis from the limbo of the "idiopathic" as our knowledge increases, and it may well prove not to be "spontaneous."

Lactic Acid Metabolism

Only one pathway of lactate production and utilization has been recognized, and there is no good evidence to suggest that a biologically significant alternate pathway exists in mammalian tissues. While a direct oxidizing enzyme, lactic oxidase, has been described in bacteria,[138] mammalian tissues oxidize lactate solely through the mediation of the enzyme lactic acid dehydrogenase (LDH) which catalyzes a reversible reaction which requires the participation of the pyridine nucleotide, coenzyme I (NAD, $NADH_2$, DPN, $DPNH_2$) as a hydrogen acceptor or donor:

Equation 1:

$$\text{Pyruvate} + \text{NADH}_2 \overset{\text{LDH}}{\longleftrightarrow} \text{Lactate} + \text{NAD}$$

The reaction has an equilibrium constant which favors the production of lactate at physiological pH. However, the direction of the reaction is controlled by the relative concentration of all of the reactants: Pyruvate, lactate, $NADH^-$, H^+, and NAD. Such an equilibrium may be conveniently expressed by the mass action form of equation.[1]

Equation 2:

$$[\text{Lactate}] = [\text{Pyruvate}] \times K\frac{[\text{NADH}^-]\,[\text{H}^+]}{[\text{NAD}]}$$

The enzyme LDH has been found in all tissues of the body and is located in the extramitochondrial, extramichrosomal cell sap.[16,17]

Since production and utilization of lactate occur over the same reversible pathway, and since this pathway is available in all mammalian tissues thus far examined, the concepts of lactate production and removal in the intact organism must involve the sum of the simultaneous individual rates and directions of reactions in individual tissues and organs. It was initially pointed out by Eggleton and Evans[34] and later confirmed directly and indirectly in experiments by Drury and Wick[30] and by Huckabee,[75] that formation and removal of lactate varies from tissue to tissue at any given moment, and that lactate may be produced by one group of tissues while it is simultaneously being utilized by other tissues.

The ability of various tissues to produce or utilize lactate varies considerably and is related to the intracellular oxidation-reduction state, the ratio of LDH concentration to the concentration of other enzymes utilizing NAD, intracellular pH, and the rate of accumulation of pyruvate, as governed by its production and utilization by pathways other than that of reduction to lactate.

Studies of the metabolism of lactate by intact tissues are difficult to interpret, because of the inevitable interference with circulation, oxygenation and normal metabolism by the procedures used in such studies. However, some observations have been made which shed some light on this problem.

Skeletal muscle tissue normally produces lactate at rest and increases its production very decidedly when actively contracting.* This is probably the major source of endogenous lactate production in the intact organism.[11] Cardiac muscle, by contrast, under normal aerobic conditions extracts lactate from blood.[21,32,56,68,76]

Adipose tissue normally produces small amounts of lactate, and this production is increased by stimulation with insulin, as is lactate production by skeletal muscle.[57,127,131]

Under normal conditions lactate is removed from portal blood by the liver†. This has been thought to be a very important role of the liver in maintaining normal blood lactate concentrations, and calculations have been made which suggest that the liver is normally responsible for the metabolism of about one-third of the lactate produced by the total organism.[34] The ability to dispose of a lactate load has been utilized as a test of hepatic function[15,18,101] and elevated levels of blood lactate have been observed in patients with liver disease.[15,18,101,121]

Studies by Drury and Wick demonstrated the ability of the extrahepatic tissues to remove considerable amounts of lactate in the hepatectomized-eviscerated preparation, but sharply elevated and increasing levels of blood lactate in their preparations would have altered normal equilibria in extrahepatic tissues.[30] It is possible that the anoxia of anesthesia and hypotension produced by the procedure may have been responsible for the very high lactate levels observed. In a series of experiments with an eviscerated preparation in which the liver was isolated from major vascular supply but not removed, Eggleton and Evans[33,34] and Russel, Long and Engel[114] were able to provide a prepara-

¶References Nos. 14, 26, 39, 40, 53, 116, 128, 129, 130, 135.

* References Nos. 34, 42, 68, 69, 102.

† References Nos. 3, 34, 64, 66-69, 76, 88, 101, 110, 114, 124, 126.

tion in which blood lactate elevations were minimal and did not increase during the procedure. This led to the conclusion that extrahepatic tissues were capable of utilizing large amounts of lactate.[34] However, there is no assurance that the liver may not have participated in some measure in the removal of lactate, since it remained in situ.

Renal tissue of the dog has been shown to remove lactate continuously and at a rate directly proportional to the level of lactate in renal arterial blood.[66,89] Erythrocytes produce lactate as the normal major end product of energy production and are responsible for a significant proportion of the endogenous lactate production at rest.* Little or no lactate flux has been demonstrated across the pulmonary circulation, and it would appear that this tissue does not contribute in a major way either to production or to removal of lactate.[33,34,59] Fetal tissue does not produce large amounts of lactate.[47]

It would appear that arterial lactate concentrations represent the sum total of events going on in all localities, assuming that cellular membranes are freely permeable to lactate and pyruvate. The evidence bearing on this question is incomplete, but studies of blood and tissue water lactate concentrations are fairly uniform in agreement that lactate equilibrates rapidly between intracellular and extracellular spaces and is governed by the considerations of the Donnan equilibrium as to its distribution across membranes.‡ The fact that there is not simultaneous equilibrium of lactate and pyruvate across cell membranes may account for some part of the disagreement in interpretation of the role of lactate and pyruvate ratios in blood as determinants of anaerobic metabolism and adequacy of perfusion and oxygenation.[34,93] Huckabee stressed the necessity for examination of arterial rather than venous lactate content when knowledge of whole body aerobic-anaerobic relationships is being sought.[72]

In light of these considerations it is apparent that the accumulation of a significant amount of lactate depends upon the development of a situation in which more lactate is being produced than removed. Such a situation might involve the production of very large amounts of lactate by a single region of the body (as in muscular exercise),§ by most tissues of the body (as in primary anoxia)¶ or by the inability to metabolize lactate produced at normal rates, as might be the case in the presence of liver disease[15,18,102,121] or pharmacological intoxication with agents specifically affecting the utilization of lactate.[8,36,62,133]

Recently acquired knowledge, reviewed by Dawson, Goodfriend and Kaplan,[28] indicates that mammalian lactic dehydrogenase exists as two distinct molecular forms. The two basic molecular forms have been labeled H (the form predominant in extracts of heart muscle) and M (the form predominant in skeletal muscle). The active enzyme units each consist of a total of four molecules of the enzyme and are patterned as one of five possible combinations: H_4, H_3M, H_2M_2, H_1M_3, M_4.

These would be merely items of incidental intelligence if it were not for the fact that the kinetics of H and M LDH are distinctly different. The H type, predominant in cardiac muscle, is strongly inhibited by the presence of high concentrations of pyruvate.[108] This provides a mechanism for insuring that the major route of pyruvate formed by cardiac muscle will be the respiratory pathway of the Krebs cycle, rather than conversion to lactate, a less efficient producer of energy. On the other hand, skeletal muscle contains M LDH as predominant, and this form retains its ability to catalyze reduction of pyruvate to lactate at high pyruvate concentrations, thus allowing the less well oxygenated skeletal muscle to respond to demands for rapid energy output by the contraction of an oxygen debt.

The individual mammalian tissues differ in their content of M and H units of LDH and it has recently been demonstrated that the ratios of M and H LDH concentration may be altered in certain tissues following chronic exposure to such stimuli as denervation, exposure to high or low oxygen concentrations, or maturation from prenatal to postnatal conditions.[28] It is clear, then, that the response of any tissue to a given set of concentrations of LDH substrates, coenzymes and pH will be governed not only by its hereditary ratio of M and H LDH, but also by any acquired changes in ratio of M to H LDH as the result of exposure to a variety of physiological environmental variants. Such an alteration could be responsible for the tolerance of trained athletes to strenuous exercise and anoxia and the different patterns of lactate production manifested in shock by conditioned and unconditioned animals.*

The intracellular concentration of pyruvate may also be seen (Equation 2, page 451) to influence lactate production by a tissue. Direct evidence of such an effect is provided by experiments in which blood lactate levels are seen to rise following infusions of pyruvate or of its precursors, glucose and sucrose.[29,72] Similar results follow the admin-

*References Nos. 19, 55, 115, 122.

‡ References Nos. 27, 34, 66, 71, 81, 94, 102.

§ References Nos. 2, 10, 34, 44, 61, 63, 65, 73, 79, 82, 86, 92-95, 98, 102, 106, 122.

¶ References Nos. 7, 31, 46, 54, 63, 65, 74, 80, 112, 122.

* References Nos. 31, 46, 65, 87, 88, 92, 94, 96.

istration of insulin, known to increase glucose utilization by adipose and muscle tissue, and by epinephrine, known to cause mobilization of hepatic glycogen.† Huckabee noted, however, that elevation of blood lactate by such procedures is accompanied by equivalent elevations of blood pyruvate, thus suggesting that the change in lactate concentration under these conditions is simply a response of the steady state to a new concentration of pyruvate and is not related to increased availability of reduced coenzyme I ($NADH_2$).[72]

The response of the isolated LDH system to pH changes is predictable, but in the intact animal the mechanisms are less clear. It has been shown that exposure of intact yeast cells to increasing H^+ concentrations leads to increased lactate production, which could be predicted by consideration of Equation 2.[22] The intact mammal, however, responds to a decrease in H^+ concentration with an increased output of lactate, which is contrary to the expected effect on the LDH equilibrium.[33,76,80] Such a response indicates that the effect of such a pH change in the intact muscle must register itself elsewhere than on the LDH system, and that the magnitude of that effect is such that it can overcome the direct effect of pH on the LDH system.

The elimination of the possibility of a major pH effect on $NADH_2$/NAD ratios, narrows the source of the pH effect down to the availability of pyruvate to the LDH system.[72] While direct evidence of this has not been presented, it appears most likely that the observed pH effect on lactate production is largely the result of an effect upon the production and disposition of pyruvate, such that the creation of alkalosis either increases the production of pyruvate or inhibits the disposition of pyruvate by non-LDH mediated pathways. Such a mechanism, regardless of its mediation, provides a rapidly available source of strong acid (lactic acid) in the presence of either metabolic or respiratory alkalosis and serves as an admirable compensatory mechanism.[72,135]

The remaining major influence of the set of the LDH equilibrium is the ratio of reduced to oxidized NAD present in the extra-mitochondrial cell sap. Consideration of Equation 2 leads quickly to the conclusion that this reflection of the redox potential of the cell will be primarily in the determination of the ratio of lactate to pyruvate produced, assuming pH and LDH isozyme concentration to remain stable. The significance of this relationship has been emphasized by Huckabee in a series of papers.[72-76] The ratio of $NADH_2$ to NAD will be influenced by a number of factors, all related to the oxidation and reduction of NAD. NAD is the coenzyme required by a number of enzyme systems, both intra- and extra-mitochondrial in location, and serves as an extremely important mediator of hydrogen transport within the cell. These considerations and their relationship to the control of glycolysis have been reviewed in detail by Boxer and Devlin.[17]

The sources of variables which may influence the ratio of $NADH_2$ to NAD are several. Since the respiratory pathway represents the major route of oxidation of reduced NAD in most mammalian cells, oxygenation of the cell plays a major role. This can be affected in the intact animal by primary anoxia, circulatory failure, respiratory failure, severe anemia, interference with oxygen carrying capacity of hemoglobin (for example, methemoglobinemia) or localized alterations in tissue perfusion. Clinical examples of the accumulation of lactate as the result of the existence of these conditions are frequent and have been well documented.†

In the presence of adequate oxygen, the oxidation of $NADH_2$ remains vulnerable at two points. NAD does not appear to be capable of crossing the mitochondrial membrane, and thus must depend upon intermediates for transfer of its hydrogen to the intramitochondrial respiratory chain. Two such intermediate systems which have been proposed include the alpha-glycerophosphate dehydrogenase (AGPD) and β-hydroxybutyric acid dehydrogenase (BHBD) systems, whose substrates are able to cross the mitochondrial membrane and thus may serve as transhydrogenation systems for $NADH_2$, as indicated in Figure 1.[17]

†References Nos. 1, 8, 107, 115, 125.

†References Nos. 7, 20, 31, 46, 74, 80, 92, 97, 112, 123, 128.

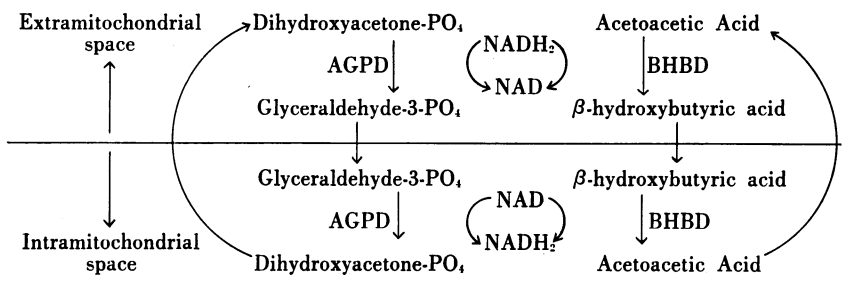

Figure 1.—Diagram of two proposed pathways for the transmission of hydrogen from reduced extramitochondrial $NADH_2$ to oxidized intramitochondrial NAD without physical transfer OF NAD from extra- to intramitochondrial space.

TABLE 1.—*A Partial List of Drugs Which Have Been Described as Inhibiting Tissue Respiration*[133]

p-Aminophenol	Antabuse
Barbiturates	Antihistamines
Diethylstilbestrol	Adrenergic Blocking Agents
Sulfonamides	Chlorpromazine
Salicylates	Phenformin Hydrochloride

Abnormalities, congenital or acquired, in the activity of these two hydrogen transfer systems have not been described in mammals, but they are indicated here as possible sources of diminished $NADH_2$ oxidation, especially under conditions of hypoxic stress when their adequacy might be crucial.

At the other end of the oxidative chain lies the Krebs tricarboxylic cycle and its close association with the respiratory chain. Deficiency in Krebs cycle activity has been conjectured and discarded as responsible for certain of the events in development of diabetic ketoacidosis.[83] On the other hand, a significant number of pharmacologically active agents, in adequate concentration, can be shown to interfere with hydrogen transport and respiration of the Krebs cycle and the respiratory chain.[133] Such an interference with normal cellular respiration leads to altered redox potentials, the accumulation of $NADH_2$ and increased lactate production. A partial list of some of the drugs known to possess this capability when in adequate concentration is included in Table 1. Clinical and experimental examples of what may be such an effect are offered by the reports of lactic acidosis accompanying phenformin, guanidine and possibly tetracycline intoxication.[14,53,119,128-130]

The oxidation of certain metabolites is mediated by NAD dependent enzyme systems, resulting in the accumulation of large amounts of $NADH_2$. Such an effect leads to an increase in the $NADH_2/NAD$ ratio and thus to increased lactate production. Ethyl alcohol is such a metabolite and the metabolism of ethanol has been shown to inhibit the metabolism of an exogenous lactate load.[26,91,120] It is possible that the increased lactate observed in the acidosis of methyl alcohol poisoning and the acidosis reported to have occurred following paraldehyde administration may be examples of the same mechanism.‡

The relationship of elevated blood lactate to contraction of an oxygen debt was first pointed out by Hill, Long and Lupton.[65] Friedman and coworkers first suggested that the relationship between the observed ratio of blood lactate to pyruvate would provide a more accurate indication of the state of oxygenation of the tissues than lactate levels alone.[45,46] Huckabee introduced the concept of "excess lactate§" in order to differentiate that lactate expected to be present as the result of the normal relationship of lactate to pyruvate, from that lactate observed in excess of the expected, which is produced as the result of an altered redox state in the tissues.[72] In addition, he proposed—and presented evidence to substantiate the proposal—that the quantity of excess lactate is related to the adequacy of oxygenation of tissues in the intact animal and in isolated segments of the circulation.[72-76] Furthermore, his evidence suggests that the concentration of excess lactate present is directly related to the ratio of reduced to oxidized NAD ($NADH_2/NAD$). While both the concept and its application have recently been subjected to question,[60,82,95,104] it is clear that all patients with lactic acidosis, in whom the values are available, have had significant amounts of excess lactate present, and that 55 per cent or more of the total blood lactate was present as excess lactate. The concept of excess lactate has proven of great usefulness, not only in the consideration of the sources of lactic acidosis but in determination of the prognosis of patients with elevated lactate from any cause[130] or from shock[20] (in both of which situations excess lactate of more than four or five mEq per liter is associated with an extremely poor prognosis), in the evaluation of respiratory distress in infants[139] and of congestive heart failure in adults.[79]

It is important to note the significance of lactate in lactic acidosis. It is the anion, lactate, which is measured in the blood by conventional methods of lactate determination. However, it is lactic *acid* which is produced by the reaction mediated by LDH:

Equation 3:*

$$CH_3\text{-}CO\text{-}COO^-H^+ + NADH^- + H^+ \xrightarrow{LDH} CH_3\text{-}CHOH\text{-}COO^-H^+ + NAD$$

The significance of this lies in the end product of pyruvate metabolism which results from this mechanism: lactic acid. Lactic acid is a strong organic acid, with a pK′ of approximately 3.86, and is ionized almost completely. Thus for every mole of lactate produced, one mole of H^+ must be buffered. The other major metabolic fate of pyruvate, under aerobic conditions:

*CH_3-CO-COOH=pyruvic acid. CH_3-CHOH-COOH=lactic acid.

‡References Nos. 12, 13, 37, 62, 134.

§Excess lactate (XL) is calculated by the following formula[72]: $XL=(L_n-L_o)-(P_n-P_o)(L_o/P_o)$, where L_o=expected normal value of lactate, P_o=expected normal value of pyruvate, and L_n and P_n= actual values of lactate and pyruvate found, respectively.

Equation 4:

$$CH_3\text{-}CO\text{-}COO^-H^+ + NADH_2 + 3O_2 \xrightarrow{\text{Krebs Cycle}} 3H_2CO_3$$

leads to the production of weakly ionized carbonic acid, which is easily excreted by pulmonary and renal pathways and requires much less buffering than lactic acid. Depending upon the balance of factors which influence rates of anaerobic glycolysis and respiration as previously discussed, the disposition of the bulk of pyruvate may take either pathway:

Equation 5:*

$$CH_3\text{-}CO\text{-}COOH + NADH_2 \begin{cases} \xrightarrow[\text{LDH}]{\text{Anaerobic}} CH_3\text{-}CHOH\text{-}COO^- + H^+ \\ \xrightarrow[\text{Aerobic}]{\text{Krebs Cycle} + 3O_2} 3CO_2 + 3H_2O \end{cases}$$

Of additional significance is the fact that energy derivation via anaerobic glycolysis is considerably less efficient than that through the respiratory pathway. For reasons that are not fully understood, but very probably are related to the inefficient energy production of anaerobic glycolysis, tissues utilizing anaerobic glycolysis as the major pathway of energy production oxidize more glucose and produce lactic acid at a much higher rate than would be predicted from their baseline glucose uptake under aerobic conditions.[109]

Clinical Considerations

The clinical presentation of lactic acidosis is relatively uniform, usually consisting of the rather sudden onset, over a period of a few hours, of confusion, lethargy, Kussmaul respirations, and in most cases, coma. The usual presentation is that of unexplained acidosis in a previously ill patient. The explanation of the hyperpnea, tachypnea and change in mental awareness is not usually readily apparent and the differential diagnosis must include not only the significant causes of metabolic acidosis, reviewed recently by Waters and coworkers[135] and Winters and Dell,[136] but such situations as primary hyperventilation due to cerebral damage and the initial respiratory alkalosis not infrequently observed with the onset of gram-negative septicemia.

The clinical state of the patient, in addition to hyperpnea and tachypnea, which are constant features of the disease, and altered mental state from mild confusion to coma, may also include varying degrees of dehydration, evidence of vascular collapse (hypotension, tachycardia, hypothermia,[7,130] venous constriction) and evidence of the underlying disease.

Two quite confusing situations have been reported. The onset of lactic acidosis immediately following treated diabetic ketoacidosis has been reported in cases presented by Daughaday,[26] Ewy,[39] and Tranquada,[130] and their coworkers. That this can occur, emphasizes the importance of repeated determinations of serum acetone during the therapy of diabetic coma. The disappearance of significant amounts of serum acetone and continued or increasing metabolic acidosis should lead to consideration of hyperlacticemia as a possible cause.

The other confusing situation is that represented by three of the patients with lactic acidosis reported by Huckabee.[78] These patients had poliomyelitis, and required a mechanical respirator. In this situation, a low blood bicarbonate and pCO_2 is usually interpreted as indicative of metabolic alkalosis related to hyperventilation by the respirator. Huckabee initially pointed out the direct relationship of the hypocapnia of hyperventilation and increased levels of blood lactate.[72] More recently Eichenholz, in experiments with anesthetized and hyperventilated dogs, showed that the initial compensation for the respiratory alkalosis by the production of lactate was quite adequate, but that the continued hyperventilation and bicarbonate loss led eventually to a severe metabolic acidosis with decided increase in blood lactate.[35] Similar conclusions are suggested by the study of Attar, Desmond and Colley[5] of the effects in animals, of hyperbaric oxygenation in vascular collapse due to hemorrhage. Hyperventilation, significant elevation of blood lactate and the development of mild acidosis were observed, although direct determinations of muscle and liver oxygen tensions were supernormal during the hyperbaric oxygenation. It seems likely that a similar chain of events may have resulted in lactic acidosis in the cases reported by Huckabee, particularly in view of the decreased serum bicarbonate recorded for these patients, which could not have occurred without an increase in ventilation.

A survey of Table 2, which records the major underlying diseases present in 71 reported cases of lactic acidosis* reveals several items of interest.

*CH_3-CO-COOH=pyruvic acid. CH_3-CHOH-COOH=lactic acid.

*References Nos. 14, 26, 39, 40, 53, 78, 116, 128-130, 135.

TABLE 2.—*A Summary of the Underlying Diseases of 71 Patients With Lactic Acidosis**

Disease or Condition	*Number*
Uremia (BUN >35 mg per 100 ml	29
Diabetes mellitus	29
Bacterial infection	26
Pyelonephritis, acute or chronic	17
Arteriosclerotic heart disease	12
Acute pancreatitis	12
Pneumonia	11
Chronic alcoholism	10
Leukemia	9
Cirrhosis	8
Gram-negative septicemia	7
Pregnancy	7
Other heart disease	7
Acute gastrointestinal bleeding	5
Acute alcoholism	4
Chronic pulmonary disease	4
Poliomyelitis	4
Peritonitis	3
Acute hepatitis	3
Acute fatty metamorphosis of liver	3
Ascending cholangitis	3
Small bowel infarction	3
Hypothyroidism	2
Miscellaneous (1 each—liver abscess, myelofibrosis, pituitary necrosis, peripheral gangrene, pulmonary embolism, carcinoma of small bowel)	7

*References Nos. 14, 26, 39, 40, 53, 78, 116, 128, 129, 130, 135.

The conditions represented in this survey cannot be considered to have significance with respect to the distribution of underlying diseases in lactic acidosis, nor with respect to the frequency of lactic acidosis in patients with the listed diseases, since they do not represent the result of a systematic survey of these disease conditions for the presence or absence of lactic acidosis. For example, the relatively high incidence of diabetes mellitus in the reported cases may or may not have significance with respect to that disease. The fact is that the majority of the cases were reported by physicians whose opportunities to observe patients are largely concerned with diabetes. Likewise, eight of the nine cases of leukemia with lactic acidosis were observed by physicians who were dealing wholly with chemotherapeutic studies of lymphomas.

A number of the listed conditions are normally associated with decreased tissue oxygenation. Such conditions as arteriosclerotic heart disease (in which are included both patients with acute myocardial infarctions and congestive heart failure attributable to this etiology), pneumonia, other heart disease, acute gastrointestinal bleeding, chronic pulmonary disease and small bowel infarction are representative. In these situations lactate production regularly increases[77,128,129] and in some patients with these diseases, but certainly not in all, the increase may result in lactic acidosis. In this group the development of lactic acidosis frequently represented a preterminal event of relatively brief duration. Question remains as to why lactic acidosis develops only in certain patients with these conditions and not all of them.

The incidence of significant bacterial infection, as evidenced by local and systemic effects (fever, tachycardia, leukocytosis, interference with renal or pulmonary function, positive blood culture) is notable. Some of these patients were hypotensive as the result of infection, particularly those with Gram-negative bacillary septicemia. Nineteen of the 24 patients with significant infections recorded by Tranquada, Grant and Peterson[130] harbored one or more Gram-negative bacilli, and seven of them had Gram-negative septicemia. It is well known that the endotoxins of these bacteria may cause vascular collapse and reduced tissue perfusion and oxygenation.[51,85,111,132] The additional effects of infection, including localized interference with blood flow, the increased metabolic rate of hyperthermia and resultant redistribution of blood flow would reinforce the effects of other influences leading to increased lactate production.[43]

The frequency of acute pancreatitis, proved at autopsy or suggested clinically by the presence of characteristic symptoms and elevated serum amylase levels, is worthy of note. In two patients reported by Tranquada, Bernstein and Grant[130] acute pancreatitis appeared to be the primary underlying cause of lactic acidosis. In the other patients in whom this finding has been reported, it is not clear whether pancreatitis was primary or secondary to the severe acidosis. The reported high incidence of the association of acute pancreatitis and severe metabolic acidosis due to lactic acid in methyl alcohol intoxication, as well as the recent report of the frequency of the observation of elevated serum amylase in diabetic ketoacidosis, suggests that severe metabolic acidosis may play a role in the pathogenesis of acute pancreatitis.[13,41] Shubin and Weil report a high incidence of elevated serum transaminase and lactic dehydrogenase in patients with shock.[118] It may be that observations of elevations of serum concentrations of normally intracellular enzymes in severe illness and shock represent primarily the disorganization and deterioration of energy sources which normally prevent the leakage of intracellular substances into the extracellular space.

Seventeen of the 61 patients about whom such information was available had severe disturbances of hepatic function. Although the evidence is not complete on this point, it appears that the liver functions normally to remove significant amounts of lactate from the blood. It is not unlikely that significant disturbance of this function may impair the ability to deal with rates of peripheral lactate production which would not normally result

in significant elevation of blood lactate or acidosis. Ethyl alcohol is known to be metabolized initially by alcohol dehydrogenase, an enzyme concentrated primarily in the liver, with the resultant reduction of very large amounts of NAD.[91,120] The ingestion of ethanol has been shown to delay the disappearance of an administered load of lactate[26] and it may be that acute alcoholism can play a permissive role in the development of lactic acidosis similar to that of severe liver disease.

The high incidence of uremia undoubtedly reflects the frequency of cardiovascular insufficiency with resultant decreased renal blood flow. Although the kidney has been shown to take up lactate consistently,[68,89] we could find no studies of the relative role played by the kidney in the total economy of lactate in the intact animal or human. It is possible that deranged renal function or decreased renal perfusion may have an effect similar to that of severe hepatic disease, with respect to lactate metabolism. A further possibility, that of decreased renal excretion of lactate as a cause of the accumulation of lactate, is not supported by any evidence. Although there is not total agreement as to the role of the kidney in lactate excretion, it appears that lactate represents a threshold substance which does not appear in the urine in significant amounts until relatively high blood concentrations are achieved.† Even in the presence of very high levels of blood lactate the amount excreted in the urine is insignificant with respect to the rates of total production and disposition of lactate by other pathways.[77,80]

Field and coworkers suggested that the origin of lactic acidosis in their patients with leukemia is the very high rate of lactate production by leukemic leukocytes crowding small blood vessels and impeding their own oxygenation.[40] Scheerer and coworkers accepted this explanation for their patient.[116]

Table 3 presents the age and sex distribution for the reported cases of lactic acidosis. The significance of the fact that two-thirds of the patients were age 41 or above and that the sex ratio was 2:1 female to male can only be speculated upon at this time.

Laboratory Observations

Initial lactate concentrations in the 40 patients observed by Tranquada and coworkers averaged 17.5 mM/L.[130] The range of initial blood lactate levels in that series and others, in patients recognized to have lactic acidosis is from about 7 mM/L to 42 mM/L.

†References Nos. 50, 63, 80, 89, 98, 122.

TABLE 3.—*Age and Sex Distribution of Reported Cases of Lactic Acidosis in Which Figures Were Available*

	Years	*Number of Patients*
Mean Age	49	....
Range	17-82	....
Grouping	0-20	5
	21-40	14
	41-60	19
	>60	19
Total		57
Sex		
Male		16
Female		32
Total		48

The arterial pH is always reduced. Except in instances where respiratory acidosis complicates the picture of lactic acidosis, or where therapy with $NaHCO_3$ has already been given, a pronounced reduction in blood bicarbonate and pCO_2 is to be expected. Both Huckabee[78] and Waters, Hall and Schwartz[136] commented upon the rather constant reciprocal relationship of blood lactate and HCO_3 concentrations. Serum chloride may be normal or low, depending upon the duration of the acidosis. Serum potassium, in the absence of previous significant potassium depletion, will be elevated to the upper range of normal or above. Tranquada and coworkers[130] have observed a rather consistent and pronounced elevation of serum inorganic phosphorus in ten patients in whom the determination was made. This may prove to be a useful procedure in the differentiation of lactic acidosis, if further experience confirms this finding.

When measured, the levels of serum lactic dehydrogenase, the transaminases, and amylase are frequently found to be elevated. The significance of this finding is discussed above. Elevated blood urea nitrogen and creatinine is commonly found. Chemical evidence of deranged liver function has been reported in 20 of 64 cases.

These latter findings seem to be nonspecific changes and are not of much value in arriving at the diagnosis of lactic acidosis. In a few cases serum uric acid levels were found to be decidedly elevated.[131] Whether this finding is related to the accompanying azotemia or to the inhibition of renal uric acid excretion noted in the presence of elevated levels of circulating lactate is unknown.[50,58] The presence of significant amounts of serum acetone (a moderate or greater reaction of undiluted serum on Acetest® or similar reagent) leads to a diagnosis of ketoacidosis, unless the acidosis persists after disappearance of elevated ketone levels (see above). Blood sugar may be low, normal, or elevated. The urine pH is usually quite low, but occasionally is not.

Etiology of Lactic Acidosis

While the preceding considerations appear to provide some basis for the appearance of lactic acidosis in some patients, three significant questions, discussed by Tranquada, Grant and Peterson,[130] remain unanswered. It is clear that lactic acidosis does not develop in all patients with the above diseases. What is it about these particular subjects which led to the development of lactic acidosis? At least 24 of the 71 reported cases did not manifest underlying disease which could clearly be related to physiological conditions favoring the development of lactic acidosis. What, then, is the etiologic derivation of this derangement in those patients? Furthermore, under some conditions significant elevations of blood lactate may occur without the development of significant acidosis.[77,130] In what respect do these patients differ from those in whom acidosis develops with similar levels of blood lactate?

From a review of the diverse clinical situations from which lactic acidosis results, it seems likely that we are dealing with a syndrome of multiple possible origins, and that in any given patient the syndrome may result from one or more causes. In addition to the well recognized influences of lactate production discussed above, several hypothetical situations may be proposed. An alteration in distribution of lactic dehydrogenase isozymes, with a preponderance of the M type, due either to an hereditary abnormality or an acquired change mediated by prolonged inactivity, acute illness or infection, might result in an impaired ability to deal with situations tending to cause lactate accumulation. Likewise an hereditary or acquired deficiency in the enzyme systems normally responsible for the aerobic oxidation of $NADH_2$ might allow a normal existence until significant anoxic stress was placed upon the individual. The possible influence of drug toxicity cannot be dismissed, and has been discussed above.

The control of the balance between anaerobic glycolysis and aerobic respiration of mammalian cells is imperfectly understood, but further knowledge in this area may uncover further possible locations in which errors of metabolism might favor the development of lactic acidosis.* It is possible that unrecognized "compensated shock," as suggested by Huckabee, may exist in the majority of these patients with compartmentalized areas of tissue hypoxia due to decreased tissue perfusion.[77] Corday and coworkers demonstrated pronounced decreases in splanchnic blood flow as a compensatory mechanism in various types of shock.[25] The resulting decrease in portal flow, and the relatively large area of poorly perfused tissue resulting from such a change could be conceived of as significant influences toward the accumulation of lactic acid.[38]

*References Nos. 17, 48, 49, 84, 105, 137, 138.

Therapy

The course of the syndrome may lead to death within a matter of hours, or the condition may respond to therapy temporarily only to return hours or days later, or it may respond to relatively simple measures with complete recovery. In general, patients who have shown the least change in mental state have had the best prognosis.

The therapy of lactic acidosis has been discussed in detail by Huckabee,[78] Waters, *et al.*,[135] Tranquada, *et al.*,[129,130] Daughaday, *et al.*,[26] Field, *et al.*,[40] Moore, *et al.*,[100] and by Ewy, *et al.*[39] It is generally agreed that immediate steps should be taken to correct any underlying source of tissue anoxia which can be recognized. Likewise, correction of the acidosis with infusions of $NaHCO_3$, rather than sodium lactate, seems desirable,[117,130,135] although theoretical considerations suggest that some degree of acidosis may aid in the disposition of lactate.[33,76,129] Moore, *et al.*, have used TRIS (2-amino-2-hydroxymethyl 1, 3-propane diol) buffer effectively in correction of the lactic acidosis resulting from inadequate perfusion during cardiopulmonary by-pass procedures.[100] Ewy, *et al.*, had what appears to be a good result in one case with use of extracorporeal dialysis.[39] Tranquada, *et al.*,[130] had equivocal results in three cases in which they used peritoneal dialysis with a lactate containing dialysis fluid, and uninterpretable results in one case incompletely dialyzed with dialysis fluid in which lactate had been replaced with acetate.[127] Recently, Tranquada and coworkers presented the results of the treatment of five patients with intravenous methylene blue.[129] This redox agent had a demonstrable effect on all five patients, resulting in a lowering of the L/P ratio, a pronounced decrease of excess lactate, and may have contributed to the survival of one patient. Nevertheless, methylene blue cannot be said to be a specific for lactic acidosis although it may be used as an adjunct to therapy until more specific means or techniques become available.

Of the 58 reported cases in which results of therapy can be interpreted, there were only six survivors of lactic acidosis. It seems clear that either this syndrome represents a pre-terminal event which eludes therapeutic skill, or that a better understanding of the mechanisms involved will be required before more specific measures can be employed. It is likely that the truth lies somewhere between the two.

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